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Research Article

Is There Predictive Significance of HALP Score in Metastatic RCC Patients Treated with Nivolumab?

Mesut Yilmaz

[1]Department of Medical Oncology, Bakırkoy Sadi Konuk Training and Research Hospital, Istanbul, Turkey

Abstract

Objectives: In the treatment of metastatic RCC, nivolumab has been used with increasing frequency in recent years. Systemic inflammation plays an important role in the initiation and progression of cancer. In this study, we aimed to investigate whether the HALP score, which indicates systemic inflammation, has a predictive significance in patients receiving nivolumab treatment for mRCC.

Methods: 45 patients who were treated with nivolumab after first-line anti-angiogenic therapy for mRCC in our clinic and whose files were analyzed retrospectively were included in the study. The cut-off value for the HALP score was calculated using the X-tile software program.

Results: HALP score was found to be high (≥16.98) in 26 patients and low (<16.98) in 19 patients. Mean progression-free survival (PFS) was statistically significantly longer in the high HALP group compared to the low group (12.0 months versus 6.0 months). A significant correlation was found between PFS and serum albumin level, while a negative and weak correlation was found between serum LDH levels.

Conclusion: We showed that the HALP score is associated with prognosis in patients receiving nivolumab treatment for mRCC. The reliability of this index, which shows systemic inflammation with a low-cost and easily applicable method, should be demonstrated by large-scale studies involving more patients.

Keywords: HALP score, nivolumab, progression free survival, renal cell carcinoma.

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Renal cell cancer (RCC) constitutes approximately 90% of kidney cancers and as a result of the development of imaging methods, the frequency of early-stage RCC has increased in the last two decades, while the frequency of metastatic RCC (mRCC) has decreased.[1] Currently, immunotherapy agents (anti-CTLA-4 and anti-PD-1/PD-L1) have become standard in mRCC therapy. Nivolumab, a PD-1 inhibitor, was approved by the FDA after showing a longer overall survival (25.0 months versus 19.6 months) compared to everolimus in the group of patients who received anti-angiogenic therapy.[2]

It is known that systemic inflammation plays an important role in the initiation, growth, and metastasis processes of cancer.[3] Recently, an index called the HALP score, calculated by the counts of hemoglobin, albumin, lymphocyte, and platelets has been defined. The HALP score evaluates both the immune system and the nutritional status of the patient. It has been reported to be a good prognostic marker in various types of cancer, including gastrointestinal and genitourinary cancers.[4,5]

In this study, we aimed to investigate whether the HALP score has predictive significance in patients receiving nivolumab treatment for mRCC.

Address for correspondence: Mesut Yilmaz, MD. Bakirkoy Sadi Konuk Egitim ve Arastirma Hastanesi Tıbbi Onkoloji Klinigi, Istanbul, Turkey
Phone: +90 506 976 44 12 **E-mail:** mesutyilmaz12@yahoo.com

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Methods

Patients

The files of patients with a pathologically confirmed diagnosis of mRCC who were treated in Bakırköy Dr. Sadi Konuk Training and Research Hospital Medical Oncology Clinic between March 2017 and February 2020 were retrospectively reviewed. 45 patients who received nivolumab treatment after a first-line anti-angiogenic therapy were included in the study. In the patient files, those missing albumin, hemogram, and LDH values before nivolumab treatment were excluded from the study. Those with chronic inflammatory diseases such as acute infection and rheumatologic diseases that would increase systemic inflammation other than mRCC were not included in the study. Clinicopathological characteristics and laboratory values were collected from patient files and electronic records. The HALP score was calculated as hemoglobin level (g/dl) x albumin level (g/dl) x lymphocyte count (/L) / platelet count (/L). Progression-free survival was defined as the time elapsed from the initiation of nivolumab to radiological demonstration of progression, discontinuation of the drug for toxicity, or death.

Statistical Analysis

X-tile software program (Yale University) was used to calculate the HALP score cut-off value.[6] The X-tile software was able to compare the p-values of different cut-off values for a continuous variable and determine the best cut-off value with the most significant p-value. Chi-square test was used to analyze an association of clinicopathologic data with HALP. The Kaplan-Meier survival method was used to estimate progression-free survival (PFS), with a log-rank test used to test significant differences. HALP score corresponding to p=0.0 was accepted as the cut-off value.

In the study, the general values of the data are given as mean, standard deviation, median minimum, maximum, frequency, and ratio values by using descriptive statistical methods. The normality of data distribution was examined using the Kolmogorov-Smirnov test and histograms. Mann-Whitney U test was used for paired group comparison of quantitative independent data that were not normally distributed. Chi-square test was used in the analysis of qualitative independent data. Spearman correlation test was used for correlation analysis. SPSS version 22.0 package program was used in the analysis of the data. The results were evaluated at a 95% confidence interval. P<0.05 was considered statistically significant.

Results

Of the 45 patients included in our study, 30 were male and 15 were female. The mean age of all patients was 54.6±11.9 years. Thirty-three patients had received sunitinib treatment before nivolumab, and 12 patients had been treated with pazopanib. The ECOG (Eastern Cooperative Oncology Group) performance score (PS) of 29 patients was 0, and that of 16 patients was 1. When the patients were classified according to their best radiological responses, 22 had progressive disease, 3 had stable disease, 18 had a partial response and 2 had a complete response. Mean albumin and LDH (Lactate dehydrogenase) values were 36.08 (26.0-45.0) g/dl and 290.04 (136-1549) U/L, respectively. The mean progression-free survival (PFS) was 9.6 months (3.0-49.0 months) in the entire patient group. The demographic, pathological, and clinical characteristics of the patients are shown in Table 1.

The cut-off value for the HALP score was calculated using the X-tile software program and was found to be 16.98 (Fig. 1). Patients with a score of 16.98 and above were grouped as high HALP and those below as low HALP. There were 26 patients in the high HALP group and 19 patients in the low HALP group. The mean PFS was statistically significantly longer in the high HALP group compared to the low HALP group (6.0 months versus 12.0 months, p<0.05). A significant correlation was found between PFS and serum albumin level according to the Spearman correlation test (r=0.403, p<0.05). A weak and negative correlation was found between PFS and serum LDH levels (r=-0.225, p=0.137) (Fig. 2). The mean age in the high HALP group was statistically greater (49.2 months versus 58.5 years, p<0.05). There was no statistically significant difference between the female and male patient distribution in both groups. Similarly, there was no statistically significant difference between the two groups in terms of ECOG-PS, best radiological response, number of metastasis sites, and metastasis sites.

Discussion

The role of immunity and nutritional status in predicting prognosis in cancer patients has recently been investigated with increasing interest.[7] Low hemoglobin levels have been associated with rapid disease progression and poor survival outcomes, especially in patients with advanced-stage cancer. In a meta-analysis by Xia et al.,[8] an association was shown between anemia and early recurrence and short survival in localized RCC patients who treated with nephrectomy. Serum albumin is a negative acute phase reactants marker that is synthesized in the liver, shows protein level in the blood, and is used in the assessment of nutritional status, and the relationship between hypoalbuminemia and poor survival outcomes has been investigated in the literature for many cancer types. In a study investigating the effect of nutritional deficiencies on prognosis in RCC patients, Ko et al.[9] showed the negative pre-

Table 1. Clinical and demographic features of the patients

	Low HALP (<16.98) (n=19)	High HALP (≥16.98) (n=26)	p
HALP	11.3	33.5	p=0.00
Age (years)	49.2 (30-65)	58.5 (32-77)	p=0.011
Gender (n)			NS
Female	5	10	NS
Male	14	16	NS
Albumin (g/L)	34.1 (26-45)	37.5 (27-45)	0.022
LDH (U/L)	344.5 (136-1549)	250 (147-956)	0.081
PFS (months)	6.0 (3-13)	12.0 (3-49)	p<0.05
Number of metastatic sites (n)	2.9	2.7	NS
CNS metastasis (n)	3	5	NS
Lung metastasis (n)	15	24	NS
Liver metastasis (n)	6	4	NS
Bone metastasis (n)	14	20	NS
First line therapy (n)			
Sunitinib	15	18	NS
Pazopanib	3	9	NS
Nephrectomy			
Yes	15	25	NS
No	4	1	NS
Fuhrman grade			
1	-	-	NS
2	2	2	NS
3	5	8	NS
4	12	16	NS
Sarcomatoid pattern			
Yes	3	2	NS
No	16	24	NS
ECOG-PS			
0	9	20	NS
1	10	6	NS
Best radiologic response			
CR	-	2	NS
PR	7	11	NS
SD	1	2	NS
PD	11	11	NS

HALP: Hemoglobin, albumin, lymphocyte, and platelet score; LDH: Lactate dehydrogenase; CNS: Central nervous system; NS: Non-significant; PFS: Progression-free survival; ECOG-PS: Eastern cooperative oncology group-performance status; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

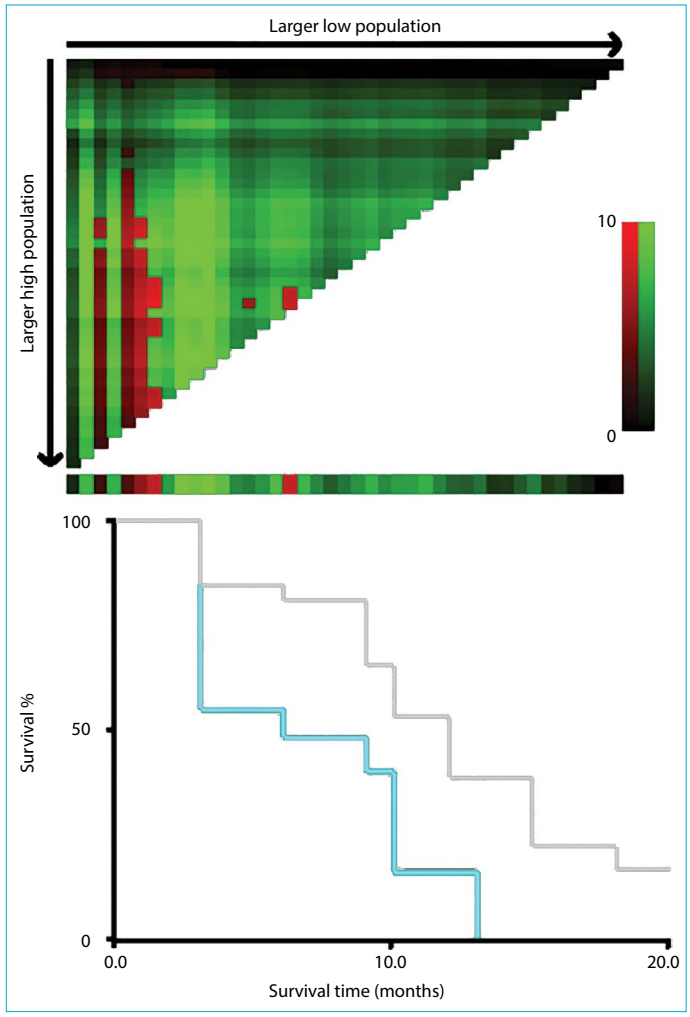

Figure 1. X-tile software program was used to calculate the HALP score cut-off value.

HALP: Hemoglobin, albumin, lymphocyte, and platelet score.

dictive effect of albumin level below 35 g/L. It has been shown in previously published studies that circulating immune inflammatory cells such as platelets, lymphocytes, and neutrophils increase the potential for proliferation, invasion, and metastasis in cancer cells. Also, the association of inflammation with poor survival outcomes has been demonstrated in many cancer patients, including RCC.[10] When these results are evaluated together, platelet level is a negative risk factor in cancer patients; hemoglobin, albumin, and lymphocyte levels are positive risk factors. In this study, we aimed to investigate whether the HALP score, a new index calculated using these four parameters, affects prognosis in mRCC patients who have previously received first-line tyrosine kinase treatment and used nivolumab in the second-line treatment.

In this study, we also investigated the relationship between LDH level and PFS. LDH is a glycolysis enzyme that catalyzes the conversion of pyruvate to lactate, and aerobic glycolysis is an important characteristic of tumor metabolism.[11] As a result of the high rate of glycolysis in tumor cells, lactate increases in the tumor microenvironment and an acidic environment occurs. Cancer cells are more resistant to this acidic environment than normal cells, and the immune response to tumor antigens is weakened in an acidic environment. As a

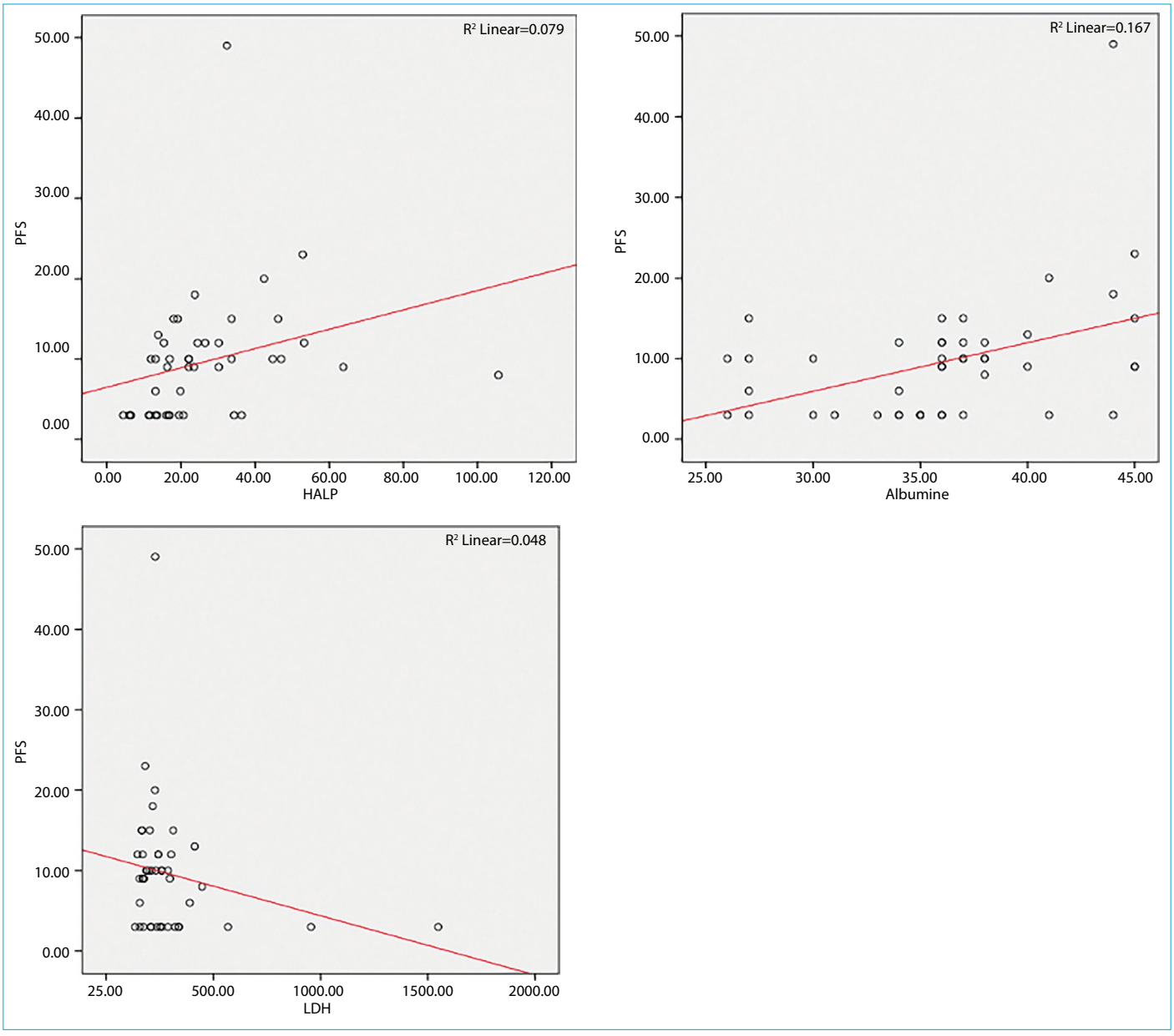

Figure 2. Correlation curves between progression free survival and HALP, albumin, LDH.

PFS: Progression-free survival; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; LDH: Lactate dehydrogenase.

result, the proliferation and invasion of cancer cells become possible. Also, after the development of bone, lung, and bone metastases in cancer patients, the level of LDH in the blood increases.[12] In their meta-analysis, Shen et al.[13] showed that high serum LDH is associated with poor prognosis in both metastatic and nonmetastatic RCC patients. In this study including 6629 patients, it was found that high LDH level was associated with poor PFS. In our study, we found a negative correlation between PFS and LDH in metastatic RCC patients receiving nivolumab treatment.

Peng et al.[14] investigated the prognostic significance of the HALP score in their study including 1360 RCC patients with nephrectomy. They have shown that the HALP score is an independent predictor for cancer-specific survival in RCC, and they say that it can predict prognosis more accurately than the TNM staging system. In our study, we found a statistically significantly longer PFS in the group with high HALP scores in mRCC patients who received nivolumab treatment in the second-line treatment.

In another retrospective analysis, the relationship between HALP score and PFS in small cell lung cancer patients treated with platinum and etoposide was investigated, and similar to our study, longer PFS was shown in patients with higher HALP scores.[15]

A clinical or pathological biomarker that predicts the efficacy of immune checkpoint inhibitors used in the treatment of advanced-stage RCC has not been defined yet. De Giorgi et al.[16] retrospectively investigated the relationship between the systemic inflammatory index and body mass index with survival in stage 4 RCC patients treated with nivolumab. They showed that there was worse survival in patients with a high systemic inflammatory index calculated using lymphocyte, platelet, and neutrophil counts. Similarly, in our study, we found that the PFS value was worse in the patient group with low HALP score showing high inflammation. In the same study, as an indirect indicator of nutritional status, the relationship between body mass index (BMI) and survival in patients treated with nivolumab was examined, and worse overall survival was found in patients with a BMI <25. In line with this finding, we also found a significant positive correlation between serum albumin level and PFS in our study.

There are also some limitations of our study. First, a retrospective analysis method with potential bias in patient selection was used. Second, patients from only one center were evaluated and the number of patients was small. A multi-center study involving more patients is necessary to reach a more precise judgment. Although we did not include patients with comorbidities that might affect inflammation or who used drugs, all factors that may affect hemoglobin, albumin, lymphocyte, and platelet levels may not have been excluded. Also, since an optimal cut-off value for the HALP score could not be defined, we calculated this with the X-tile software program in our study. More studies are needed to determine a standard cut-off value.

As a result, we showed that the HALP value before nivolumab treatment was associated with PFS. We found worse PFS results in patients with low HALP scores. Prospective studies involving more patients are needed to confirm these results.

Disclosures

Ethics Committee Approval: The study protocol was approved by Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee with 20/01/2020 dated and 2020-02-12 numbered decision.

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References

1. Motzer RJ, Jonasch E, Agarwal N, Beard C, Bhayani S, Bolger GB, et al; National comprehensive cancer network. Kidney cancer, version 3.2015. J Natl Compr Canc Netw 2015;13:151–9.
2. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373:1803–13.
3. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 2009;12:223–6.
4. Jiang H, Li H, Li A, Tang E, Xu D, Chen Y, et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. Oncotarget 2016;7:72076–83.
5. Peng D, Zhang CJ, Gong YQ, Hao H, Guan B, Li XS, et al. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. Sci Rep 2018;8:794.
6. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252–9.
7. Efremova M, Rieder D, Klepsch V, Charoentong P, Finotello F, Hackl H, et al. Targeting immune checkpoints potentiates immunoediting and changes the dynamics of tumor evolution. Nat Commun 2018;9:32.
8. Xia L, Hu G, Guzzo TJ. Prognostic Significance of Preoperative Anemia in Patients Undergoing Surgery for Renal Cell Carcinoma: A Meta-analysis. Anticancer Res 2017;37:3175–81.
9. Ko K, Park YH, Lee JW, Ku JH, Kwak C, Kim HH. Influence of nutritional deficiency on prognosis of renal cell carcinoma (RCC). BJU Int 2013;112:775–80.
10. Huszno J, Kolosza Z, Mrochem Kwarciak J, Rutkowsi T, Skladowksi K. The role of neutrophil lymphocyte ratio, platelet lymphocyte ratio, and platelets in the prognosis of metastatic renal cell carcinoma. Oncology 2019;97:7–17.
11. Gatenby R, Gillies R. Why do cancers have high aerobic glycolysis? Nat Rev Cancer 2004;4:891–9.
12. Zhang J, Yao YH, Li BG, Yang Q, Zhang PY, Wang HT. Prognostic value of pretreatment serum lactate dehydrogenase level in patients with solid tumors: a systematic review and meta-analysis. Sci Rep 2015;5:9800.
13. Shen J, Chen Z, Zhuang Q, Fan M, Ding T, Lu H, et al. Prognostic Value of Serum Lactate Dehydrogenase in Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. PLoS One 2016;11:e0166482.
14. Peng D, Zhang CJ, Tang Q, Zhang L, Yang KW, Yu XT, et al. Prognostic significance of the combination of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients with renal cell carcinoma after nephrectomy. BMC Urol 2018;18:20.

15. Shen XB, Zhang YX, Wang W, Pan YY. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score in Patients with Small Cell Lung Cancer Before First-Line Treatment with Etoposide and Progression-Free Survival. Med Sci Monit 2019;25:5630–9.

16. De Giorgi U, Procopio G, Giannarelli D, Sabbatini R, Bearz A, Buti S, et al. Association of Systemic Inflammation Index and Body Mass Index with Survival in Patients with Renal Cell Cancer Treated with Nivolumab. Clin Cancer Res 2019;25:3839–46.