Correlation of PD-L1 Tumor Expression and Treatment Outcomes in Patients with Renal Cell Carcinoma Receiving Sunitinib or Pazopanib:

Results from COMPARZ, a Randomized Controlled Trial

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Running Title (limit 60 characters): PD-L1 correlation with outcome in RCC patients in COMPARZ

Keywords: Renal cell carcinoma, pazopanib, sunitinib, PD-L1, PD-1 inhibitors

Support: This study was funded in part by GlaxoSmithKline Pharmaceuticals, the Trust family, Loker Pinard and Michael Brigham Funds for Kidney Cancer Research for Dr. Choueiri at Dana-Farber Cancer Institute, the Dana-Farber/Harvard Cancer Center Kidney Cancer Program, and the Dana-Farber/Harvard Cancer Center Kidney Cancer SPORE P50 CA101942-01.

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COI Disclosure: T.K. Choueiri has received a research grant from Pfizer and consultant/advisor compensation from AVEO, Pfizer, Novartis, GlaxoSmithKline, Genentech, and Bayer/Onyx. S. Signoretti has received a commercial research grant from GlaxoSmithKline and consultant/advisor compensation from GlaxoSmithKline. P. Benson is an employee of MEDTOX Inc., which received compensation from GlaxoSmithKline for this study. P. de Souza has received board membership compensation from Pfizer and Janssen, speaker compensation from Janssen, and travel compensation from GlaxoSmithKline; his institution received a grant from Boehringer Ingelheim. T. Powles has received consultant/advisor compensation from GlaxoSmithKline, Pfizer, and Novartis, and speakers’ bureau compensation from GlaxoSmithKline. R.J. Motzer has received compensation from GlaxoSmithKline for travel to ESMO 2012 to present study results, and consultant compensation from Pfizer, Genentech, and AVEO Oncology; his institution received grants from GlaxoSmithKline, Genentech, Pfizer, Novartis, and AVEO Oncology. D.J. Figueroa, Y. Liu, R. Gagnon, K. Deen, C. Carpenter, and L. Pandite are employees of GlaxoSmithKline. A.P. Fay has no conflicts to declare. T.H. Ho has no conflicts to declare.

Counts:

Abstract (limit 250): 250
Text (limit 5,000): 3,036
Translational relevance (limit 120-150): 137
Tables/figures (limit 6): 4 tables, 2 figures
References (limit 50): 34

Supplementary material provided

Type of manuscript: Original Research
Translational Relevance

Immune checkpoint molecules such as programmed death-1 (PD-1) and its ligand (PD-L1) are negative regulators of T-cell-mediated antitumor response. PD-L1 is aberrantly expressed in several malignancies, including clear cell renal cell carcinoma (ccRCC), and this may be associated with an unfavorable prognosis and adverse clinico-pathologic features. However, the prognostic impact of tumoral PD-L1 overexpression remains unclear in ccRCC patients treated with VEGF-targeted agents. By evaluating the association of PD-L1 expression with clinical outcomes in patients who received sunitinib or pazopanib in COMPARZ, the largest randomized trial of targeted agents in ccRCC, we show that PD-L1 expression is associated with shorter survival in patients with metastatic RCC. Our results may help predict response to available targeted therapies, and may assist in the design and patient selection strategies of future clinical trials of therapies that target the PD-1 axis.
ABSTRACT

**Background:** The interaction of programmed death-1 ligand (PD-L1) with its receptor (PD-1) on T cells inactivates antitumor immune responses. PD-L1 expression has been associated with poor outcomes in renal cell carcinoma (RCC) but has not been investigated in advanced RCC patients receiving vascular endothelial growth factor (VEGF)-targeted therapy.

**Methods:** Formalin-fixed paraffin-embedded (specimens were collected at baseline from patients in the COMPARZ trial. Tumor cell PD-L1 expression by immunohistochemistry was evaluated using H-score (HS). Dual PD-L1/CD68 staining was used to differentiate PD-L1 tumor expression from tumor-associated macrophages. Intratumor CD8-positive T cells were quantified morphometrically. Associations between biomarkers and survival were investigated using the log-rank test.

**Results:** HS data were available from 453 of 1110 patients. Sixty-four percent of patients had negative PD-L1 expression (HS=0). Patients with HS>55 (n=59, 13%) had significantly shorter overall survival (OS) than those with HS≤55 in both pazopanib and sunitinib arms (median 15.1 vs 35.6 and 15.3 vs 27.8 months, respectively, P=0.03). In both arms, median OS was shortest in patients with HS>55 and intratumor CD8-positive T-cell counts >300 (9.6 and 11.9 months with pazopanib and sunitinib, respectively). Median OS in patients with HS≤55 and CD8-positive T-cell counts ≤300 was 36.8 and 28.0 months with pazopanib and sunitinib, respectively. Progression-free survival results were similar to OS results.

**Conclusions:** Increased tumor cell PD-L1, or PD-L1 plus tumor CD8-positive T-cell counts, were associated with shorter survival in metastatic RCC patients receiving VEGF-targeted agents. These findings may have implications for future design of randomized clinical trials in advanced RCC.

**Word count = 250**
INTRODUCTION

Kidney cancer accounts for at least 3% of malignant diseases (1). The incidence and mortality of renal cell carcinoma (RCC) seem to be rising, and approximately 65,000 new cases are diagnosed every year in the United States (2), resulting in more than 13,000 deaths, usually from metastatic disease.

Clear cell RCC (ccRCC), the most common type of RCC, is characterized by a dysregulation of hypoxia-inducible transcription factors resulting in the activation of several genes that regulate angiogenesis, such as vascular endothelial growth factor (VEGF) (3). Detailed investigation of these genetic pathways has identified multiple targets for therapeutic intervention; in the last decade, agents targeting the VEGF ligand and its receptors (VEGFR-1, -2, and -3) have become the standard of care for patients with advanced disease (3).

Sunitinib and pazopanib, as compared with interferon or placebo, respectively, have significantly improved progression-free survival (PFS) benefit in patients with advanced disease, and are widely established as first-line therapies in this setting (4, 5). Recently, a large phase III, randomized trial (COMPARZ) compared the efficacy and safety of pazopanib versus sunitinib as first-line systemic treatment of patients with metastatic RCC (6). This noninferiority study showed that pazopanib and sunitinib have similar efficacy, but different safety and quality-of-life profiles (7). Although a number of potential biomarkers to predict response to targeted therapy have been investigated in RCC, none have entered clinical practice (8).

The understanding of how tumor cells evade antitumor immune response has provided a rationale for new therapeutic strategies (9). Immune checkpoint molecules such as programmed death-1 (PD-1) and the PD-1 ligand (PD-L1) are key regulators of T-cell-mediated response. The interaction of PD-1 with its ligand (PD-L1 or B7-H1) negatively regulates T-cell activation (10). Therefore, by overcoming this adaptive mechanism with therapies that inhibit the
PD-1/PD-L1 pathway, the effectiveness of T-cell responses against tumor cells can be restored (11).

PD-L1 is aberrantly expressed in ccRCC, and this is often associated with worse prognosis and adverse clinico-pathologic features (12-18). Preliminary data for monoclonal antibodies that block the interaction of PD-1 and its ligand have shown encouraging results in patients with RCC, as well as other tumors such as melanoma and non-small cell lung cancer (19). In addition, preliminary data on a limited number of patients with RCC showed that PD-L1 expression may be a potential biomarker of response to PD-1 inhibitors (19-21).

In this study, we evaluate the correlation between the expression of PD-L1 on tumor cell membrane and clinical outcomes in a large cohort of patients with metastatic RCC who received pazopanib or sunitinib as part of the COMPARZ trial (NCT00720941).
MATERIAL AND METHODS

Patients and samples

We analyzed data from patients who were enrolled in the COMPARZ clinical trial, which was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for participation in the clinical trial.

Between August 2008 and September 2011, this phase III study enrolled 1110 patients with metastatic ccRCC to randomly receive pazopanib (n=557) or sunitinib (n=553) at standard dosages. The primary endpoint was PFS, and the study was designed to evaluate the noninferiority of pazopanib versus sunitinib. Secondary end points included overall survival (OS), safety, and quality of life (6). Formalin-fixed paraffin-embedded tumor blocks were available from 453 patients who provided consent for tissue analysis: 221 of 557 in the pazopanib arm and 232 of 553 in the sunitinib arm. Archival tumor tissue samples were collected at baseline from these 453 patients.

Immunohistochemistry

PD-L1 expression was retrospectively evaluated by immunohistochemistry using the monoclonal anti-PD-L1 mouse IgG1 antibody (clone 5H1) on the Leica automated immunohistochemistry platform (MEDTOX Laboratories, St. Paul, MN, USA) as previously described (22). All cases were also stained for CD8 using a commercially available monoclonal mouse antibody (4B11) on the Leica Bond platform using recommended antigen retrieval conditions and an alkaline phosphatase red detection system. Formalin-fixed paraffin-embedded tonsil tissue was used as positive and negative control material for each staining run.

PD-L1 expression on tumor cell membrane was determined semi-quantitatively on a 0+ to 3+ scale: 0+, no appreciable staining above background; 1+, any degree of cytoplasmic or membranous staining above background, but less than 2+ or 3+; 2+, moderately to intensely
positive membranous staining in single or small groups of cells, or moderate cytoplasmic
staining; 3+, intensely positive membranous staining matching or exceeding control material, in
more than single or small groups of cells (Figure 1A). H-scores (HS) [HS= (% cells 3+)*3 +
(% cells 2+)*2 + (% cells 1+)] were evaluated, and a case was considered positive when any
tumor cell positivity was detected (HS>0) (23).

In all cases showing any possible staining for PD-L1, a dual-color PD-L1/CD68 stain was
performed on adjacent sections using the Leica Bond automated immunohistochemistry
platform to differentiate PD-L1 expression by tumor cells from that by tumor-associated
macrophages (TAMs). Staining was carried out sequentially, first for PD-L1 and then for CD68
(clone 514H12), using an HRP linker antibody conjugate with DAB and alkaline phosphatase
red detection system, respectively. The number of TAMs expressing PD-L1 was noted
separately and semiquantitatively graded as absent, rare, moderate, or numerous. The TAM
PD-L1 staining was not included in the final PD-L1 HS. For all patients, intratumor CD8-positive
(CD8+) cells were quantified morphometrically (number of CD8+ cells/mm² of tumor tissue) using
a proprietary digital image analysis and counting program (BioImagene; Ventana/Roche Medical
Systems, Tucson, Arizona, USA) on CD8-stained slides scanned at 20x on an automated whole
slide imaging system (iScan BioImagene; Ventana/Roche Medical Systems). The intensity of
the inflammatory response at the periphery of the tumor and its interface with surrounding
stroma was graded using a semi-quantitative scale (Supplementary Figure S1).

Statistical analysis

The objectives of this study were to investigate the association between PD-L1
expression on tumor cells and treatment outcome; the primary objective was correlation with
overall survival (OS) and the secondary objective was the correlation with PFS. Other objectives
included the correlation between PD-L1 expression on tumor cells and the corresponding TAMs,
and the association of intratumoral peripheral CD8+ T-cell counts with OS and PFS. A test of the
combined association between CD8 counts/PD-L1 HS and clinical outcome was also performed. Overall survival was defined as the time period between initiation of targeted therapy and the date of death or censoring on the day of the last follow-up visit. Patient and tumor characteristics were summarized descriptively. Progression-free survival was defined as the time period from initiation of targeted therapy to disease progression, death, or censoring at the last follow-up visit; patients who discontinued treatment before progression continued disease assessments until progression or initiation of another cancer therapy. Those initiating another therapy were censored at the time of the last disease assessment before initiating the other therapy.

The association between PD-L1 HS and treatment outcomes (OS and PFS) was explored by the log-rank test across a sliding window of HS. The HS threshold was the minimum H-score with log-rank $P<0.05$. Multivariate analysis (Cox proportional hazards regression) was adjusted by individual adverse risk factors: Karnofsky Performance Score (KPS), lactate dehydrogenase (LDH), and number of metastatic sites. In Cox analysis of OS, data from pazopanib and sunitinib patients were combined. The association of rate of response (complete response or partial response vs stable disease or progressive disease) for patients with PD-L1 levels above and below the threshold was assessed using logistic regression.

All statistical analyses were post-hoc; computations were performed using SAS v.9.2 (SAS Institute Inc., Cary, North Carolina, USA), and a $P$ value (two-sided) $<0.05$ was considered statistically significant.
RESULTS

Patient and tumor characteristics

Patient and tumor characteristics are described in Table 1. The KPS was 90 or 100 for 164 patients (74%) in the pazopanib arm and 169 patients (74%) in the sunitinib arm. In addition, the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk scores were considered favorable, intermediate, and poor for 64 (29%), 127 (57%), and 26 (12%) patients in the pazopanib arm, respectively, and 55 (24%), 142 (61%), and 24 (10%) patients in the sunitinib arm, respectively. The OS and PFS in the subset of patients who were included in the PD-L1 analysis (n=453) were comparable to the outcomes reported in the COMPARZ trial (Supplementary Table S1).

PD-L1 expression on tumor cells and immune cells

Formalin-fixed paraffin-embedded specimens were available from 453 of 1110 patients. Overall, membranous PD-L1 expression in tumor cells was detected (HS>0) in 163 of 453 patients (36%); HS ranged from 0 to 290 (Table 2). A total of 85 patient samples (18.8%) showed a robust PD-L1 staining (2+ or 3+) (Tables 3 and 4). Interestingly, a robust PD-L1 signal was seen in fewer core biopsies than in tissue samples from surgical resections, although the numbers are too small to make definitive comparisons (Table 3).

Overall, the dual staining with PD-L1 and CD68 identified 157 samples with moderate to numerous PD-L1-positive (PD-L1+) macrophages (Figure 1B). In some of the cases, PD-L1 expression was determined to be exclusively on macrophages and no tumor expression was noted; these cases were excluded from the analysis. The correlation of PD-L1 expression on tumor cells and macrophages is summarized in Table 4.

In addition, the inflammatory response as represented by the presence of peripheral CD8+ T cells in the invasive margin surrounding the tumor was graded as very strong in 36
cases, strong in 31 cases, moderate in 161 cases, weak in 132 cases, and minimal in 38 cases. In 88 cases, no invasive tumor/stromal margin was present in the tissue block analyzed.

**Correlation of PD-L1 expression on tumor cells with treatment outcomes**

An HS of >55 was found to be the threshold at which log-rank analysis demonstrated statistically significant association between HS and OS \( (P=0.0302, \text{Figure 2}) \). In the pazopanib arm, 25/221 patients (11.3%) had HS>55 (median OS, 15.1 months) and 196 had HS ≤55 (median OS, 35.6 months). In the sunitinib arm, 34/232 patients (14.7%) had HS>55 (median OS, 15.3 months) and 198 patients had HS≤55 (median OS, 27.8 months). At higher HS cutoff values, patients had a shorter OS. For example, in patients with HS>125, median OS was 5.1 and 8.9 months in the pazopanib (n=8) and sunitinib (n=7) arms, respectively (Supplementary Figure S2). Similarly, patients with HS>125 had significantly shorter PFS in both the pazopanib (3.1 vs 10.2 months) and sunitinib (4.0 vs 8.4 months) arms \( (P=0.017) \).

A covariate analysis was performed to adjust the association of PD-L1 expression and OS for potential confounding factors. In a multivariate analysis (N=450), a model that includes number of metastatic sites and KPS, PD-L1 expression (HS>55 vs HS ≤55) was an independent prognostic indicator of poor OS \( (\text{HR}=1.43, P=0.028) \). The number of metastatic sites (>2 vs ≤2 \( [\text{HR}=1.52, P<0.0001] \)) and KPS (70-80 vs 90-100 \( [\text{HR}=1.55, P=0.0005] \)) were also indicators of poor OS.

In addition, using an H-score threshold of 55, as we did for the PFS and OS endpoints, we did not find statistically significant differences in the rates of response for patients with PD-L1 levels above versus below the threshold (sunitinib \( P=0.6 \); pazopanib \( P=0.7 \)).
Combined effect of PD-L1 H-Score and CD8 level on OS

A combination of higher PD-L1 tumor expression and higher intratumor CD8$^+$ cell counts correlated with shorter OS. In both arms, patients with both HS $>$55 and intratumoral CD8$^+$ T-cell counts $>$300 had the shortest OS (11.9 months for sunitinib and 9.6 months for pazopanib).
DISCUSSION

Several studies have been conducted to determine the predictive and/or prognostic value of PD-L1 expression in pre-treatment specimens (24). To our knowledge, this is the largest series in a randomized clinical trial to correlate higher PD-L1 expression on tumor cells with worse clinical outcomes in patients with metastatic RCC (and solid tumors) receiving standard first-line VEGF-targeted therapy.

Thompson and colleagues reported that PD-L1 expression was associated with aggressive features such as higher TNM stage, tumor size, or Fuhrman grade, and increased risk of cancer-specific mortality in 196 patients with RCC (25). In another study of 306 patients with ccRCC, 23% of patients were deemed PD-L1 positive and were more likely to present higher risk of cancer-specific mortality (risk ratio: 2.0, 95% confidence interval: 1.27, 3.15; P=0.003) adjusting for TNM stage and grade (12). Interestingly, the correlation between PD-L1 expression and adverse prognostic features as well as OS was identified with PD-L1 expression in both tumor cell membrane and tumor infiltrating lymphocytes (22). In our analysis, we showed that higher PD-L1 tumor expression was an independent prognostic marker for OS in patients treated with pazopanib or sunitinib.

High levels of tumor-infiltrating immune cells, particularly CD8+ T cells, have been associated with adverse clinical outcomes in RCC, possibly due to an impairment of antitumor immune responses (26). Similarly, higher expression of PD-L1 in these cells has been also correlated with more aggressive features in RCC (22). In our study, higher numbers of infiltrating macrophages were correlated with PD-L1 tumor expression.

Recently, we investigated the correlation between PD-L1 tumor expression and clinical outcome in patients with metastatic RCC who were enrolled in an older and smaller phase III placebo-controlled clinical trial of pazopanib (VEG105192; NCT00334282) (27). Using a similar
HS methodology for scoring, patients in the pazopanib arm with HS>3 (23/113, 20%) had a trend toward shorter OS (7.3 vs 11 months; $P=0.14$) and a shorter PFS (2.3 vs 5.5 months; $P=0.02$). Interestingly, a much lower level of PD-L1 expression was observed in this clinical trial when compared with patients enrolled in the COMPARZ trial. It is important to note that although patients with PD-L1$^+$ tumors have shorter PFS/OS on pazopanib treatment, the data from the VEG105192 trial showed that patients with PD-L1$^+$ tumors continue to benefit from pazopanib (27), suggesting that tumor PD-L1 expression is a prognostic marker.

In a phase I study of an anti-PD-1 monoclonal antibody (nivolumab) in metastatic RCC, melanoma, and non-small cell lung cancer, therapeutic blockade of the PD-1/PD-L1 pathway produced encouraging responses in patients with RCC. For PD-L1$^+$ tumors, an objective response rate of 36% (9/25) was observed compared with no response in the PD-L1-negative tumors ($P=0.006$) (28), suggesting that PD-L1 expression in tumor cells may be a promising biomarker for agents that block the PD-1/PD-L1 pathway. More recent data with nivolumab suggest that although PD-L1$^+$ tumors have numerically higher response rates (22%) than PD-L1-negative tumors (8%), responses can be seen in PD-L1-negative tumors (20). Clinical trials have reported encouraging results with combinations of agents blocking the PD-1/PD-L1 axis, either with other immune checkpoint blockers or VEGF-targeted therapies (29, 30). The correlation between tumor PD-L1 expression and prognosis in patients with RCC receiving VEGF-targeted therapies supports the hypothesis that this molecule may also serve as a predictive biomarker for agents targeting PD-1 or PD-L1.

In addition to PD-L1 expression on tumor membranes, PD-L1 expression in immune cells may correlate with treatment response. Preliminary data from a phase I expansion cohort of patients with RCC (as part of a larger cohort of patients with solid tumors) treated with an anti-PD-L1 antibody (MPDL3280A) revealed an overall response rate of 20% in PD-L1$^+$ patients compared to 10% in patients with negative PD-L1 tumor expression (21, 31). Interestingly, we
showed that increased baseline PD-L1 expression, or increased PD-L1 expression plus intratumor CD8+ T-cell counts $>300$ at baseline, was associated with shorter OS in patients treated with sunitinib or pazopanib, suggesting that these patients may be ideal candidates for a therapeutic strategy that targets the PD-1/PD-L1 axis.

The tumor microenvironment is recognized to encompass important factors supporting tumor growth and progression (32). Similarly, mechanisms of resistance may be driven by interactions between stromal and tumor cells that can modulate response to targeted therapies (33). The immune system can also play an important role in treatment response. For example, activated intratumor lymphocytes can induce PD-L1 expression on tumor cells or surrounding immune cells by releasing several cytokines (33). A recent study of biomarker expression in patients with metastatic ccRCC found that VEGF-targeted therapy caused a significant reduction in vessel density (CD31) and PD-L1 expression, but no correlation between PD-L1 expression and clinical outcome was reported (34). In addition, exposure to sunitinib, but not pazopanib, resulted in reduced expression of the immune cell markers CD45 and CD3 (34). The questions of how different VEGF-targeted therapies may impact the expression of regulatory T-cell molecules and other biomarkers and how that could be associated with treatment outcome in metastatic RCC patients still need to be addressed.

Although we have evaluated a large cohort, our study has limitations. First, there is potential selection bias in any retrospective analysis. However, there was no statistical difference between the PFS and OS of the PD-L1 study population when compared to the overall COMPARZ population. Second, the impact of PD-L1 expression on response to VEGF-targeted therapies remains undefined. In this analysis, we defined as primary endpoints the correlation between PD-L1 expression and survival outcomes (OS or PFS). Therefore, future studies, especially those based on current trials combining VEGF-targeted therapies with anti-PD-1 therapies, should address that question. In addition, several methodologies with different
PD-L1 immunohistochemistry protocols are used to assess PD-L1 in other studies; direct comparisons of our results with those of other investigations should be done with caution. We evaluated baseline PD-L1 expression, but the question of how different VEGF-targeted therapies may influence the expression of this biomarker in post-treatment biopsies still needs to be investigated. Finally, although we evaluated patients who were part of a clinical trial, we found that information was missing which could classify patients according to prognostic risk score groups. Therefore, in the multivariate analysis we include only known (ie, data not missing) single variables that impact the prognosis of RCC. The strengths of our study include the large number of patients who were part of a well-conducted clinical trial and the adjustment of the analysis for the prognostic risk factors previously associated with worse prognosis.

In conclusion, our study shows that PD-L1 expression is associated with treatment outcome in metastatic RCC patients treated with VEGF-targeted therapies. Increased levels of PD-L1, or increased PD-L1 plus tumor CD8+ T-cell counts, were independently associated with shorter survival. The role of PD-L1 as a predictor of survival on VEGF-targeted therapy needs to be validated in prospective clinical trials; a phase I trial of pazopanib plus the PD-1 inhibitor MK-3475 is underway (NCT02014636). Results from this and other trials may have major implications for the design of future trials that include PD-1/PD-L1 inhibitors.
ACKNOWLEDGMENTS

Financial support for medical editorial assistance was provided by GlaxoSmithKline Pharmaceuticals, Philadelphia, Pennsylvania. We thank William Sinkins, PhD, at ProEd Communications, Inc, Beachwood, Ohio, for his assistance in preparation of this manuscript. This study was funded in part by GlaxoSmithKline Pharmaceuticals, the Trust family, Loker Pinard and Michael Brigham Funds for Kidney Cancer Research for Dr. Choueiri at Dana-Farber Cancer Institute, the Dana-Farber/Harvard Cancer Center Kidney Cancer Program, and the Dana-Farber/Harvard Cancer Center Kidney Cancer SPORE P50 CA101942-01.
REFERENCES


### Table 1. Patient characteristics

<table>
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<th>Characteristic</th>
<th>Pazopanib (N=221)</th>
<th>Sunitinib (N=232)</th>
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<td>Median age, years (range)</td>
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<td>62 (33-86)</td>
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<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>158 (71)</td>
<td>178 (77)</td>
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<tr>
<td>Female</td>
<td>63 (29)</td>
<td>54 (23)</td>
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<tr>
<td>Prior nephrectomy, n (%)</td>
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<td>205 (88)</td>
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<td>KPS, n (%)</td>
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<td>70 or 80</td>
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<td>60 (26)</td>
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<td>90 or 100</td>
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<td>169 (74)</td>
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<td>LDH, n (%)</td>
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<td>&gt;1.5x ULN</td>
<td>17 (8)</td>
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<tr>
<td>≤1.5x ULN</td>
<td>204 (92)</td>
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<td>Metastatic sites at baseline, n (%)</td>
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<td>≤2</td>
<td>151 (68)</td>
<td>152 (65)</td>
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<td>MSKCC risk category, n (%)</td>
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<td>Favorable</td>
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<tr>
<td>Intermediate</td>
<td>127 (57)</td>
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<tr>
<td>Poor</td>
<td>26 (12)</td>
<td>24 (10)</td>
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<tr>
<td>Unknown</td>
<td>4 (2)</td>
<td>11 (5)</td>
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Abbreviations: KPS, Karnofsky performance score; LDH, lactate dehydrogenase; MSKCC, Memorial Sloan-Kettering Cancer Center; ULN, upper limit of the normal range.
Table 2. PD-L1 expression levels in available samples

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<th>Treatment</th>
<th>H-Score, n (%)</th>
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<td>Sunitinib</td>
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Table 3. Comparison of PD-L1 expression between full tissue sections and core biopsies

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<th>Specimen</th>
<th>PD-L1 semi-quantitative score</th>
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<td>2+</td>
<td>3+</td>
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<td>All, n (%)</td>
<td>289 (63.8)</td>
<td>79 (17.4)</td>
<td>51 (11.3)</td>
<td>34 (7.5)</td>
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<td>Full tissue, n (%)</td>
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<td>66 (16.6)</td>
<td>50 (12.6)</td>
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<td>Core biopsy, n (%)</td>
<td>37 (66.1)</td>
<td>13 (23.2)</td>
<td>1 (1.8)</td>
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Table 4. Correlation of PD-L1 expression between tumor and macrophages

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<tr>
<th>Immunohistochemistry score of tumor sample</th>
<th>PD-L1+ macrophages</th>
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</tbody>
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FIGURE LEGENDS

Figure 1. Ad hoc semiquantitative scoring scheme for PD-L1 expression by tumor cells in RCC (panel A) and example of prominent peripheral inflammatory response and corresponding PD-L1 expression (panel B).

Figure 2. Association of overall survival (OS) with PD-L1 expression status on tumor cell membrane.
Figure 1A

3+ Intensely positive membranous staining, matching or exceeding control material, in more than single or small groups of cells

2+ Moderately to intensely positive membranous staining in single or small groups of cells, or moderate cytoplasmic staining

1+ Any degree of cytoplasmic or membranous staining above background (but less than 2 or 3+)

0+ No appreciable staining above background
Figure 1B

CD8

PD-L1/CD68
Figure 2

H-score: low (≤55) vs high (>55)

- Pazopanib low
- Pazopanib high
- Sunitinib low
- Sunitinib high

H-score: low (≤125) vs high (>125)

- Pazopanib low
- Pazopanib high
- Sunitinib low
- Sunitinib high

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib low (196)</td>
<td>35.6 (27.2, 40.8)</td>
</tr>
<tr>
<td>Pazopanib high (25)</td>
<td>15.1 (8.4, 45.1)</td>
</tr>
<tr>
<td>Sunitinib low (198)</td>
<td>27.8 (23.7, 32.9)</td>
</tr>
<tr>
<td>Sunitinib high (34)</td>
<td>15.3 (11.2, 30.5)</td>
</tr>
</tbody>
</table>

\[ P = 0.0302 \]

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib low (213)</td>
<td>33.1 (26.7, 40.4)</td>
</tr>
<tr>
<td>Pazopanib high (8)</td>
<td>5.1 (4.2, NR)</td>
</tr>
<tr>
<td>Sunitinib low (225)</td>
<td>27.4 (21.4, 32.0)</td>
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<tr>
<td>Sunitinib high (7)</td>
<td>8.9 (2.6, 38.1)</td>
</tr>
</tbody>
</table>

\[ P < 0.001 \]
Clinical Cancer Research

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Clin Cancer Res  Published OnlineFirst December 23, 2014.

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Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-14-1993

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