# Renal Cell Carcinoma Therapy in 2010: Many Options With Little Comparative Data

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## Keywords

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Abstract: As a component of the American Recovery and Reinvestment Act of 2009, comparative effectiveness (CE) studies have been established as a priority in medical research. In the setting of metastatic renal cell carcinoma (mRCC), the theme of CE research is particularly applicable, given the recent approvals of several targeted agents with somewhat overlapping indications. Herein, ongoing comparative clinical trials are discussed that may resolve clinical equipoise in using these agents. Furthermore, ongoing biomarker analyses are reviewed that may ultimately identify subpopulations with unique benefit from specific targeted therapies. Finally, available cost-effectiveness data for targeted therapies in mRCC are presented. The amalgam of these studies may offer the oncologist greater clarity in clinical decision-making.

## Introduction

On February 17, 2009, the American Recovery and Reinvestment Act (ARRA) was signed into law by President Barack Obama.<sup>1</sup> The initiative provided a total of \$1.1 billion for comparative effectiveness (CE) research, specifically intended to "conduct, support or synthesize research that compares the clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions."2 Although cost-benefit analyses and examination of other nonclinical endpoints exist under the umbrella of CE research, another fundamental goal is to juxtapose treatment options for specific patient populations to optimize clinical outcome.<sup>3</sup> In the setting of oncology, this goal is achieved in part through the conduct of randomized controlled clinical trials (RCTs) or metaanalyses of such trials.<sup>4</sup> However, acknowledging that accrual to these trials most often includes a small proportion of the patient population being investigated, larger population-based studies are often necessary to compare the generalized effect of treatment interventions. Biomarker studies conducted in parallel with these analyses have the potential to further optimize the approach,



Figure 1. An overview of a suggested approach to comparative effectiveness research in oncology.

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identifying subpopulations that may obtain a greater benefit from selected therapies. For example, several studies have shown a favorable cost-effectiveness profile with the 21-gene recurrence score (derived from reverse transcription polymerase chain reaction), now widely employed in breast cancer to aid patients and clinicians in deciding between chemotherapy and endocrine therapy.<sup>5,6</sup> The amalgam of approaches employed in CE research (costeffectiveness studies, RCTs, population-based studies, and biomarker analyses) have been incorporated into a practical schema, outlined in Figure 1.

Perhaps, CE research is nowhere more applicable than in the treatment of metastatic renal cell carcinoma (mRCC). A decade ago, the oncologist was faced with a limited arsenal of therapeutic options; use of conventional immunotherapy (ie, interferon [IFN] or interleukin-2 [IL-2]) elicited limited durable responses.<sup>7-10</sup> Within the past 4 years, 6 targeted agents have been added to the oncologists' armamentarium. The clinical trials leading to the approval of these agents have assessed a wide spectrum of subpopulations with mRCC (Table 1).<sup>11-17</sup> These studies have allowed for the development of comprehensive algorithms with treatment options designated for specific subgroups.<sup>18</sup> Although these algorithms do provide substantial aid in decision-making, there are still many clinical scenarios in which further guidance is needed. For example, an oncologist encountering a treatment-naïve patient with mRCC is offered 3 distinct category 1 (ie, consensus) recommendations from the current National Comprehensive Cancer Network (NCCN) guidelines, as outlined in Table 2. For the oncologist to discern the relative merits of these agents, further clinical research is needed. The current review will focus on comparative trials that may resolve such areas of clinical equipoise, and will further focus on strategies in CE research as they pertain to mRCC.

# **First-line Therapy**

## Head-to-Head Trials

Updated results from a phase III trial assessing the vascular endothelial growth factor-tyrosine kinase inhibitor

FDA-approved Agent/ Regimen	Comparator	Number of Patients	Patient Population
Sorafenib <sup>11</sup>	Placebo	769	Cytokine-refractory (83%)
Sunitinib <sup>15</sup>	IFN	750	Treatment-naïve
Bevacizumab + IFN <sup>12</sup>	Placebo + IFN	649	Treatment-naïve
Bevacizumab + IFN <sup>16</sup>	IFN	732	Treatment-naïve
Temsirolimus <sup>13</sup>	IFN or temsirolimus + IFN	626	Treatment-naïve patients with poor-prognosis RCC*
Everolimus <sup>14</sup>	Placebo	416	Previous sunitinib and/or sorafenib (prior bevacizumab and cytokine also allowed)
Pazopanib <sup>17</sup>	Placebo	435	Treatment-naïve or 1 prior cytokine therapy

Table 1.	An	Overview	of Pivotal	Phase I	II Trials o	f Targeted	Therapi	es for	Metastatic	Renal	Cell	Carcinoma	(RCC	C)
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\*Poor prognosis defined by at least 3 of 6 predictors of short survival: 1) lactate dehydrogenase >1.5 times the upper limit of normal, 2) hemoglobin level below the lower limit of normal, 3) corrected serum calcium more than 10 mg/dL, 4) time from initial diagnosis of RCC to randomization of <1 year, 5) Karnofsky performance status of 60 or 70, or 6) metastases in multiple organs.

FDA=US Food and Drug Administration; IFN=interferon.

(VEGF-TKI) sunitinib (Sutent, Pfizer) have shown an overall survival (OS) benefit with the agent in comparison to IFN in 750 treatment-naïve patients with mRCC (26.4 vs 21.8 months, P=.013).15 In addition, median progression-free survival (PFS) was improved with sunitinib therapy (11 vs 5 months, P<.001). A distinct VEGF-TKI, pazopanib (Votrient, GlaxoSmithKline), has been compared to placebo in a separate phase III study. Of the 435 patients randomized, 233 were treatment-naïve and 202 were cytokine refractory.<sup>17</sup> A benefit in PFS has been observed in this study (9.2 vs 4.2 months, P<.0000001), though survival data were not available at the time of most recent analysis. The clinical benefit outlined for both sunitinib and pazopanib have led to a category 1 recommendation as first-line therapy for treatment-naïve patients with mRCC. In deciding amongst these 2 agents, the ongoing phase III COMPARZ trial will be of utmost importance (Figure 2).<sup>19</sup> In this study, a planned 876 patients with treatment-naïve, clear cell mRCC will be enrolled and randomized in a 1:1 fashion to sunitinib or pazopanib administered at standard doses. Until results of this study are available, the oncologist is faced with counseling the patient between 2 agents with apparently similar efficacy and safety profiles.

A separate head-to-head trial seeks to identify the optimal dose of sunitinib therapy. Preclinical evidence suggests that "withdrawal" of sunitinib (as in the 2-week off period in the standard dosing regimen) could trigger more aggressive tumor angiogenesis.<sup>20</sup> Furthermore, studies assessing a continuous, daily schedule of sunitinib in

 Table 2. Category 1 Recommendations Guiding the Use of

 Targeted Systemic Therapy for Clear Cell Metastatic Renal Cell

 Carcinoma in Treatment-naïve and Cytokine-refractory Patients

Patient Population	First-line	Second-line
Treatment-naïve	Sunitinib Bevacizumab + Interferon Pazopanib Temsirolimus*	Everolimus†
Cytokine refractory	Sorafenib Sunitinib Pazopanib	None

Adapted from National Comprehensive Cancer Network (NCCN) Guidelines, v.2.2010.

Note: Category 1 recommendations reflect a consensus amongst the experts comprising the NCCN panel.

\*A category 1 recommendation has been assigned specifically for use of temsirolimus as first-line therapy in patients with poor-prognosis metastatic renal cell carcinoma.

<sup>†</sup>A category 1 recommendation has been assigned specifically for use of everolimus after tyrosine kinase inhibitor therapy.

gastrointestinal stromal tumor (GIST) and non-small cell lung cancer (NSCLC) suggest reasonable efficacy and improved tolerability.<sup>21,22</sup> Subsequently, reported phase II data of a continuous, daily schedule of sunitinib in cytokine-refractory mRCC yielded similar results, with a



Figure 2. Selected ongoing trials for treatment-naïve patients with metastatic renal cell carcinoma (mRCC).

BeST=A Randomized Phase II Study of VEGF, RAF kinase and mTOR Combination Targeted Therapy (CTT) with Bevacizumab, Sorafenib and Temsirolimus in Advanced Renal Cell Carcinoma; COMPARZ=A Study of Pazopanib Versus Sunitinib in the Treatment of Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma; INTORACT=INvestigation of TORisel and Avastin Combination Therapy; RECORD-2=REnal Cell cancer treatment with Oral RAD001 given Daily-2; RECORD-3=REnal Cell cancer treatment with Oral RAD001 given Daily-3.

median PFS and OS of 8.2 months and 19.8 months, respectively, and manageable toxicities.<sup>23</sup> These encouraging data have led to a phase III trial randomizing patients with treatment-naïve mRCC to sunitinib on either a stan-

dard schedule (50 mg oral daily, 4 weeks on and 2 weeks off) or a continuous schedule (37.5 mg oral daily).<sup>24</sup> With a planned accrual of 282 patients, the results of this study are eagerly anticipated.

## **Combination** Therapy

Outside of sunitinib and pazopanib, a category 1 recommendation exists for a third regimen for first-line therapy of clear cell mRCC: bevacizumab with IFN. This regimen is supported by 2 phase III studies. In the double-blind, placebo-controlled AVOREN (AVastin fOr RENal cell cancer) study, 649 patients were randomized to either bevacizumab (Avastin, Genentech) with IFN or placebo with IFN. Although the study failed to identify an improvement in OS, a benefit in PFS was demonstrated (10.4 vs 5.5 months, P=.0001) in those receiving bevacizumab.12 Cancer and Leukemia Group B trial 90206 utilized a similar randomization, albeit without a placebo control.<sup>16</sup> The study identified similar results in a cohort of 732 patients, with an improvement in PFS from 4.9 months to 8.4 months (P<.0001). No difference in OS was observed.

These data for bevacizumab with IFN lead to yet another conundrum in the management of mRCChow do the data for bevacizumab compare to those for sunitinib and pazopanib? Unfortunately, no trial exists to answer this question in a straightforward fashion. Ongoing studies seek to determine whether the clinical activity of bevacizumab can be complemented by the addition of various other targeted therapies. For instance, in the randomized, phase II RECORD-2 trial (REnal Cell cancer treatment with Oral RAD001 given Daily-2), 360 patients will be assigned to receive either bevacizumab with IFN or bevacizumab plus the mammalian target of rapamycin (mTOR) inhibitor everolimus (Afinitor, Novartis).<sup>25</sup> A prior phase II analysis conducted in 59 patients with mRCC had reported encouraging activity, with a PFS of 9 months in treatment-naïve patients and 6 months in treatment-refractory patients.<sup>26</sup> A larger phase III analysis will employ a similar randomization to assess the mTOR inhibitor temsirolimus (Torisel, Wyeth).27 In this study, 800 patients will be assigned to receive bevacizumab with either IFN or temsirolimus. Finally, the Eastern Cooperative Oncology Group BeST study (A randomized phase II study of VEGF, RAF kinase and mTOR combination targeted therapy [CTT] with Bevacizumab, Sorafenib and Temsirolimus in advanced renal cell carcinoma) will randomize patients to 1 of 4 arms, 3 of which contain bevacizumab. In this study, 360 patients with mRCC will receive either bevacizumab alone, bevacizumab and temsirolimus, bevacizumab and sorafenib (Nexavar, Bayer HealthCare), or sorafenib and temsirolimus.<sup>28</sup> Importantly, early experiences point to potential pitfalls in efforts to combine bevacizumab with other therapies. A phase I analysis suggesting high rates of hypertension and vascular/hematologic toxicity with the combination of sunitinib and bevacizumab has led to the halting of a Southwest Oncology Group phase II analysis randomizing patients to sunitinib or sunitinib and bevacizumab.<sup>29</sup>

# Second-line Therapy

At present, the only US Food and Drug Administration (FDA)-approved targeted agent for second-line therapy of mRCC after failure of anti-angiogenic agents is everolimus. The approval came on the basis of a phase III trial in which 416 patients who had failed prior therapy with sunitinib and/or sorafenib were randomized in a 2:1 fashion to receive either everolimus or placebo.<sup>14</sup> The study demonstrated a 3-month improvement in PFS with everolimus (4.9 vs 1.9 months, P<.001), although no improvement in OS was identified. Notably, only 2% of patients had a partial response as a best response to everolimus therapy. In contrast, several VEGF-TKIs have been assessed in the same setting in phase II studies, with more encouraging response and PFS data. Although cross-trial comparisons are not possible, these data underscore the need to explore second-line VEGF-TKI therapy. As noted in Table 3, permutations of sunitinib and sorafenib in sequence can yield response rates of 10-15%, with stable disease in a majority of patients.<sup>30-33</sup> The novel VEGF-TKI axitinib (Pfizer) has shown an impressive overall response rate of 22.6% in sorafenib pretreated patients.34

On the basis of these data, several trials are under way to determine the ideal second-line strategy. One such trial examines whether repeat challenge with a VEGF-TKI or use of an mTOR inhibitor represents the optimal approach. In this study, 480 patients with mRCC who have progressed on first-line therapy with sunitinib will be treated with either sorafenib or temsirolimus at standard doses.<sup>35</sup> The primary endpoint of this study is PFS, and the study is to be completed in May 2011. Another trial in the second-line setting will randomize 650 patients who have failed 1 prior systemic therapy to either sorafenib or axitinib.<sup>36</sup> Given the activity seen with axitinib in the aforementioned phase II study in sorafenib failures, data from this trial (which is expected to complete accrual in July of 2010) are eagerly anticipated.

# **Optimizing Sequence**

#### Sequencing Targeted Agents

As previously noted, current guidelines suggest use of an mTOR inhibitor (everolimus) after failure of a VEGF-TKI on the basis of phase III data.<sup>14</sup> The ongoing RECORD-3 trial (REnal Cell cancer treatment with Oral RAD001 given Daily-3) will assess whether this sequence can be reversed.<sup>37</sup> In this study, 390 treatmentnaïve patients with mRCC will be randomized to receive

First-line Therapy → Second-line Therapy	N	Study Design	Efficacy	
Anti-angiogenic therapy → Sunitinib or sorafenib <sup>32</sup>	30	Retrospective	ORR, 56% with sunitinib (n=16), 7% with sorafenib (n=14) Median TTP, 10.4 months	
Sorafenib → Sunitinib <sup>31</sup>	51	Retrospective	PR, 15%; SD, 51%	
Sunitinib → Sorafenib <sup>31</sup>	51	Retrospective	PR, 9%; SD, 55%	
Bevacizumab → Sunitinib <sup>30</sup>	61	Prospective phase II	PR, 23%; SD, 59%; tumor shrinkage in 52%	
VEGF-targeted therapy → Temsirolimus <sup>33</sup>	15	Retrospective	SD, 33%; PD, 20%	
Sorafenib → Axitinib <sup>34</sup> 62		Prospective phase II	ORR, 22.6% Median PFS, 7.4 months	

**Table 3.** Available Data for Sequential Use of AgentsFollowing Angiogenesis Inhibitors

ORR=overall response rate; PD=progressive disease; PFS=progressionfree survival; PR=partial response; SD=stable disease; TTP=time to progression; VEGF=vascular endothelial growth factor.

either sunitinib or everolimus. At the time of progression, patients will cross over to the opposite treatment arm. The primary endpoint of this study is PFS after first-line therapy; as such, the trial offers the only randomized comparison of mTOR inhibitors versus VEGF-TKIs in this setting. PFS after second-line therapy will also be compared as a secondary endpoint. Presumably, summated PFS data from the 2 lines of therapy could serve as an indicator of which sequence is superior.

#### Sequencing Immunotherapy

The role of immunotherapy in the era of targeted agents remains somewhat unclear. Importantly, several studies of targeted agents do incorporate patients with prior IFN or IL-2 exposure. As referenced in the NCCN guidelines, sorafenib is indicated after failure of cytokine therapy.<sup>18</sup> In the pivotal trial leading to the agent's approval, 68% of 903 patients enrolled had received prior IFN therapy, and 42% had received prior IL-2.<sup>11</sup> The study identified a benefit in PFS as compared to placebo (5.5 vs 2.8 months, P<.01), and it appears that this benefit persisted across all subgroups assessed, independent of use or nonuse of prior cytokine therapy. As a more recent example, the pivotal trial comparing pazopanib to placebo was originally conceived as a trial including only cytokine failures.<sup>38</sup> However, with emerging data supporting anti-angiogenic therapy, treatment-naïve patients were incorporated. Ultimately, a PFS benefit was observed in those patients who had received prior cytokine therapy (7.4 vs 4.2 months, P<.001), as compared with the study population overall.

Reversing the sequence of treatment (ie, offering immunotherapy after failure of targeted treatments) requires further clinical study. Retrospective series have highlighted concerns with offering IL-2 after angiogenesis inhibitors. In one reported experience, 16 patients who received IL-2 after sunitinib, sorafenib, or bevacizumab were assessed.<sup>39</sup> In those patients receiving sunitinib or sorafenib, only 6 of 10 were able to proceed to a second week of therapy with IL-2. A range of toxicities were encountered amongst these patients, including severe cardiac adverse events (cardiomyopathy and sudden fatal cardiac arrest), bullous pemphigoid, and bowel ischemia. Thus, although there are merits to offering IL-2 in selected treatment-naïve patients, use of the agent after targeted therapies should likely be discouraged pending further data.

# **Selecting Appropriate Patients**

A key element of CE research is the identification of patient subsets with a higher response to relevant therapies. For instance, the previously described 21-gene recurrence score now offers the oncologist a tool to discern the relative benefits of chemotherapy and endocrine therapy in certain patients with breast cancer.<sup>40</sup> Admittedly, no tool is as firmly established in the setting of RCC; nonetheless, there is mounting evidence supporting the prognostic and predictive role of several biomarkers. As one example, the von Hippel Lindau (VHL) protein is a critical protein in renal carcinogenesis. In its native form, a complex of VHL and E3 ligase bind hypoxia inducible factor-a (HIF- $\alpha$ ) and induce ubiquitination and subsequent degradation of the protein.<sup>41</sup> However, in the setting of VHL mutation, HIF- $\alpha$  is stabilized and may lead to transcriptional activation of numerous growth factors, including VEGF and platelet-derived growth factor (PDGF). VHL mutation occurs in approximately 75-90% of patients with mRCC, and the prevalence of this mutation challenges its use as a relevant biomarker.

More recently, preclinical work has identified distinct mutations leading to differential expression of HIF- $\alpha$ 

subtypes.<sup>42</sup> In the first (termed the H2 phenotype), only HIF-2 $\alpha$  is expressed. In contrast, the H1H2 phenotype expresses both HIF-1 $\alpha$  and HIF-2 $\alpha$ . Importantly, wildtype, H1, and H1H2 phenotypes are equally prevalent, increasing their utility as a candidate biomarker. In retrospective series, the H2 phenotype appears to have a higher proliferative index (Ki-67) as compared to the H1H2 and wild-type phenotypes. The H2 phenotype therefore has the potential to identify a subpopulation of mRCC patients with more aggressive disease. Gene profiling studies point to further utility of the HIF- $\alpha$  signature. Patients with both the H2 and H1H2 phenotype appear to transcribe genes related to angiogenesis, suggesting an increased susceptibility to agents targeting the VEGF axis. In contrast, patients with the H2 phenotype have a signature that emphasizes mTOR signaling, suggesting that agents directed at this moiety may be particularly relevant. Though further testing is necessary to establish the predictive and prognostic capabilities of the H1H2 and H2 phenotypes, these early data are encouraging.

A distinct gene profiling tool has been used to characterize patients with clear cell RCC independent of the H2 and H1H2 phenotypes.<sup>43</sup> Using the Stanford custom array platform, 2 distinct profiles were identified in 177 patients, termed consensus cluster A (ccA) and consensus cluster B (ccB). In comparison to other standard clinical parameters (including grade and performance status), classification of ccA and ccB subtype offered better stratification of OS. Prospective assessment is necessary to determine whether ccA/ccB subtyping may serve to predict response to selected therapies. However, the test appears to be akin to gene signatures being explored in other settings (ie, the 70-gene signature in breast cancer).<sup>44</sup>

Several potential biomarkers have been identified from prospective clinical efforts. Assessment of serum VEGF-A and VEGFR2, and PDGF in a series of 42 patients with clear cell mRCC treated with sunitinib suggested that the change in VEGF-A level could predict clinical benefit from the agent.<sup>45</sup> Separately, extensive correlative studies have been paired to a randomized phase II trial assessing sorafenib with or without lowdose IFN. In this study, phosphorylated Akt (pAkt) levels predicted clinical benefit.<sup>46</sup> pAkt is a mechanistically relevant moiety, sitting downstream of multiple receptor tyrosine kinases (RTKs).<sup>47</sup> Numerous Akt inhibitors are presently under clinical development, including perifosine (Keryx Biopharmaceuticals), which has shown activity in phase II trials in mRCC.48-50 If pAkt levels predict clinical benefit with VEGF-TKIs, there may be theoretical rationale for offering these agents with Akt inhibitors in selected patients.

With respect to mTOR inhibitors, biomarker studies accompanying the pivotal trial of temsirolimus examined the role of PTEN and HIF-1 $\alpha$  in predicting clinical outcome.<sup>51</sup> Although no correlation was noted between PTEN or HIF-1 $\alpha$  status and OS, PFS, or response rate, a cited potential caveat was the global nature of the clinical trial, leading to potential variations in specimen collection and preservation. More limited data are available from the pivotal trial of everolimus.<sup>14</sup> Early reports show consistent decreases in soluble VEGFR2 with continuing therapy; however, whether this predicts clinical outcome is unknown at this time.

The data presented herein suggest multiple candidate biomarkers in RCC. Looking ahead, a key step will be prospective application of these biomarkers in clinical research. Several potential prospective trial designs have been proposed, as delineated in Figure 3.<sup>52</sup>

# The Cost of Comparative Research

Cost-effectiveness analyses remain a fundamental part of CE research. In the setting of mRCC, data in this regard are slowly emerging. Markov models based on data from the phase III TARGET study (Treatment Approaches in Renal cancer Global Evaluation Trial) comparing sorafenib to best supportive care (BSC) suggested lifetime per patient costs of \$85,571 with sorafenib and BSC, as compared to \$36,634 with BSC alone.53 When assessed incrementally, the cost of sorafenib was \$75,354 per life year gained (LYG). As such, the agent appeared to fall within acceptable norms for cost of care (\$50,000-\$100,000). A subsequent Canadian study validated this analysis, showing a cost of \$36,046 per LYG, falling within an acceptable threshold in the Canadian healthcare system (\$130,960 per LYG).<sup>54</sup> Similar to sorafenib, the cost-effectiveness of sunitinib has been evaluated on the basis of pivotal phase III data.55 In contrast to IFN (the comparator arm), the incremental cost-effectiveness ratio of sunitinib was \$67,215 per LYG, also falling within acceptable standards. Although more challenging, several cost-effectiveness analyses have looked across available first-line therapeutic options. One "meta-analysis" assessing available data for sunitinib, sorafenib, bevacizumab, and temsirolimus identified a wide range of figures for each agent, although it appeared as though sunitinib had the most favorable profile.<sup>56</sup> Two other studies have similarly identified sunitinib as the most cost-effective option for first-line therapy.<sup>57,58</sup>

Although the cost of targeted therapies often seems insurmountable, the cost-effectiveness analyses described suggest that several available agents meet acceptable standards. Furthermore, there are trends that both payor and patient should be alerted to. One of the most extensive experiences in targeted therapy is with trastuzumab, a monoclonal antibody directed at human epidermal



Figure 3. Proposed trial designs to evaluate clinical biomarkers.

Adapted from Sargent DJ et al. J Clin Oncol. 2005;23:2020-2027.

growth factor receptor 2 (HER2).<sup>59-61</sup> While the agent exceeded cost-benefit thresholds when applied in the metastatic setting, the incremental cost of the agent dropped substantially when 1) the agent was transitioned into the adjuvant setting and 2) when appropriate patient selection was employed, using fluorescence in situ hybridization analysis for HER2 testing.<sup>62,63</sup> Employing this paradigm, testing of targeted therapies for mRCC in the adjuvant setting and further exploration of relevant biomarkers (both currently under way) may improve the cost-effectiveness profile of these agents.<sup>64</sup>

## Conclusions

As per the ARRA, the Institute of Medicine has prioritized various areas of CE research, with oncology representing a heavy area of investment.<sup>1</sup> Within oncology, the landscape in RCC is ripe for producing CE data-multiple comparative trials are under way, biomarker analyses are ongoing, and preliminary data suggest that the targeted agents employed in this disease meet acceptable thresholds in cost-effectiveness analyses. Moving forward, a challenge to the research community will be balancing CE research goals with the development of novel therapies. Given the finite number of patients willing and able to participate in clinical trials, oncologists will have to decide whether studies juxtaposing well-characterized agents (as in CE research) take precedence over studies examining investigational agents. With multiple salient clinical questions looming, it is critical that participation in clinical trials be encouraged when feasible.

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