Original Research

Statins and survival outcomes in patients with metastatic renal cell carcinoma

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Received 30 July 2015; received in revised form 2 October 2015; accepted 7 October 2015
Available online 11 December 2015

Keywords: HMG-CoA reductase inhibitors; Prognosis; Renal cell carcinoma; Statins; Targeted therapy

Abstract  Background: A growing body of evidence has demonstrated the anti-neoplastic activity of statins. The objective of this study was to investigate the effect of statin use on survival in patients with metastatic renal cell carcinoma (mRCC) treated in the modern therapy era.

Patients and methods: We conducted a pooled analysis of mRCC patients treated on phase II and III clinical trials. Statistical analyses were performed using Cox regression and the Kaplan–Meier method.

Results: We identified 4736 patients treated with sunitinib (n = 1059), sorafenib (n = 772), axitinib (n = 896), temsirolimus (n = 457), temsirolimus + interferon (IFN)-α (n = 208), bevacizumab + temsirolimus (n = 393), bevacizumab + IFN-α (n = 391) or IFN-α (n = 560), of whom 511 were statin users. Overall, statin users demonstrated an improved overall survival (OS) compared to non-users (25.6 versus 18.9 months, adjusted hazard ratio [aHR] 0.801, 95% confidence interval [CI] 0.659–0.972, p = 0.025). When stratified by therapy type, a benefit in OS was demonstrated in statin users compared to non-users in individuals receiving therapy targeting vascular endothelial growth factor (28.4 versus 22.2 months, aHR 0.749, 95% CI 0.584–0.961, p = 0.025) or mammalian target of rapamycin (18.6 versus 14.0 months, aHR 0.784, 95% CI 0.605–0.999, p = 0.041).

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http://dx.doi.org/10.1016/j.ejca.2015.10.008
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1. Introduction

Statins are a class of drugs that reduce cholesterol by inhibiting HMG-CoA reductase, the rate-limiting enzyme involved in cholesterol biosynthesis [1]. They are the cornerstone of therapy for patients with hypercholesterolaemia and are used to prevent and treat cardiovascular disease. Statins are among the most commonly prescribed drugs worldwide and their use has been increasing over the past decade.

A growing body of preclinical studies has demonstrated the anti-neoplastic activity of statins. At the cellular level, statins have been linked to blocking cell-cycle progression, inducing apoptosis, and inhibiting cell-signaling pathways involved in tumour invasion and metastasis [1]. In vivo studies in animal models have further demonstrated the anti-proliferative effects of statins [2]. In humans, recent observational studies have shown that statin use is associated with a decreased risk of cancer-specific mortality in prostate, colorectal and breast cancer [3–5]. Several clinical trials have investigated the efficacy of statins on survival in patients with cancer; however, these were limited in size and results are inconclusive [6].

Studies exploring the benefits of statins in renal cell carcinoma (RCC) are widely lacking. Previous epidemiological studies of statins and the risk of RCC provide conflicting results with some studies demonstrating a reduced overall risk [7, 8], some showing no association [9–13], and a single study demonstrating an increased risk [14]. Several studies explore the association between statin use and disease progression in localized RCC. In one analysis, statin use was associated with a 33% recurrence risk reduction following surgery. No observational study to date has evaluated the effect of statins on survival in metastatic RCC (mRCC). One clinical trial in RCC patients with bone metastases explored the combination of zoledronic acid with fluvastatin or atorvastatin on bone biomarkers and skeletal events [15]. This pilot study of 11 patients, 6 of whom received concurrent targeted therapy, demonstrated that combination therapy affected certain bone biomarkers but did not consistently improve skeletal events. The trial did not document survival. The efficacy of statins combined with modern therapies targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways has not been broadly described.

Currently, no study to date has evaluated the effect of statins in patients with mRCC treated with targeted therapy. Elucidation of the impact of statins in this population is highly relevant to optimizing the evolving treatment landscape for patients with metastatic disease. In this analysis, we utilize a large clinical trials database to investigate the effect of statins on survival outcomes in patients with mRCC treated in the targeted therapy era.

2. Patients and methods

2.1. Study design

We conducted a pooled analysis of patients with mRCC treated on phase II (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423 and NCT00835978) and phase III (NCT00083889, NCT00065468, NCT00678392, NCT00474786, NCT00631371 and NCT00920816) clinical trials sponsored by Pfizer. We identified 4736 patients treated for mRCC between January 2003 and June 2013. Patients who did not receive at least one dose of study treatment or had missing concomitant medication information were excluded from the multivariate analysis (n = 720).

Baseline demographic, clinical and laboratory data were collected. Statin users were defined as patients receiving a statin at baseline. The decision to start a statin and choice of agent was at the discretion of the treating physician. Patient follow-up consisted of imaging assessment every 4–12 weeks until disease progression or withdrawal. Treatment-associated toxicities were defined and evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0.

2.2. Treatment outcomes

Overall survival (OS) was defined as the time from initiation of therapy to death from any cause. Progression-free survival (PFS) was defined as the time from initiation of therapy to date of progression or death from any cause, whichever came first.
2.3. Statistical analysis

The primary outcome was to assess OS in statin users compared to non-users. PFS and toxicity were secondary end-points. Distributions of OS and PFS were calculated using the Kaplan–Meier method. Median OS and PFS along with 95% confidence intervals (CIs) were reported. Associations between OS and PFS were assessed using the Wald chi-square test from Cox regression in multivariable analysis, adjusted for age, sex, race, histology, prior therapy, sites of metastasis, International mRCC Database Consortium (IMDC) risk factors, baseline dyslipidaemia and body mass index (BMI) [16]. In the OS analysis of the overall cohort, we additionally adjusted for angiotensin system inhibitor use [17]. Subgroup efficacy analyses were performed by line and type of therapy.

3. Results

3.1. Patient and disease characteristics

Overall, the majority of patients were less than 65 years of age, male, with good performance status and clear-cell histology (Table 1). Statin users were older and...
In the overall cohort, OS was significantly longer in statin users compared to non-users (adjusted hazard ratio \[\text{aHR} = 0.801, 95\% \text{ CI} 0.659–0.972, p = 0.025, \text{medians of 25.6 versus 18.9 months}\]) (Table 2, Fig. 1). In multivariable analysis, statin use was an independent predictor of OS for the total cohort (Table 3). PFS was similar between statin users and non-users (aHR 1.018, 95\% CI 0.867–1.196, p = 0.823, medians of 7.9 versus 6.9 months).

When stratified by mRCC therapy, OS was significantly longer in statin users compared to non-users in patients receiving VEGF-targeted therapy (aHR 0.749, 95\% CI 0.584–0.961, p = 0.023, medians of 28.4 versus 22.2 months) or mTOR-targeted therapy (aHR 0.657, 95\% CI 0.445–0.972, p = 0.035, medians of 18.6 versus 14.0 months). There was no statistically significant improvement in OS for patients receiving IFN-\(\alpha\) therapy (aHR 1.292, 95\% CI 0.703–2.275, p = 0.410, medians of 15.6 versus 14.8 months). When stratified by line of therapy, OS was significantly longer in statin users compared to non-users in patients receiving sunitinib, sorafenib, axitinib, bevacizumab or bevacizumab + IFN-\(\alpha\). mTOR therapy users were categorised as patients receiving temsirolimus, temsirolimus + IFN-\(\alpha\) or temsirolimus + bevacizumab.

3.2. Treatment exposure

Patients received treatment with sunitinib (n = 1059), sorafenib (n = 772), axitinib (n = 896), temsirolimus (n = 457), temsirolimus + interferon (IFN)-\(\alpha\) (n = 208), bevacizumab + temsirolimus (n = 393), bevacizumab + IFN-\(\alpha\) (n = 391) or IFN-\(\alpha\) (n = 560), of whom 1759 received first-line therapy. Overall, there were 511 (10.8\%) statin users, of whom four patients received more than one type of statin. The most frequently utilized statins were atorvastatin (n = 212), simvastatin (n = 203), pravastatin (n = 33), rosuvastatin (n = 32), lovastatin (n = 25) and fluvastatin (n = 10).

3.3. Impact of statin use on survival

In the overall cohort, OS was significantly longer in statin users compared to non-users (adjusted hazard ratio \[\text{aHR} = 0.801, 95\% \text{ CI} 0.659–0.972, p = 0.025, \text{medians of 25.6 versus 18.9 months}\]) (Table 2, Fig. 1). In multivariable analysis, statin use was an independent predictor of OS for the total cohort (Table 3). PFS was similar between statin users and non-users (aHR 1.018, 95\% CI 0.867–1.196, p = 0.823, medians of 7.9 versus 6.9 months).

When stratified by mRCC therapy, OS was significantly longer in statin users compared to non-users in patients receiving VEGF-targeted therapy (aHR 0.749, 95\% CI 0.584–0.961, p = 0.023, medians of 28.4 versus 22.2 months) or mTOR-targeted therapy (aHR 0.657, 95\% CI 0.445–0.972, p = 0.035, medians of 18.6 versus 14.0 months). There was no statistically significant improvement in OS for patients receiving IFN-\(\alpha\) therapy (aHR 1.292, 95\% CI 0.703–2.275, p = 0.410, medians of 15.6 versus 14.8 months). When stratified by line of therapy, OS was significantly longer in statin users compared to non-users in patients receiving second-line therapy (aHR 0.704, 95\% CI 0.511–0.971, p = 0.032, medians of 23.3 versus 17.5 months). In patients treated with first-line sunitinib, there was a trend towards a prolonged OS in statin users compared to non-users, though this was not statistically significant (OS: aHR 0.910, 95\% CI 0.694–1.192, p = 0.493, medians of 26.9 versus 19.3 months).

Table 2

<table>
<thead>
<tr>
<th>Impact of statin use on OS and PFS.</th>
<th>N</th>
<th>OS</th>
<th>P Value</th>
<th>aHR (95% CI)</th>
<th>PFS</th>
<th>P Value</th>
<th>aHR (95% CI)</th>
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<tbody>
<tr>
<td>Overall cohort (n = 4736)</td>
<td></td>
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<tr>
<td>Statin users</td>
<td>511</td>
<td>25.6</td>
<td><strong>0.025</strong></td>
<td>0.801 (0.659–0.972)</td>
<td>7.9</td>
<td>0.823</td>
<td>1.018 (0.867–1.196)</td>
</tr>
<tr>
<td>Statin non-users</td>
<td>4225</td>
<td>18.9</td>
<td></td>
<td></td>
<td>6.9</td>
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<tr>
<td>Overall cohort by type of therapy (n = 4736)</td>
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<tr>
<td>VEGF therapy (n = 3118)</td>
<td></td>
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<tr>
<td>Statin users</td>
<td>365</td>
<td>28.4</td>
<td><strong>0.023</strong></td>
<td>0.749 (0.584–0.961)</td>
<td>8.5</td>
<td>0.882</td>
<td>1.015 (0.832–1.239)</td>
</tr>
<tr>
<td>Statin non-users</td>
<td>2753</td>
<td>22.2</td>
<td></td>
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<td>8.3</td>
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<td>mTOR therapy (n = 1058)</td>
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</tr>
<tr>
<td>Statin users</td>
<td>84</td>
<td>18.6</td>
<td><strong>0.035</strong></td>
<td>0.657 (0.445–0.972)</td>
<td>5.5</td>
<td>0.783</td>
<td>1.047 (0.754–1.456)</td>
</tr>
<tr>
<td>Statin non-users</td>
<td>974</td>
<td>14.0</td>
<td></td>
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<td>5.8</td>
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<tr>
<td>IFN-(\alpha) therapy (n = 560)</td>
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<td></td>
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<tr>
<td>Statin users</td>
<td>62</td>
<td>15.6</td>
<td>0.410</td>
<td>1.292 (0.703–2.275)</td>
<td>5.0</td>
<td>0.635</td>
<td>0.865 (0.475–1.575)</td>
</tr>
<tr>
<td>Statin non-users</td>
<td>498</td>
<td>14.8</td>
<td></td>
<td></td>
<td>3.7</td>
<td></td>
<td></td>
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<tr>
<td>Overall cohort by line of therapy (n = 3701)</td>
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<tr>
<td>First-line therapy (n = 2264)</td>
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</tr>
<tr>
<td>Statin users</td>
<td>277</td>
<td>26.9</td>
<td>0.493</td>
<td>0.910 (0.694–1.192)</td>
<td>8.1</td>
<td>0.248</td>
<td>1.139 (0.913–1.421)</td>
</tr>
<tr>
<td>Statin non-users</td>
<td>2007</td>
<td>19.3</td>
<td></td>
<td></td>
<td>7.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-line therapy and beyond (n = 1417)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Statin users</td>
<td>140</td>
<td>23.3</td>
<td><strong>0.032</strong></td>
<td>0.704 (0.511–0.971)</td>
<td>6.7</td>
<td>0.567</td>
<td>0.923 (0.702–1.213)</td>
</tr>
<tr>
<td>Statin non-users</td>
<td>1277</td>
<td>17.5</td>
<td></td>
<td></td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aHR = adjusted hazard ratio; CI = confidence interval; IFN-\(\alpha\) = interferon-\(\alpha\); mTOR = mammalian target of rapamycin; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor.

P-values are from two-sided log-rank test. Bolded p-values denote statistically significant differences between groups.

a HR from multivariable analysis, adjusted for age, sex, race, histology, prior therapy, sites of metastasis, International mRCC Database Consortium risk factors, baseline dyslipidaemia and body mass index. In the overall survival analysis of the overall cohort, we additionally adjusted for angiotensin system inhibitor use.

b VEGF therapy users were categorised at patients receiving sunitinib, sorafenib, axitinib, bevacizumab or bevacizumab + IFN-\(\alpha\). mTOR therapy users were categorised as patients receiving temsirolimus, temsirolimus + IFN-\(\alpha\) or temsirolimus + bevacizumab.
Fig. 1. Kaplan–Meier estimates of OS for (A) the overall cohort, (B) patients receiving VEGF-targeted therapy, (C) patients receiving mTOR-targeted therapy and (D) patients receiving IFN-a therapy stratified by statin users versus non-users.
3.4. Impact of statin use on response rate

When evaluating the total cohort, overall response rates were similar between statin users and non-users (27.6% versus 24.1%, \( p = 0.652 \)), of which the majority of patients demonstrated a partial response (23.8%). There were limited complete responses in the cohort (\( n = 33 \)).

3.5. Adverse events

Overall, dyslipidaemia was reported in 856 patients (18.1%): 14% of statin users and 19% of non-users.

Table 3
Multivariable analysis of statin use status as a predictor for OS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( P ) value aHR (95% CI)</td>
</tr>
<tr>
<td>Statin use (yes versus no)</td>
<td>0.025</td>
</tr>
<tr>
<td>Age (&lt;65 versus ( \geq 65 ))</td>
<td>0.061</td>
</tr>
<tr>
<td>Sex (female versus male)</td>
<td>0.561</td>
</tr>
<tr>
<td>Race (Asian versus white)</td>
<td>0.873</td>
</tr>
<tr>
<td>Race (black versus white)</td>
<td>0.931</td>
</tr>
<tr>
<td>Race (other versus white)</td>
<td>0.445</td>
</tr>
<tr>
<td>ECOG (1–2 versus 0)</td>
<td>(&lt; 0.001 )</td>
</tr>
<tr>
<td>Baseline dyslipidaemia (no versus yes)</td>
<td>0.508</td>
</tr>
<tr>
<td>Histology (non-clear cell versus clear cell)</td>
<td>(&lt; 0.001 )</td>
</tr>
<tr>
<td>Prior nephrectomy (no versus yes)</td>
<td>0.776</td>
</tr>
<tr>
<td>Any prior therapy (no versus yes)</td>
<td>(&lt; 0.001 )</td>
</tr>
<tr>
<td>Presence of bone metastases (no versus yes)</td>
<td>(&lt; 0.001 )</td>
</tr>
<tr>
<td>Presence of liver metastases (no versus yes)</td>
<td>(&lt; 0.001 )</td>
</tr>
<tr>
<td>IMDC risk group (intermediate versus low)</td>
<td>(&lt; 0.001 )</td>
</tr>
<tr>
<td>IMDC risk group (poor versus low)</td>
<td>(&lt; 0.001 )</td>
</tr>
<tr>
<td>BMI category (obese versus normal/underweight)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI category (overweight versus normal/underweight)</td>
<td>0.001</td>
</tr>
<tr>
<td>ASI (no versus yes)</td>
<td>(&lt; 0.001 )</td>
</tr>
</tbody>
</table>

Bolded \( P \)-values denote statistical significance.

aHR = adjusted hazard ratio; ASI = angiotensin system inhibitors; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IMDC = International mRCC Database Consortium.

The frequency of grade III–V toxicities was similar between statin users and non-users (Table 4). Grade III–IV liver function test abnormalities were low for the total cohort and similar between groups. Additionally, the frequency of arterial thrombotic events (1.6%) and myositis (0.1%) were low and similar between groups.

4. Discussion

This is the largest study to date evaluating the impact of statins on survival in mRCC. The clinical trial database...
utilized in this analysis contains prospectively collected information and is a valuable tool for evaluating specific clinical parameters and outcomes. The database contains over 4700 patients treated with a wide range of systemic therapies in the modern era.

Here, we demonstrate that statin users had an improved OS compared to statin non-users. Statin use has been associated with improved disease-free survival and mortality for some cancers including prostate cancer, the most common genitourinary cancer [5]. A limited number of studies have evaluated the effect of statin use on RCC development and progression. A case–control study of 500,000 veterans found that statin use resulted in a 48% risk reduction of RCC [8]. A smaller, population-based study confirmed the protective effects of statin, but only in women without a history of hypertension [13]. With regard to statin use and prognosis after nephrectomy for RCC, one study demonstrated improved RCC progression and another demonstrated improved OS in statin users [18, 19]. To our knowledge, no study to date has evaluated the effect of statins in metastatic RCC.

Thick the molecular mechanisms underlying this observation have not been fully characterised, several preclinical studies have attempted to elucidate the effects of statins in RCC. Woodard and colleagues demonstrated that fluvastatin could induce apoptosis and suppress proliferation of RCC cells via inhibitory effects on the Akt/mTOR signaling pathway, a central player in the pathogenesis of RCC [20]. Another study demonstrated that simvastatin exerted its anti-tumour effects by suppressing interleukin-6-induced phosphorylation of JAK2 and STAT3 [21]. In vivo, simvastatin inhibited tumour growth and induced tumour cell apoptosis; statins have been further shown to inhibit angiogenesis and prevent metastases in these RCC mouse models [22].

Several studies suggest a synergistic interaction between statins and VEGF or mTOR-targeted agents; however, no studies have been conducted with the combination of these agents in RCC [23, 24]. The addition of lovastatin to VEGF inhibitor therapy resulted in more robust AKT inhibition in mesothelioma cells than was seen with either agent alone [24]. Additionally, synergistic perturbations of the AKT pathway were demonstrated with everolimus and fluvasatin in leukaemia cells [23]. In our clinical cohort, a benefit in OS was observed in statin users receiving either VEGF or mTOR-targeted therapy.

Optimizing the pharmacokinetic properties of statins will likely be a critical determinant to maximizing their role as anti-cancer agents. While nanomolar plasma concentrations have been utilized for the treatment of lipid disorders, non-physiologic statin concentrations are often employed in order to elicit robust anti-cancer responses [25]. Theoretically, for statins to exert significant anti-neoplastic effects, they should be able to enter extra-hepatic malignant cells via the circulation. Extensive first-pass metabolism and high levels of serum protein binding, however, limit their systemic bioavailability [6]. Furthermore, there is a delicate balance between statin lipophilicity and hepatoselectivity. In our cohort, the most frequently utilized statins were lipophilic and included simvastatin, atorvastatin and fluvastatin, which enter hepatocytes and extra-hepatic cells via non-selective passive diffusion [6]. On the other hand, hydrophilic statins, such as pravastatin and rosuvastatin, enter hepatocytes via an active transporter expressed in liver tissue, are thus more hepatoselective and achieve limited systemic drug levels [6].

Given that statins mainly function in the liver, a possible mechanism by which they can, in part, exert their beneficial effects is through inhibition of liver metastasis development and progression, a negative prognostic factor in patients with mRCC [26]. In our cohort, even after adjustment for the presence of liver metastases, statin users demonstrated an improved OS compared to non-users.

Exploiting the anti-cancer effects of drugs used for non-cancer indications represents a provocative approach to drug discovery and development. Metformin, aspirin and angiotensin system inhibitors provide a model for this paradigm. Efforts to capitalise on the cross-disease benefits of such agents have the potential to expand the treatment armamentarium for cancer patients.

Though this is the largest database using prospectively collected clinical trials information to assess the impact of statin use in mRCC, there are several limitations. All patients in the database were enrolled in clinical trials, which could result in decreased generalisability of the study findings. Statin users represented a small percentage of the population analysed and patient selection for statin therapy use was at the discretion of the treating physician and could be subject to bias. Additionally, given that data collection was not specifically designed to examine statin use, there was variability in regards to the choice of agent; data were also lacking on actual dosing, schedule and duration. Moreover, indications for treatment and modifications of therapy were at the discretion of the treating physician. There was also geographical variation with regard to statin use in our study. We did not analyse the impact of statin therapy continuation after initiation of the study drug; although based on the low toxicity from concomitant use of statins, we do not expect a high discontinuation rate. Finally, although patients who received a broad range of targeted therapies were included in the analysis, not every agent approved to treat mRCC was represented. There were a relatively small number of patients receiving IFN-α and, therefore, a potential benefit in this subgroup cannot be completely excluded.
In conclusion, we demonstrate that statin use may improve survival outcomes in patients with mRCC treated in the era of targeted therapy. Statins may have a synergistic interaction with VEGF and mTOR-targeted therapy in RCC. Preclinical studies utilizing physiologic concentrations of statins are required to further investigate the mechanisms underlying these interactions. Furthermore a better understanding of drug pharmacokinetics as they pertain to the anti-cancer effects of statins is warranted before embarking on RCC clinical studies with these agents.

Conflict of interest statement

Rana R. McKay has received institutional research funding from Pfizer and Bayer. Laurence Albige has received research funding from Novartis and Pfizer and has an advisory role at Novartis, Pfizer, Amgen and Sanofi. Toni K. Choueiri has received institutional research funding from Pfizer and has an advisory role at Pfizer, Novartis, GlaxoSmithKline, Genentech, Merck and Bayer and Onyx. Daniel Y.C. Heng has an advisory role at AVEO, Pfizer, Novartis and Bayer. Xun Lin and Ronit Simantov are employees at Pfizer. The remaining authors have no disclosures.

Funding

This work was supported by Pfizer, Inc. Additionally, this research was supported in part by the Dana-Farber/ Harvard Cancer Center Kidney SPORE, the Trust Family, Michael Brigham and Loker Pinard Funds for Kidney Cancer Research at the Dana-Farber Cancer Institute for Toni K. Choueiri.

Acknowledgements

The authors thank the patients and investigators who participated in the clinical trials used for this analysis. No writing assistance was provided for this work.

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