Clinical Commentary: The Use of Clinical Biomarkers to Inform Treatment Decisions in Advanced Renal Cell Carcinoma

Daniel J. George, MD

Abstract
Recent advances in targeted therapies have provided physicians additional options for treating patients with advanced renal cell carcinoma (aRCC). However, identifying biomarkers that can help predict a patient’s response to a particular therapy remains elusive. Given that most targeted therapies have a relatively tight therapeutic index, and yet have recommended dosages that are the same for patients regardless of differences in height, weight, age, sex, race, comorbidities, drug target, or metabolic profiles, the use of predictive biomarkers would seem imperative to personalize up-front treatment for patients with aRCC and/or to adjust the therapeutic dosage. One readily available and potentially helpful approach is to comprehensively and longitudinally track treatment-emergent adverse events (teAEs) in individual patients as pharmacodynamic markers for dose optimization. With VEGF-targeted therapies, several drug-related AEs are believed to be directly or indirectly related to the effect of targeting VEGF in normal tissues; as such, these AEs may act as on-treatment indicators of the activity of the drug. These data suggest that early emergence of AEs related to VEGF-targeted therapy may be associated with tumor sensitivity to this class of agents and support the strategy of using teAEs as early clinical biomarkers to guide on-treatment management decisions.

AJHO. 2017;13(12):11-18

Introduction
The clinical development of targeted therapies has improved outcomes for many patients with advanced/metastatic renal cell carcinoma (a/mRCC) in the past 10 years, but not for all patients. VEGF-targeted therapies are the recommended and most commonly used first-line treatment option for the majority of patients with aRCC.1 Most patients demonstrate an initial clinical response to treatment. However, some patients exhibit no response to treatment because of primary resistance mechanisms, whereas others will eventually progress when being treated because of acquired resistance to VEGF-targeted therapies.2 Unlike many cytotoxic chemotherapies, which can have narrow therapeutic indices—and therefore are dose-adjusted according to body weight, body mass index, liver enzymes, or renal function—targeted therapy in patients with aRCC is generally given at the same dosage, or with a limited dosing range, for the entire population.

Unfortunately, many patients do not realize the full benefits of targeted therapy because of inadequate dosing or intolerable toxicity. Indeed, variability in patient responsiveness to treatment is evident, and personalized treatment using various targeted agents can improve outcomes in many patients with RCC.3 For example, a recent prospective, multicenter evaluation of more than 500 patients from the Canadian Kidney Cancer information system, who were treated between 2011 and 2015, demonstrated significantly improved overall survival (OS) when sunitinib was initiated at the standard dosing schedule, with subsequent schedule/dosage alterations based on toxicity, compared with standard first-line sunitinib or standard pazopanib dosing.4

In a related situation, a subgroup analysis of the COMPARZ noninferiority trial showed that patients treated with first-line sunitinib or pazopanib who underwent dosage reductions or interruptions achieved longer median progression-free survival (PFS), suggesting that individualized dosing due to toxicity may
not compromise effectiveness of either agent. Results from the ongoing randomized phase II/III STAR trial are expected to confirm the benefits of personalized treatment in RCC. The study is currently underway and evaluating patients with aRCC who receive physician-directed continuous or interrupted treatment with sunitinib or pazopanib; results are expected to be reported in 2018.

These and other study findings suggest that prospective trials investigating the influence of dose individualization on treatment outcome are warranted and that patient- or disease-specific factors may be responsible for differences in treatment responsiveness. Such personalized approaches to treatment suggest potential biomarkers that could be exploited to identify patients who are more likely to respond to treatment. The use of predictive biomarkers early in the treatment course can vastly improve our ability to personalize treatment for patients with aRCC by: 1) identifying patients who are likely to benefit from targeted treatments and 2) allowing for greater personalization of dosing to optimize the therapeutic index in individual patients before dose-limiting toxicities occur.

There are currently no validated predictive biomarkers to aid in personalization of medication for patients with aRCC. There are, however, validated prognostic models to predict survival of a patient with aRCC based on clinical and laboratory factors. The Memorial Sloan Kettering Cancer Center (MSKCC) model that was developed during the cytokine era is one of the older, but still utilized, prognostic scores available. Five risk factors in the MSKCC model predict shorter survival: Karnofsky Performance Scale Index score (KPS) <80%, time from diagnosis to treatment <1 year, lactate dehydrogenase >1.5 x upper limit of normal (ULN), serum-corrected calcium >10 mg/dL, and serum hemoglobin <lower limit of normal (LLN). Patients with 0, 1-2, and ≥3 of these risk factors are designated as having favorable, intermediate, or poor risk status, respectively. Modified MSKCC scoring was used to select poor-risk patients in the pivotal trial for temsirolimus in aRCC. Patients were designated poor risk if they had ≥3 of 6 risk factors for survival, and treatment guidelines recommend temsirolimus for the first-line treatment of these poor-risk patients.

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model is also widely used for prognostic scoring. Six factors in the IMDC model predict shorter survival in patients with mRCC treated with VEGF-targeted therapy: KPS <80%, time from diagnosis to treatment initiation <1 year, serum-corrected calcium >ULN; hemoglobin <LLN, absolute neutrophil count >ULN, and platelets >ULN. Patients with 0, 1-2, and ≥3 risk factors are classified as having favorable, intermediate, or poor risk, respectively. Both MSKCC and IMDC prognostic criteria have been used to stratify patients in recent randomized, controlled phase III trials in aRCC.

Multiple molecular factors have been investigated for their potential prognostic and/or predictive power in RCC. Tissue-based biomarker expression has often been measured using immunohistochemistry (IHC), despite its drawbacks. Of the more extensively.

### FIGURE. Proposed Treatment Algorithm for Patients with Advanced Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>Disease Responsiveness</th>
<th>Anti-VEGF Sensitive</th>
<th>Anti-VEGF Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF Tolerant</td>
<td>Continue anti-VEGF</td>
<td>Future combinations: anti-VEGF, other biologic targets, and immunotherapy</td>
</tr>
<tr>
<td>Anti-VEGF Intolerant</td>
<td>Continue anti-VEGF at modified dosage</td>
<td>Immunotherapy</td>
</tr>
</tbody>
</table>

- **Patient Tolerance**
  - **Anti-VEGF Tolerant**: Continue anti-VEGF
  - **Anti-VEGF Intolerant**: Continue anti-VEGF at modified dosage
  - **Anti-VEGF Refractory**: Future combinations: anti-VEGF, other biologic targets, and immunotherapy

www.ajho.com
studied tissue-based markers, meta-analyses suggest that low carbonic anhydrase IX expression, high PD-L1 expression, high Ki-67 expression, and high nuclear expression of hypoxia-inducible factor-1 alpha (HIF-1α, but not overall HIF-1α expression) measured by IHC in RCC tumors correlate with poor survival. Multipatform analyses incorporating techniques that measure somatic DNA copy alterations, DNA methylation, mRNA expression, microRNA expression, and protein expression allow a more complete picture of the molecular alterations occurring in individual patients and the potential for identifying molecular subgroups of patients likely to respond to a particular therapy type. Although no single molecular marker has been validated as predictive in aRCC, a combination of multiple molecular biomarkers may eventually prove useful in the manner that multiple factors are used to arrive at an IMDC prognostic risk score. Various studies are currently underway to identify gene signatures that might be more or less predictive regarding treatment outcomes.

Despite significant attention to the molecular aspects of aRCC, identifying predictive biomarkers for the management of RCC is a challenge. With VEGF-targeted therapies, specific treatment-emergent adverse events (teAEs) are believed to act as surrogate markers of the activity of the drug. Therefore, the patient’s tolerance to VEGF-targeted therapy may be directly related to the individual’s sensitivity to VEGF-targeted therapy. This suggests that teAEs can be exploited as clinical biomarkers to be used to guide treatment decisions (Figure). A number of potential clinical biomarkers have been identified that are commonly seen in patients treated with VEGF-targeted therapy as a class, and therefore may be viewed directly or indirectly as being related to the effects of systemic VEGF inhibition, including hypertension, hypothyroidism, hand-foot syndrome, and fatigue/asthenia. A summary of clinical studies reporting an association between on-treatment clinical biomarkers and efficacy with VEGF-targeted therapy in patients with mRCC is shown in the Table.

Hypertension
Treatment-induced hypertension is frequently reported in patients treated with agents that target VEGF (17%-40% in phase III trials of patients with mRCC). Although the pathophysiology underlying the relationship between VEGF-targeted agents and systolic blood pressure (BP) is not entirely known, it is associated with an increase in systemic vascular resistance resulting from a decrease in nitric oxide release in peripheral vascular beds, leading to vasoconstriction. A number of studies have shown that the development of treatment-related hypertension is associated with clinical benefit in patients treated with VEGF-targeted agents. Treatment with antihypertensive medication does not affect this improvement in clinical outcome; therefore, hypertension should be managed appropriately.

The majority of retrospectively analyzed clinical trial data in patients with mRCC treated with VEGF-targeted therapy, including VEGF receptor tyrosine kinase inhibitors (VEGFR-TKIs) and the anti-VEGF monoclonal antibody bevacizumab in combination with interferon-α, show a positive correlation between hypertension and OS. VEGFR-TKI–induced hypertension is also predictive of prolonged PFS, OS, and improved objective response rate (ORR) in patients with mRCC in the community setting. Similarly, phase II dose titration of axitinib showed that patients with greater increases in diastolic BP had prolonged median PFS (16.6 vs 5.7 months, for ≥10 mm Hg increase vs <10 mm Hg increase; P < .001). However, there was only a weak correlation between steady-state axitinib exposure and diastolic BP change (R² = 0.225), and steady-state axitinib exposure was not strongly correlated with PFS. The results of this study suggest a complex relationship between the dosage of VEGF-targeted therapy, BP, and efficacy, and might suggest that BP should not be used exclusively to guide VEGFR-TKI dosing.

Tumor Vascularity
Primary RCC and its metastases are highly vascular. Therefore, imaging techniques that can identify changes in vascularity could be used as clinical biomarkers. Although the gold standard for assessing vascularity is histology, this method necessitates an invasive biopsy procedure, does not allow assessment of the entire tumor, and cannot account for tumor heterogeneity.

Functional in vivo imaging techniques that provide quantitative data regarding blood flow include dynamic contrast-enhanced MRI (DCE-MRI), DCE-CT, DCE-ultrasound (DCE-US), diffusion-weighted MRI, arterial spin label MRI (ASL-MRI), and fluorodeoxyglucose-PET (FDG-PET). Data from prospective clinical trials show initial evidence for DCE-CT, DCE-MRI, DCE-US, ASL-MRI, and FDG-PET in predicting response to VEGF-targeted agents (reviewed in Nathan and Vinayan and Bex and colleagues). Evidence is best for DCE-US as a predictive marker of response to VEGF-targeted therapy in prospective trials that include patients with mRCC. Additionally, European guidelines for contrast-enhanced ultrasound recommend the use of DCE-US to monitor response to therapy in patients with mRCC, in dedicated centers with appropriate software. Advantages of DCE-US are its...
**TABLE On-Treatment Clinical Biomarkers Associated With Efficacy During VEGFR TKI Therapy in Patients With a/mRCC**

<table>
<thead>
<tr>
<th>Clinical Biomarker</th>
<th>Treatment</th>
<th>Main Findings</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>Sunitinib[^21]</td>
<td>• Patients who developed hypertension (sBP ≥140 mm Hg) had improved PFS (HR, 0.241; P &lt; .001) and OS (HR, 0.284; P &lt; .001)</td>
<td>Retrospective pooled analysis of 3 prospective clinical trials in patients with mRCC (N = 544)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib[^24]</td>
<td>• Association between hypertension and PFS remained significant in a combined AE multivariate model of patients who developed hypertension at any time (HR for PFS, 0.37; P &lt; .0001; HR for OS, 0.36; P &lt; .0001) and by the 12-week mark for OS (HR, 0.68; P = .0036), but not PFS (HR, 0.81; P = .1305)^a</td>
<td>Retrospective pooled analysis of 5 prospective clinical trials in patients with mRCC (N = 770)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib[^24]</td>
<td>• Patients who developed hypertension had a PFS (RR, 0.42; P &lt; .001) and OS (RR, 0.40; P &lt; .001) benefit vs patients with no hypertension[^a]</td>
<td>Retrospective analysis of 1 hospital in Finland in patients with mRCC (N = 181)</td>
</tr>
<tr>
<td><strong>VEGFR TKI (sunitinib or sorafenib) or IL-2-based immunotherapy[^22]</strong></td>
<td>Sunitinib[^24]</td>
<td>• Patients who developed hypertension (sBP ≥140 mm Hg) within 4-12 weeks of treatment had improved OS (HR, 0.70; P = .0014)^a</td>
<td>Retrospective analysis of Danish national cohort in patients with mRCC (N = 588)</td>
</tr>
<tr>
<td><strong>Axitinib[^24]</strong></td>
<td>Axitinib[^24]</td>
<td>• Patients who developed hypertension (dBP ≥90 mm Hg) had significantly longer mPFS (16.5 vs 6.4 months; HR, 0.53; P = .019), and numerically longer mOS (25.8 vs 13.9 months; HR, 0.74; P = .228) vs patients with dBP &lt;90 mm Hg in an 8-week post hoc, exploratory, retrospective analysis</td>
<td>Post hoc, exploratory retrospective analysis of 2 phase II trials in patients with mRCC (N = 112)</td>
</tr>
<tr>
<td><strong>Axitinib[^24]</strong></td>
<td>Axitinib[^24]</td>
<td>• Patients with greater increases in dBP from baseline (≥10 vs &lt;10 mm Hg) had longer mPFS (16.6 vs 5.7 months; HR, 0.40; P &lt; .001)</td>
<td>Prospective phase II dose-escalation trial in patients with mRCC (N = 213)</td>
</tr>
<tr>
<td><strong>Bevacizumab + interferon-α[^23]</strong></td>
<td>Bevacizumab + interferon-α[^23]</td>
<td>• Development of hypertension at 2 months was an independent predictor of OS (HR, 0.622; P = .046[^a])</td>
<td>Retrospective analysis of phase III trial in patients with mRCC (N = 366)</td>
</tr>
<tr>
<td><strong>Tumor vascularity (DCE-US)</strong></td>
<td>Antiangiogenic agents[^31]</td>
<td>• A decrease of &gt;40% AUC correlated with OS (P = .05) and FFP (P = .005)</td>
<td>Prospective, multicenter study of patients with cancer of various solid tumor types (N = 539, including 157 with RCC)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib[^23]</td>
<td>• 1 DCE-US parameter correlated with OS (time to peak intensity; P = .007[^11])</td>
<td>Prospective, single-center study in patients with mRCC (N = 38)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib[^23]</td>
<td>• 2 DCE-US parameters correlated with DFS (time to peak intensity, P = .0002; slope of the wash-in, P = .02)</td>
<td>Prospective, single-center study in patients with mRCC (N = 38)</td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>Sunitinib or sorafenib[^24]</td>
<td>• Patients who developed hypothyroidism with sunitinib (6 studies; N = 260) had no difference in PFS versus patients without hypothyroidism (HR, 0.82; P = .220[^10])</td>
<td>Meta-analysis of 11 mRCC studies (N = 500)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib or sorafenib[^24]</td>
<td>• Patients who developed hypothyroidism with sunitinib or sorafenib (3 studies; N = 205) had a PFS benefit versus patients without hypothyroidism (HR, 0.59; P = .003)</td>
<td>Meta-analysis of 11 mRCC studies (N = 500)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib or sorafenib[^24]</td>
<td>• Patients who developed hypothyroidism with sunitinib (4 studies; N = 147) had an OS benefit over patients without hypothyroidism (HR, 0.52; P = .01)</td>
<td>Meta-analysis of 11 mRCC studies (N = 500)</td>
</tr>
<tr>
<td></td>
<td>Sorafenib or sunitinib[^24]</td>
<td>• Patients who developed hypothyroidism had longer PFS (HR, 0.348; P = .01)^[a]</td>
<td>Prospective single-center study in patients with mRCC (N = 83)</td>
</tr>
<tr>
<td></td>
<td>Sorafenib or sunitinib[^24]</td>
<td>• Development of subclinical hypothyroidism (TSH &gt;3.77 -μM/mL with normal T3 and T4 levels) within the first 2 months of treatment was an independent predictor of OS (HR, 0.31; P = .014[^a])</td>
<td>Prospective exploratory study in patients with mRCC (N = 87)</td>
</tr>
<tr>
<td><strong>VEGFR TKI</strong></td>
<td>Sorafenib[^24]</td>
<td>• Compared with patients with severe hypothyroidism, euthyroid patients had an increased risk for progression or death (HR for PFS, 3.15; P = .0093) and death (HR for OS, 9.51; P = .0159[^a])</td>
<td>Retrospective single-center analysis in patients with mRCC (N = 65)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib[^24]</td>
<td>• Patients who developed hypothyroidism had longer mPFS (10 vs 17 mos; P = .001), mOS (39 vs 20 months; P = .019), and higher ORR (46.7% vs 13.7%) vs euthyroid patients</td>
<td>Retrospective single-center analysis in patients with mRCC (N = 81)</td>
</tr>
<tr>
<td><strong>Hand-foot syndrome</strong></td>
<td>Sunitinib[^24]</td>
<td>• Patients who developed grade 2 hypothyroidism had significantly longer mPFS (25.3 vs 9.9 months; HR, 0.40; P = .042) and numerically longer mOS (46.0 vs 22.1 months; HR, 0.54; P = .2052)</td>
<td>Retrospective single-center analysis in patients with mRCC (N = 41)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib[^24]</td>
<td>• In a combined AE multivariate model, patients who developed hand-foot syndrome at any time (HR, 0.70; P = .0152) or by the 12-week mark (HR, 0.64; P = .218) had improved OS[^22]</td>
<td>Retrospective pooled analysis of 5 prospective clinical trials in patients with mRCC (N = 770)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib or pazopanib[^24]</td>
<td>• Patients who experienced hand-foot syndrome had longer mPFS (27.6 vs 9.3 months; P &lt; .001) and mOS (69.0 vs 17.8 months; P &lt; .001) than patients not experiencing this toxicity[^24]</td>
<td>Retrospective single-center analysis in patients with mRCC (N = 104)</td>
</tr>
</tbody>
</table>
AE indicates adverse event; a/mRCC, advanced/metastatic renal cell carcinoma; AUC, area under the curve; dBP, diastolic blood pressure; DCE-US, dynamic contrast-enhanced ultrasound; DFS, disease-free survival; FFP, freedom from progression; IL-2, interleukin-2; mos, month; mOS, median overall survival; mPFS, median progression-free survival; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RR, relative risk; sBP, systolic blood pressure; TSH, thyroid-stimulating hormone; TTP, time to tumor progression; VEGF, vascular endothelial growth factor; VEGFR-TKI, VEGF receptor tyrosine kinase inhibitor.

*Multivariate analysis.

1Results are reported for patients treated on the standard sunitinib 4-weeks-on/2-weeks-off schedule.

1Independent of baseline International Metastatic Renal Cell Carcinoma Database Consortium risk group in time-dependent multivariate analyses stratified by TKI and IL-2–based immunotherapy.

cost and the lack of any contrast agent. However, DCE-US has drawbacks: It is not a whole-body technique, and it is limited to only certain detectable lesions. Therefore, it might not detect new lesions and could result in mixed responses.35

Clinical measures of tumor vascularity are not validated in mRCC. A number of ongoing prospective trials are assessing functional imaging changes with VEGF-targeted therapy in patients with mRCC.

Hypothyroidism

In small trials that routinely monitor thyroid hormone levels, hypothyroidism is reported to occur in 29% to 53% of patients with mRCC who receive VEGF-targeted therapy.35-40 In phase III trials, the incidence of hypothyroidism ranged from 1% to 19%.40 However, this number might be an underestimate because thyroid hormone levels were not routinely measured in the majority of early phase III trials.

The underlying mechanism is thought to be associated with destructive thyroiditis, resulting in follicular cell apoptosis, endothelial dysfunction, inhibition of iodine uptake, and reduced synthesis of thyroid hormone.40 The results from a number of other studies suggest that VEGFR-TKI–induced thyroid dysfunction is associated with improved clinical outcomes in patients with mRCC.35-38

A meta-analysis of prospective and retrospective studies was intended to determine whether VEGFR-TKI–induced hypothyroidism was associated with improved clinical outcomes in mRCC.41 In studies of patients treated with sunitinib or sorafenib, PFS was improved with hypothyroidism (HR, 0.59; P = .003), and OS was prolonged only in patients treated with sunitinib (HR, 0.52; P = .01), relative to patients with a normal functioning thyroid. However, it was found that by assessing only patients treated with sunitinib, hypothyroidism was no longer predictive of PFS.42 The small number of studies included in this meta-analysis (3-6 for each variable) and the clinical heterogeneity among studies (eg, the variation in the timing of hypothyroid detection) may have contributed to this discrepancy.

At this stage, the association is not believed to be sufficiently robust to qualify hypothyroidism as a biomarker. Although hypothyroidism can be treated with hormone replacement, there is some speculation that it is the thyroid dysfunction itself that might be beneficial. This was illustrated in a prospective study (N = 102) in which the median PFS was not significantly different between patients with mRCC with or without thyroid dysfunction who were treated with hormone replacement after 6 months of sunitinib treatment.39

Hand-Foot Syndrome

Up to 51% of patients with mRCC treated with VEGF-targeted therapies developed hand-foot syndrome in phase III trials.30 The underlying pathophysiology might be associated with dermal vessel alteration, endothelial cell apoptosis, or impaired vascular repair.20 Several studies have shown that the patients treated with VEGF-targeted therapies in whom hand-foot syndrome developed had significantly improved clinical outcomes compared with those in whom hand-foot syndrome did not develop. In a pooled analysis of 770 patients with mRCC from 5 prospective trials of sunitinib, PFS and OS were significantly improved in those who experienced hand-foot syndrome in univariate analyses.26 However, in a multivariate model examining
the association between 5 different AEs and survival endpoints in patients on the 4-weeks-on/2-weeks-off dosing schedule, OS, but not PFS, was significantly improved for patients who experienced hand-foot syndrome at any time point, or prior to 12 weeks in a landmark analysis. Similarly, PFS and OS were significantly prolonged in VEGFR-TKI-treated patients with mRCC who experienced hand-foot syndrome (N = 104) in a retrospective analysis.

Despite these promising results, further prospective analyses with other VEGF-targeted agents are necessary, and the relationship between hand-foot syndrome and VEGF-targeted therapies should be treated with caution.

**Fatigue and Asthenia**

Fatigue is frequently reported in patients with mRCC treated with VEGF-targeted therapies. In a pooled analysis of 770 patients with mRCC from 5 randomized clinical trials of sunitinib, clinical outcomes (PFS) in a combined AE multivariate model of patients on schedule 4/2 were significantly improved in patients who experienced fatigue/asthenia at any time point (but not for patients who had fatigue/asthenia). However, the fatigue and asthenia could be related to other factors such as co-medications, hypothyroidism, anemia, hypogonadism, or mRCC itself. Fatigue/asthenia is frequently assessed too late in its development (when it is debilitating and less reversible). This AE is better managed when identified early in the treatment course, and addressed by dosage modifications before chronic deconditioning has set in.

**Other Potential Clinical Biomarkers**

Several other biomarkers have been associated with improved response to targeted therapies, including body weight, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia. However, at this stage, the evidence for these biomarkers is cursory.

**Clinical Implications and Proposed Treatment Algorithm**

VEGF-targeted agents have been associated with AEs that might correlate with efficacy in patients with mRCC. A treatment algorithm has been proposed in which these patients are treated with an anti-VEGF agent in the first line, and treatment is continued until signs of intolerance or disease progression (Figure). Under this algorithm, patients should be monitored very closely during the first 2 months of treatment, ideally with clinical evaluations every 2 weeks, and with home monitoring and recording of teAEs in between. Patients who respond to anti-VEGF therapy but experience early signs of AEs should continue therapy with modified dosing. Patients who tolerate therapy initially and show evidence of disease response should continue on treatment with chronic monitoring for delayed toxicities. Patients who experience disease progression and intolerance to anti-VEGF therapy should switch treatment to targeted immunotherapy. Finally, for patients who tolerate anti-VEGF therapy but experience disease progression, there may be several options, including immunotherapy or a combination of targets including, but not limited to, VEGF inhibition.

No targeted immunotherapies have been approved for aRCC in the first-line setting. However, based on a phase III trial in which nivolumab improved OS compared with everolimus, nivolumab was recently approved for treatment of patients who were previously treated with a VEGFR TKI. In addition, several ongoing trials are assessing immunotherapy alone or in combination with VEGF-targeted agents as first-line treatment and in previously treated populations. The combination of targeted immunotherapy and anti-VEGF agents might be suitable for patients who tolerate VEGF-targeted therapy because there is evidence of synergy between these 2 agents.

**Conclusions**

With the development of targeted therapies that are capable of vastly improving clinical outcomes in patients with aRCC, the ability to identify patients who will respond to specific treatments becomes significantly more important, especially in light of the evolving alternative or combinatorial options with immunotherapy. Although insufficient data exist to consider whether there are similar markers for immunotherapeutic agents in RCC, teAEs in individual patients have proven informative with regard to understanding responsiveness to VEGF-targeted therapies. As highlighted, several teAEs are believed to be directly or indirectly related to the effect of targeting VEGF in normal tissues, with the most available data probably for hypertension. Currently, no predictive biomarkers for immunotherapy have proven clinically useful, as has been demonstrated for other tissue tumor types. However, ongoing studies may eventually identify patient and/or tumor characteristics that can guide physicians on the patients with aRCC who are most likely to achieve improved outcomes with immunotherapy-based treatment regimens. As much supporting data and interest currently exist around hypertension as a predictive pharmacodynamics biomarker for patients with aRCC, it would not be surprising if hypertension were to eventually become one of the first predictive biomarkers for aRCC. More studies will be telling.
Eventually, the identification and validation of clinical biomarkers that can be applied to the personalization of aRCC treatment will improve outcomes in patients, benefit the drug development process, and be economically efficient to the healthcare system. In the absence of any validated predictive biomarkers in aRCC, monitoring AEs as surrogate markers of efficacy might aid in treatment planning for individual patients.

Author affiliation: The author is professor of medicine and surgery, and director of genitourinary oncology, at the Duke Cancer Institute, Duke University School of Medicine, Durham, NC.

Address correspondence to: Daniel J. George, MD, Box 103861, Duke University Medical Center, Durham, NC 27710; tel: 919-668-4615; fax: 919-660-0178; e-mail: daniel.george@duke.edu.

Financial disclosure: Dr George reports receiving consultant fees or payment for participation in advisory boards for Bayer, Dremond, Exelixis, Medivation, Novartis, Pfizer, Sanofi, GSK, Astellas, Innocin, BMS, Genentech, Janssen, Acceleron, Merck, and Myovant Sciences. He has received grants from Exelixis, Genentech, Janssen, Novartis, Pfizer, Astellas, BMS, Millennium, Acerta, Bayer, Dremond, and Innocin. He has received honoraria from Dendreon, Novartis, Sanofi, Bayer, Medication, Biopharm, and Axex Oncology. He has received lecture fees from Dendreon, Novartis, Sanofi, and Bayer.

References


