Renal cell carcinoma (RCC) comprises 92% of all kidney cancers and has a poor prognosis, with approximately 10% of patients with metastatic disease surviving beyond 5 years. In 2006, the economic burden of metastatic RCC (mRCC) was estimated to be up to $1.6 billion worldwide and has since grown annually. With the continuing increase of the economic burden of this disease in the United States, there is a growing need for economic analyses to guide treatment and policy decisions for this patient population.

**Background:** In 2006, the economic burden of metastatic renal cell carcinoma (mRCC) was estimated to be up to $1.6 billion worldwide and has since grown annually. With the continuing increase of the economic burden of this disease in the United States, there is a growing need for economic analyses to guide treatment and policy decisions for this patient population.

**Objective:** To evaluate available comparative economic data on targeted therapies for patients with mRCC who have failed first-line targeted therapies.

**Method:** A broad and comprehensive literature review was conducted of US-based studies between January 1, 2005, and February 11, 2013, evaluating comparative economic evidence for targeted agents that are used as second-line therapy or beyond. Based on the specific search parameters that focused on cost-effectiveness and economic comparisons between vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFr) inhibitors and mammalian target of rapamycin (mTOR) inhibitors, only 7 relevant, US-based economic evaluations were found appropriate for inclusion in the analysis. All authors, who are experts in the health economics and outcomes research field, reviewed the search results. Studies of interest were those with a targeted agent, VEGF/VEGFr or mTOR inhibitor, in at least 1 study arm.

**Discussion:** As a group, targeted therapies were found to be cost-effective options in treating patients with refractory mRCC in the United States. Oral therapies showed an economic advantage over intravenous agents, presumably because oral therapies have a lower impact on outpatient resources. Based on 3 studies, everolimus has been shown to have an economic advantage over temsirolimus and to be cost-effective compared with sorafenib. No economic comparison between everolimus and axitinib, the only 2 drugs with a National Comprehensive Cancer Network category 1 recommendation for use after the failure of VEGFr tyrosine kinase inhibitors, is available.

**Conclusion:** The limited and heterogeneous sum of the currently available economic evidence does not allow firm conclusions to be drawn about the most cost-effective targeted treatment option in the second-line setting and beyond in patients with mRCC. It is hoped that ongoing head-to-head therapeutic trials and biomarker studies will help improve the economic efficiency of these expensive agents.
KEY POINTS

➤ The growing economic burden of renal cell carcinoma (RCC) in the United States indicates the need for economic analyses of current therapies to guide treatment decisions for this disease.

➤ This article is based on a comprehensive review of 7 studies that were identified within the search criteria for US-based economic data related to targeted therapies for metastatic RCC (mRCC) after failure of first-line therapies.

➤ Targeted therapies were shown to be cost-effective for the treatment of refractory mRCC.

➤ Oral therapies showed an economic advantage over intravenous agents, presumably because of their lower impact on outpatient resources.

➤ No economic comparison is yet available for the only 2 drugs (ie, everolimus and axitinib) with an NCCN category 1 recommendation for use after a vascular endothelial growth factor receptor TKI.

➤ Ongoing head-to-head therapeutic trials and biomarker studies may help to improve the economic efficiency of targeted treatments in the second-line setting and beyond for mRCC.

The US Food and Drug Administration (FDA) approval of axitinib in January 2012 brings the total of approved targeted agents for RCC to 7 in the past 7 years, making this one of the most prolific areas of cancer drug development (Table 1).11-25 The need for clarity regarding the optimal sequential use of these agents is stronger than ever, particularly given the high price of these agents.

The oral VEGF receptor tyrosine kinase inhibitors (VEGFr-TKIs) sunitinib and pazopanib, the VEGF monoclonal antibody bevacizumab plus (subcutaneously injected) interferon-α, and the intravenous (IV) mTOR inhibitor temsirolimus are recommended by the National Comprehensive Cancer Network (NCCN) as first-line therapies for the treatment of mRCC (Table 2).26 The VEGFr-TKI sorafenib is recommended for select patients only. Despite efficacy in mRCC, agents targeted against VEGF only “inhibit” the disease, making resistance almost inevitable and universal, thereby necessitating second-line therapy after the failure of initial VEGF inhibition.18,19,22-24

Because curing metastatic disease with these agents is rare, most patients require lifelong therapy and are destined to cycle through the available treatment options. Guidelines on sequential therapy for the second-line treatment of mRCC and beyond are limited, indicating a lack of clinical trial–based comparative evidence and/or consensus in this area. In the NCCN guidelines, the oral agents everolimus and axitinib are category 1 recommendations for second-line therapy (Table 2).26 Despite their clinically proven benefit in extending progression-free survival (PFS), the cost of these agents and their lack of proven survival benefit have led to controversial government reimbursement decisions in some parts of the world (eg, by the National Institute for Health and Care Excellence in the United Kingdom25).

Given the lack of prospectively collected data sets assessing the optimal sequence of targeted therapies, as well as the high price of these agents, economic analyses provide important insights into the overall costs versus benefits of targeted therapies, thus helping to inform treatment decisions. In this review, we identify comparative economic evidence beyond the first-line treatment of mRCC and discuss the potential implications of the findings.

Method

Literature Search of Comparative Economic Studies

Although we did not conduct a systematic review, we did conduct a broad, inclusive search of comparative economic evidence for targeted therapies used in the treatment of patients with mRCC after failure of initial therapy. Our search parameters were:

• The time frame was from January 1, 2005, to February 11, 2013 (lower boundary coincided with the introduction of sorafenib to the US market, marking the beginning of the targeted-therapy era in RCC)
## Table 1  Targeted Agents Approved for RCC and Pivotal Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>Drug, route of administration, approval date</th>
<th>RCC indication</th>
<th>Design of pivotal trial</th>
<th>PFS in the overall population of pivotal trial</th>
</tr>
</thead>
</table>
| Sorafenib, oral†† December 20, 2005        | Advanced RCC   | TARGET: randomized, double-blind study of sorafenib (n = 451) vs placebo (n = 452) in patients treated with 1 previous systemic therapy (primarily cytokines)18 | • Median, 5.5 mo with sorafenib vs 2.8 mo with placebo  
• HR, 0.44 (95% CI, 0.35-0.55; P < .001) |
| Sunitinib, oral‡‡ February 2, 2007         | Advanced RCC   | Randomized, open-label study of sunitinib (n = 375) vs IFN-α (n = 375) in treatment-naive patients19 | • Median, 11 mo with sunitinib vs 5 mo with IFN-α  
• HR, 0.539 (95% CI, 0.451-0.643; P < .001) |
| Temsirolimus, IV†† May 30, 2007            | Advanced RCC   | ARCC: randomized, open-label study of temsirolimus (n = 209) vs IFN-α (n = 207) vs temsirolimus + IFN-α (n = 210) in treatment-naive patients with ≥3 of 6 predictors of short survival20 | • Median, 3.8 mo with temsirolimus vs 1.9 mo with temsirolimus + IFN-α vs 3.7 mo with temsirolimus + IFN-α  
• HR, not available |
| Everolimus, oral†† March 30, 2009          | RCC therapy after failure of treatment with sunitinib or sorafenib | RECORD-1: randomized, double-blind study of everolimus (n = 277) vs placebo (n = 139) in patients previously treated with sunitinib and/or sorafenib21 | • Median, 4.9 mo with everolimus vs 1.9 mo with placebo  
• HR, 0.33 (95% CI, 0.25-0.43; P < .001) |
| Bevacizumab, IV, plus IFN-α, SC†† August 3, 2009 | Metastatic RCC with IFN-α | AVOREN: randomized, double-blind study of bevacizumab + IFN-α (n = 327) vs placebo + IFN-α (n = 322) in treatment-naive patients22 | • Median, 10.2 mo with bevacizumab + IFN-α vs 5.4 mo with placebo + IFN-α  
• HR, 0.63 (95% CI, 0.52-0.75; P = .001) |
| Pazopanib, oral†† October 19, 2009         | Adults for first-line treatment of advanced RCC and for patients who have received previous cytokine therapy for advanced disease | Randomized, double-blind study of pazopanib (n = 290) vs placebo (n = 145) in treatment-naive and cytokine-pretreated patients24 | • Median, 9.2 mo with pazopanib vs 4.2 mo with placebo  
• HR, 0.46 (95% CI, 0.34-0.62; P < .001) |
| Axitinib, oral†† January 27, 2012          | Treatment of RCC after failure of 1 previous systemic therapy | AXIS: randomized, open-label study of axitinib (n = 361) vs sorafenib (n = 362) in patients treated with 1 previous systemic therapy25 | • Median, 6.7 mo with axitinib vs 4.7 mo with sorafenib  
• HR, 0.665 (95% CI, 0.544-0.812; P < .001) |

CI indicates confidence interval; HR, hazard ratio; IFN, interferon; IV, intravenous; PFS, progression-free survival; RCC, renal cell carcinoma; SC, subcutaneous.
The databases that were searched included PubMed/MEDLINE and Ovid/EMBASE; abstracts and industry-sponsored articles were allowed.

The conference proceedings that were searched (to account for relevant data that were not published in the peer-reviewed literature) included the American Society of Clinical Oncology (ASCO), the Genitourinary Cancers Symposium, the International Society for Pharmacoeconomics and Outcomes Research, the Academy of Managed Care Pharmacy, the American Society of Health-System Pharmacists, the American Urological Association, and the International Society for Quality of Life Research.

The search was limited to studies in the English language and US-based studies (because national policy directly influences healthcare expenditures, and these studies entered the US pharmacopeia soon after FDA approval).

The search terms included “metastatic renal-cell carcinoma or mRCC or advanced renal-cell carcinoma or aRCC or stage 4 RCC,” “second-line therapy,” “targeted therapy or everolimus or RAD001 or temsirolimus or sorafenib or sunitinib or axitinib or pazopanib or bevacizumab or mTOR inhibitor or tyrosine kinase inhibitor or TKI or vascular endothelial growth factor inhibitor or VEGF inhibitor,” and “health-related quality of life, or HRQOL, or health economics or health outcomes or cost-effective” or “cost-effectiveness” (see Glossary).

All authors, who are experts in the health economics and outcomes research field, reviewed the search results. After this initial individual review, a group discussion was held to confirm which studies met our criteria and would be covered in this article. Studies of interest were those with a targeted agent—VEGF/VEGFr or mTOR inhibitor—in at least 1 study arm. Comparative outcomes of interest were health economics and outcomes research measures derived from any budget impact, cost minimization, cost-resource utilization comparison, or cost-effectiveness and cost utility analyses. Studies related to the economic burden (cost) of illness were excluded from this analysis.

Table 2  NCCN Treatment Guidelines for mRCC, by Phase 3 Evidence

<table>
<thead>
<tr>
<th>Setting</th>
<th>Category 1 evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve</td>
<td></td>
</tr>
<tr>
<td>Good or intermediate risk(^a)</td>
<td>Sunitinib, Pazopanib, Bevacizumab + IFN-α</td>
</tr>
<tr>
<td>Poor risk(^a)</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>Previously treated</td>
<td></td>
</tr>
<tr>
<td>Previous cytokine</td>
<td>Sorafenib, Sunitinib, Pazopanib(^b)</td>
</tr>
<tr>
<td>Previous tyrosine kinase inhibitor</td>
<td>Everolimus, Axitinib(^b)</td>
</tr>
<tr>
<td>Previous mTOR inhibitor</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

\(^a\)Memorial Sloan-Kettering Cancer Center risk category.
\(^b\)Axitinib has a category 1 recommendation for treatment of patients who have failed ≥1 previous systemic therapy.

IFN indicates interferon; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network.


Glossary

Select Health Economics Outcomes Research Terms

Health economics outcomes research: A broad term encompassing “a discipline that describes, interprets, and predicts the impact of various influences, especially interventions, on final end points (from survival to satisfaction with care) that matter to decision makers (from patients to society at large)”\(^a\)

Cost-effectiveness analysis: Analysis in which the consequences associated with a health technology are measured in terms of health\(^b\)

Incremental cost-effectiveness ratio: The ratio of the difference in costs between 2 alternative health technologies to the difference in effectiveness between these 2 technologies\(^b\)

Quality-adjusted life-year (QALY): Quantitatively measures the value of 1 year of life (a QALY of 1 = 1 year with normal health; a QALY of 0 = death)\(^b\)

Sensitivity analysis: Analysis that aims to assess and to determine the influence of input parameters on the outcomes of the economic evaluation study\(^b\)

Deterministic sensitivity analysis: Point estimates are assigned to the input parameters\(^b\)

Probabilistic sensitivity analysis: Probability distributions are applied to the ranges for a model’s input parameters, and samples from these distributions are drawn at random to generate an empirical distribution of the relevant measure of cost-effectiveness\(^b\)

\(^a\)Apolone G. Health Qual Life Outcomes. 2003;1:3.
Comparative Economic Evidence after First-Line mRCC Therapy

Key Findings of Identified Studies

Because of the restrictive nature of our search, the overall number of results identified was low, and only 7 studies, which are summarized in Table 3, met our criteria of interest and were included here.28-35 Of these 7 studies, 3 compared one VEGF or VEGFr inhibitor with another and 4 compared one mTOR inhibitor with another or with a VEGF or VEGFr inhibitor. The studies were heterogeneous in design, with the incremental cost-effectiveness ratios (ICERs) or quality-adjusted life-years (QALYs) associated with various treatments (Glossary) the most common economic benchmarks utilized. Both clinical trial–based and observational-based studies were identified and included. No economic studies including pazopanib were identified using the search criteria. The key findings from each of the identified studies are presented below.

One cost-effectiveness analysis, which was presented at the 2006 ASCO annual meeting, evaluated sorafenib plus best supportive care versus best supportive care alone using a decision analytic Markov model to project lifetime survival and associated costs for patients with advanced RCC.28 Of note, this analysis was based on findings from the phase 3 TARGET trial, in which the majority of patients had received previous cytokine therapy.46 Findings showed lifetime per-patient costs to be $85,571 for sorafenib plus best supportive care and $36,634 for best supportive care alone.28 Treatment with sorafenib plus best supportive care resulted in an ICER of $75,354 per life-year gained.28 Because this ICER is within the societal willingness-to-pay threshold in the United States,37 the study authors concluded that sorafenib was a cost-effective treatment option for patients with advanced RCC.

The second study was a retrospective comparison of costs associated with 2 sequences of the oral VEGFr-TKIs sorafenib and sunitinib using claims in the MarketScan research database.29 This analysis, which was published in abstract form in conjunction with the 2010 ASCO annual meeting, showed that the univariate incremental total per-patient monthly medical cost for patients who first received sunitinib and then sorafenib was $1639 more than the per-patient monthly cost for the patients who first received sorafenib and then sunitinib (P = .003). This represented an annual cost-savings of $19,668 for patients treated with sorafenib initially, which was primarily attributable to outpatient costs.29

The third study that was identified (and was published in a peer-reviewed journal) reported the results of an indirect analysis designed to evaluate the cost-effectiveness of everolimus versus sorafenib for the treatment of sunitinib-refractory mRCC based on the RECORD-1 patient population.31 The drug costs for everolimus and sorafenib were based on dosages from the RECORD-1 trial31 and a phase 2 study of sorafenib.38 Using Markov modeling with deterministic and probabilistic sensitivity analyses, the superior cost-effectiveness of everolimus over sorafenib was demonstrated, with a difference of $81,643 in the total average per-patient cost of treatment with everolimus versus sorafenib; this difference was primarily driven by drug acquisition costs (80%).31 Compared with sorafenib treatment, patients treated with everolimus had an estimated gain in life-years of 1.273 and a gain in QALYs of 0.916, resulting in an ICER of $64,155 per life-year gained, or $89,160 per QALY.31 The estimated ICER in this pretreated population fell below the cost per QALY for many other oncology medications in widespread use. Compared with sorafenib, everolimus had a high probability of being considered cost-effective at a willingness-to-pay threshold of $100,000 per QALY in patients with advanced RCC who failed therapy with sunitinib.

An indirect model–based analysis comparing temsirolimus with everolimus after failure with sunitinib or with sorafenib over a 3-year time horizon was presented at the 2010 Genitourinary Cancers Symposium.32 The estimated average monthly cost of treatment was $5248 with everolimus and $5597 with temsirolimus, resulting in annual cost-savings of $4188 for treatment with everolimus.32 The cost difference was related to the route of administration for these 2 agents (oral for everolimus vs IV for temsirolimus, or outpatient vs in-clinic management) and the need for antihistamine premedication, which is often performed in a higher acuity setting, to prevent infusion reactions with IV temsirolimus therapy. In addition, a retrospective resource utilization study of the US Oncology Network’s iKnowMed electronic medical record (EMR) system that was published in a peer-reviewed journal suggests that everolimus is associated with a lower patient burden in terms of outpatient and laboratory visits compared with temsirolimus among patients with mRCC.34 Patients receiving everolimus had significantly fewer monthly outpatient visits and monthly laboratory frequency monitoring compared with those receiving temsirolimus (mean, 1.19 vs 1.60 and 1.25 vs 2.23, respectively; both P < .05).34

Finally, data from multiple regression analyses that were presented at the 2010 meeting of the European Society of Medical Oncology (ESMO) revealed that patients receiving temsirolimus had a 28% higher frequency of outpatient visits and a 58% increase in the utilization of laboratory procedures compared with patients receiving everolimus.35 Although not a direct economic evaluation, results from this analysis provide additional evidence for differences in economic burden between the agents.
### Table 3  US-Based Cost-Effectiveness and Resource Utilization Studies with VEGF/VEGFr and mTOR Inhibitors

<table>
<thead>
<tr>
<th>Study (drugs evaluated; sponsor)</th>
<th>Study design</th>
<th>Outcomes assessed</th>
<th>Findings</th>
<th>Implications</th>
</tr>
</thead>
</table>
| Gao et al\(^{28}\) (sorafenib; Bayer Pharmaceuticals) | • Markov model to project the lifetime survival and cost associated with sorafenib + best supportive care vs best supportive care alone  
  • 3 disease states (per 3-month period): PFS, progression, death  
  • Resource utilization accounted for drugs, administrations, physician visits, monitoring, and AEs | • FACT-G, FKSI  
• Life-years gained | • Lifetime per-patient costs (2004 US$):  
• Sorafenib + best supportive care: $85,571  
• Best supportive care alone: $36,634  
• ICER: $75,354 per/life-year gained  
• Key drivers of the model results were survival after progression and PFS probabilities for both treatment grounds | • The ICER was within the established threshold that society is willing to pay ($50,000-$100,000 per life-year or per QALY). Therefore, sorafenib + best supportive care appears to be cost-effective in the management of advanced RCC |
| Moyneur et al\(^{29}\) (sorafenib, sunitinib; Bayer HealthCare) | • Retrospective claims database analysis using MarketScan to evaluate the costs of second-line therapy with sorafenib or sunitinib in the treatment of patients with RCC  
• Person-time approach was used in patients who had ≥1 switch in therapy from sunitinib to sorafenib or sorafenib to sunitinib | • Incremental PMPM medical costs  
• Outpatient costs  
• Inpatient costs  
• Pharmacy costs | • Univariate PMPM total medical costs: $9159 (sunitinib > sorafenib) vs $7520 (sorafenib > sunitinib)  
• Outpatient costs: $3400 vs $2148 (P < .001)  
• Inpatient costs: $1755 vs $1582  
• Pharmacy costs: $4004 vs $3790 | • Compared with sunitinib, treatment with sorafenib initially resulted in statistically significantly lower costs in patients with RCC, primarily because of outpatient costs |
| Ozer-Stillman et al\(^{30}\) (axitinib, sorafenib; Bayer HealthCare) | • Survival partition model to estimate direct lifetime medical costs and clinical outcomes for sunitinib-refractory patients starting second-line therapy  
• Patients partitioned into 3 health states (PFS, postprogression survival, and death) using OS and PFS Kaplan-Meier curves from AXIS | • Total costs  
• Life-years gained  
• QALYs gained | • Total per-patient costs: $127,808 for sorafenib vs $159,800 for axitinib  
• Life-years gained: 1.440 for sorafenib vs 1.423 for axitinib  
• QALYs gained: 1.016 for sorafenib vs 1.015 for axitinib | • Compared with axitinib, treatment with sorafenib after sunitinib failure is less expensive and provides a similar benefit in terms of life-years and QALYs |
| Casciano et al\(^{31}\) (everolimus, sorafenib; Novartis Pharmaceuticals) | • Markov model to simulate cohort of patients with advanced RCC who failed therapy with sunitinib  
• Cohorts modeled over 6-year time horizon in 8-week cycles from everolimus or sorafenib initiation  
• Markov disease states included stable disease without AEs, stable disease with AEs, disease progression, and death | • Cost per incremental life-year gained  
• QALYs gained | • Total average per-patient cost of treatment with everolimus vs sorafenib was $81,643, primarily because of acquisition costs (80%)  
• Patients treated with everolimus had an estimated life-year gained of 1.273 and QALY of 0.916 over sorafenib, resulting in an ICER of $64,155 per life-year gained or $89,160 per QALY  
• Sensitivity analysis demonstrated that results were robust to parameters of high uncertainty | • Everolimus was projected to be a cost-effective treatment relative to sorafenib for patients with advanced RCC who fail sunitinib  
• Estimated ICER fell below the cost per QALY for many oncology medicines in widespread use  
• Compared with sorafenib, everolimus had a high probability of being considered cost-effective at a willingness-to-pay threshold of $100,000 per QALY |
### Table 3  US-Based Cost-Effectiveness and Resource Utilization Studies with VEGF/VEGFr and mTOR Inhibitors (Continued)

<table>
<thead>
<tr>
<th>Study (drugs evaluated; sponsor)</th>
<th>Study design</th>
<th>Outcomes assessed</th>
<th>Findings</th>
<th>Implications</th>
</tr>
</thead>
</table>
| Chulikavit et al32 (everolimus, temsirolimus; Novartis Pharmaceuticals) | • Model-based analysis to estimate the average monthly cost of treatment of patients with advanced RCC with everolimus vs temsirolimus  
• Drug costs (2009 WAC), drug administration, treatment of underlying disease (physician visits and tests), AEs, and palliative care were included | • Average monthly cost | • Average monthly costs:  
• Everolimus: $5248  
• Temsirolimus: $5597  
• Difference resulted from drug and infusion costs  
• Annual cost-savings of $4188 for treatment with everolimus vs temsirolimus | • Everolimus likely provides a less costly treatment option for patients with advanced RCC who fail treatment with sunitinib or sorafenib |
| Lopes et al33 (everolimus; Novartis Pharmaceuticals) | • Excel-based budget impact model for a hypothetical health plan with 1 million members and a prevalence of 203 patients with advanced RCC, where 90% of patients receive treatment | • PMPM and PMPY costs | • Total cost of drugs, administration, and AE management:  
• Market before everolimus launch (April 2008- March 2009), $7,050,157  
• Market after everolimus launch (October 2009- September 2010), $6,741,642  
• Cost-savings of $308,515 | • The introduction of everolimus as a second- or third-line agent to VEGF-TKI resulted in a minimal budget impact |
| Vogelzang et al35 Liu et al35 (everolimus, temsirolimus; Novartis Pharmaceuticals) | • Retrospective analysis using US Oncology’s iKnowMed electronic medical records data from 462 identified patients with mRCC who initiated therapy with everolimus (oral mTOR) or temsirolimus (IV mTOR)  
• Patients followed for 6 months or until treatment discontinuation, whichever occurred earlier | • Outpatient visits  
• Inpatient visits  
• Frequency of laboratory assessments | • Mean monthly outpatient visits: everolimus 1.19 vs temsirolimus 1.60 (P <.05)  
• Mean monthly laboratory visits: everolimus 1.25 vs temsirolimus 2.23 (P <.05)  
• In multiple regression analyses, temsirolimus was associated with a 28% higher frequency (95% CI, 7%-50%) of outpatient visits and a 58% increased utilization (95% CI, 30%-86%) of laboratory procedures compared with patients receiving everolimus | • The oral mTOR inhibitor everolimus is associated with a lower patient burden in terms of outpatient and laboratory visits compared with the IV mTOR inhibitor temsirolimus |

AE indicates adverse event; FACT-G, Functional Assessment of Cancer Therapy-General; FKSI, FACT Kidney Symptom Index; ICER, incremental cost-effectiveness ratio; IV, intravenous; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; PMPM, per-member per-month; PMPY, per-member per-year; QALY, quality-adjusted life-year; RCC, renal-cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFr, vascular endothelial growth factor receptor; WAC, wholesale acquisition cost.

An Excel-based economic model comparing 2 market scenarios that was published in a peer-reviewed journal found that introducing everolimus as a second- or third-line therapy after VEGFr-TKIs results in a minimal budget impact.33 In this hypothetical plan of 1 million covered lives, with a 0.023% prevalence of mRCC and 90% of patients receiving treatment for mRCC across first-, second-, and third-line treatments, the total cost of drugs, administration, and adverse event management (from April 2008 through March 2009) was $7,050,157 before the launch of everolimus. After the launch of everolimus, the total cost was $6,741,642 (from October 2009 through September 2010), resulting in a savings of $308,515.33 These trends remained consistent across...
scenario analyses in which everolimus replaced various combinations of comparators, as well as across sensitivity analyses. However, the sensitivity analysis that evaluated inclusion of the postapproval uptake lag period (April 2009-March 2010) and set the adverse event management costs to $0 yielded lower savings in comparison with the base-case analysis.33

Axitinib is a potent VEGFr-TKI and is the only drug other than everolimus that is included in the NCCN guidelines with category 1 evidence for use in patients with mRCC after initial failure with a VEGFr-TKI.26 This recommendation is predominantly based on data that were derived from the AXIS trial.25 An economic evaluation of sorafenib versus axitinib in the AXIS trial, which was presented at ESMO 2012, was based on a partitioned survival model with 3 health states—PFS, postprogression survival, and death—that was constructed to estimate the direct lifetime medical costs and clinical outcomes for patients starting second-line therapy.30 This model was populated with the Kaplan-Meier-derived overall survival and PFS data from the AXIS trial. The investigators estimated lifetime per-patient costs to be $123,171 for sorafenib and $152,013 for axitinib, with the $28,842 cost difference mainly attributable to the higher medication cost of axitinib.30 Although the AXIS trial showed that axitinib significantly prolonged PFS compared with sorafenib (median, 6.7 vs 4.7 months; hazard ratio, 0.665; 95% confidence interval, 0.544-0.812; one-sided P < .001), this partition model found similar benefit in terms of life-years and QALYs for both drugs but a lower total per-patient cost for sorafenib.10

Discussion

Health economics research aimed at evaluating the comparative costs, cost-effectiveness, and budget impact of cancer therapies is an increasing area of focus, but large gaps remain,39 as evidenced by our comprehensive search returning only 7 studies. However, themes related to drug costs, IV versus oral therapies, oral mTOR salvage therapy, and the promising impact of molecular personalization of RCC therapy emerged from our analysis of the literature. Although drug price is a major driver of overall costs, there appears to be an advantage for oral therapies for the treatment of mRCC over those administered intravenously, presumably because of a lower economic impact on outpatient care.

Using data from a large US health insurance claims database, a retrospective analysis restricted to the period of first angiogenesis inhibitor use demonstrated that mean total cost per member per month for IV bevacizumab was approximately 2 times higher than for oral sorafenib and approximately 1.6 times higher than for oral sunitinib.40 The annualized total costs of therapy (adjusted to 2007 US dollars), including inpatient, outpatient, and drug costs, for patients with RCC who were treated with bevacizumab, sorafenib, and sunitinib were $160,212, $83,976, and $98,556 per patient, respectively.40 Therefore, the use of IV bevacizumab led to a cost increase of 56% to 71% more than the use of oral angiogenesis inhibitors.40

However, the clinical implications of this finding are not clear-cut. Although orally administered agents may result in lower outpatient costs, they may also be more likely to be associated with lower adherence and persistence rates, with a resultant negative impact on effectiveness. The data comparing adherence among oral and IV therapies are limited, and at least 1 retrospective claims database analysis suggests that schedule compliance with everolimus is higher than that with temsirolimus as second-line therapy for patients with mRCC (medication possession ratios of 0.93 vs 0.86, respectively; P < .001).41 The data on temsirolimus suggested the presence of higher toxicity than oral therapies (ie, infusion reactions), potentially generating higher monitoring demands and, as such, increasing costs.34

These hypotheses are congruent with data from other areas of medicine, but selection bias is one factor that may not be adequately captured in the reviewed literature. For example, the use of bevacizumab may be motivated by its more favorable toxicity profile, whereas the selection of temsirolimus may reflect the desire to use this drug in patients with poor performance status, as recommended in the current treatment guidelines.26 Although the data show that the oral mTOR inhibitor everolimus offers several economic options compared with other therapies in the second-line treatment setting of mRCC, a clear, economically favorable therapeutic path cannot be identified from the currently available data. This is a significant knowledge gap considering that the majority of patients receiving first-line anti-VEGF therapy will progress, at least 32.9% of patients receiving second-line therapy will experience treatment failure, and at least 16.6% of these patients will progress to receive third-line treatment.43 Although firm conclusions are not possible, our analysis is useful in that it raises several important testable hypotheses.

Of note, comparative economic analyses across treatments for mRCC are known to be problematic for numerous reasons, including the lack of available clinical comparative effectiveness data, as well as differing study designs, patient populations, clinical definitions, and instrument use for patient-reported outcomes. Such factors complicate the ability to compare economic data across multiple studies. In addition, interpretation of cost-effectiveness analyses differs depending on the determination of the willingness-to-pay threshold. Studies found in our
<table>
<thead>
<tr>
<th>NCT identifier</th>
<th>Study design; planned enrollment</th>
<th>Treatment arms</th>
<th>Primary end point</th>
<th>Secondary end points</th>
</tr>
</thead>
</table>
| NCT00903175 (RECORD-3) | Phase 2, open-label, randomized, multicenter trial (n = 390) | • Everolimus 10 mg once daily orally followed by sunitinib 50 mg once daily orally (4 wks on/2 wks off)  
• Sunitinib 50 mg once daily orally (4 wks on/2 wks off) followed by everolimus 10 mg once daily orally | PFS after first-line treatment | PFS after second-line treatment, ORR, duration of response, OS, and safety |
| NCT00720941 (COMPARZ) | Phase 3, open-label, randomized, multicenter trial | • Sunitinib 50 mg once daily orally (4 wks on/2 wks off)  
• Pazopanib 800 mg once daily orally | PFS | OS, ORR, duration of response, safety, health outcomes analysis |
| NCT00474786 (INTORSECT) | Phase 3, open-label, randomized, multicenter trial | In patients who failed first-line sunitinib therapy:  
• Sorafenib 400 mg twice daily orally  
• Temsirolimus 25 mg IV once weekly | Safety and tolerability PFS (central assessment) | PFS by investigator assessment, RR, OS, proportion of patients with PFS at 12, 24, and 36 wks by independent assessment, duration of response |
| NCT00732914 (SWITCH) | Phase 3, open-label, randomized, multicenter trial | • Sunitinib 50 mg once daily (4 wks on/2 wks off) followed by sorafenib 400 mg twice daily  
• Sorafenib 400 mg twice daily followed by sunitinib 50 mg once daily (4 wks on/2 wks off) | Total PFS | TTP, OS, disease control rate, cardiotoxicity |
| NCT01613846 (SWITCH-II) | Phase 3, open-label, randomized, multicenter trial | • Sorafenib 400 mg twice daily followed by pazopanib 800 mg once daily  
• Pazopanib 800 mg once daily followed by sorafenib 400 mg twice daily | Total PFS | TTP, PFS in first and second line, OS, disease control rate, HRQOL |

HRQOL indicates health-related quality of life; IV, intravenous; mRCC, metastatic renal cell carcinoma; NCT, National Clinical Trial; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression.

A literature search reported ICERs ranging from $64,155 to $89,160. These fit within the range of willingness-to-pay thresholds often cited in US sources ($50,000-$100,000 per QALY gained); however, the accepted threshold can vary drastically among decision makers.

The pivotal trials summarized in Table 1 established the efficacy and safety of individual targeted therapies; nevertheless, there is a general lack of head-to-head comparisons relevant to everyday clinical practice. Specific to second-line therapy, there are no prospectively collected data comparing the efficacy and safety of everolimus with those of axitinib, the 2 agents that are recommended at a class 1 level in the NCCN guidelines. Coupled with the lack of head-to-head randomized trials in which the optimal sequence of treatments for mRCC is the primary outcome, comparisons of economic analyses are difficult.

Frequently, comparators are drawn from historical data sets. For example, in the recent phase 3 AXIS trial, a small subset of patients received axitinib after previous failure with sunitinib. The trial showed a favorable clinical response for axitinib based on median PFS; however, during the formal discussion period that followed the initial presentation of the AXIS results at ASCO 2011, a number of discussants pointed out that the degree of benefit appears to approximate that of
Limitations

Our review revealed that comparative economic evidence in the treatment of mRCC in patients who have failed initial therapy with targeted agents is very limited. Our extensive search of the published literature identified only 3 studies that were published in peer-reviewed journals. To account for relevant data that were not published in the peer-reviewed literature, abstracts of several major conferences and meetings were searched, yielding an additional 4 studies that met our inclusion criteria. The designs of these studies were also heterogeneous. This lack of publicly available data and the heterogeneous nature of the data that are available minimize the conclusions that can be drawn from these studies. Furthermore, the potential pitfalls of using observational studies (eg, selection bias) to make conclusive treatment decisions or recommendations for sequencing and the choice of second-line targeted therapies need to be recognized.

The 7 studies we reviewed analyze the economic impact of the care of patients with RCC using a diverse array of approaches, each with inherent strengths and weaknesses. For example, cost-effectiveness models present methodologic challenges from the standpoint of extrapolation of outcomes data beyond trial completion. Health economics and outcomes research measures, such as QALYs, express aggregate individual utility and are considered to be the most applicable to research- or population-based decision-making rather than day-to-day use. The aggregate nature of the QALY makes it useful for comparisons of outcomes across multiple studies. As such, economic analyses based on clinical trials may not directly reflect costs in the real-world clinical practice setting. With 7 potential choices at present, it is possible that lifestyle considerations, the adverse event profile, convenience, and hidden economic incentives may begin to play a role in drug selection.

Claims database analyses, budget impact analyses, and model-based cost comparisons present their own methodologic challenges. For example, claims database analyses generally use International Classification of Diseases, Ninth Revision codes that can potentially lead to the inclusion of false-positive cases, and only costs from the perspective of the payer are included.40 Budget impact analyses are primarily intended to inform healthcare decision makers; therefore, similar to cost-effectiveness analyses, the analyses do not include cost implications from the societal perspective.31 The limitations of model-based cost comparisons include a lack of generalizability of results to all patients with RCC, given that the probabilities are generally taken from clinical trials and are often based on a series of assumptions, which may underestimate or overestimate costs and benefits.31

The dearth of head-to-head comparator studies of RCC and consensus methodologies for economic analyses represents a major limitation and a key research opportunity in this field at the present time.
Conclusion

The limited number of economic studies related to targeted treatment options in the second-line setting and beyond in patients with mRCC does not allow firm conclusions to be drawn about the most cost-effective targeted treatment option in this setting. We hope that ongoing head-to-head therapeutic trials and biomarker studies will improve our ability to evaluate the economic efficiency of these expensive agents. Analysis of real-world utilization data may provide a more accurate understanding of the economic impact of these medications in the use of patients outside the controlled environment of clinical trials. However, this needs to be balanced against the potential pitfalls of using observational studies (eg, selection bias) to make conclusive treatment decisions or recommendations for the sequencing and the choice of second-line targeted therapies.

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Author Disclosure Statement

Dr Wong is on the advisory boards of Merck, Genentech, and Bristol-Myers Squibb. Drs Wang and Liu are employees and stockholders of Novartis Pharmaceuticals. Mr Chudikavt is an employee of LA-SER Analytica International and a consultant to Novartis Pharmaceuticals.

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The profusion of new therapies for advanced kidney cancer—there are now 8 drugs available to treat the disease with the promise of more in development—has raised many questions, including their comparative effectiveness, quality of life, sequencing, and the cost of current and future therapies. Wong and colleagues have analyzed 7 studies that compared the cost of these therapies, showing that intravenous therapies with bevacizumab and temsirolimus were more costly than the oral therapies sorafenib and everolimus; however, these drugs are now mostly second-, third-, or fourth-line agents.

**PAYERS:** Wong and colleagues point out that cost comparisons of the most frequently used frontline oral agents, sunitinib and pazopanib, and the most frequently used second-line agents, everolimus and axitinib, have not been published or conducted. I expect that the Comparing the Efficacy, Safety, and Tolerability of Pazopanib versus Sunitinib (COMPARZ) study will be analyzed from a cost perspective. Because these drugs are equivalent in progression-free survival and overall survival and are similarly priced, it would be surprising if there was much difference in their drug acquisition costs. However, the apparent improved quality of life and patient acceptance of pazopanib could paradoxically increase its overall cost, because of the resultant longer duration of use of pazopanib (defined as a higher “persistence rate” for pazopanib). Ideally, other studies, perhaps using payer databases, will soon compare the 2 market leaders pazopanib and sunitinib.

More than 50% of US patients receive second-line therapy for advanced renal cancer, most often with sorafenib, everolimus, or axitinib. The drug acquisition costs may be significantly different among these agents. Sorafenib is dosed at 400 mg twice daily and is frequently dose de-escalated because of hand-foot syndrome. Everolimus is dosed at 10 mg daily and is also often dose de-escalated to 5 mg daily. However, axitinib is often dose-escalated from 5 mg twice daily to 10 mg twice daily, with a potential doubling of the drug acquisition cost. In addition, axitinib may have a higher persistence rate.

The analysis of the costs of therapy with everolimus versus sorafenib will need to take into account treatment for diarrhea, stomatitis, and rash (ie, common toxicities of both agents), and the cost of axitinib must factor in the cost of blood pressure control (its most common toxicity).

Overall, approximately 20% to 25% of patients with advanced renal cancer receive third-line therapy, hence the economic impact is likely to be low; however, some patients have long duration (>1 year) of responses to third-, fourth-, or fifth-line therapy; therefore, the economic impact cannot be dismissed.

**RESEARCHERS:** There is much important work to be done in this field. The data from integrated health networks, such as US Oncology, Kaiser, Intermountain Healthcare, Carolinas HealthCare System, and many others, should be analyzed and published in peer-reviewed journals. Only then will we have a robust database that will allow researchers to draw firmer conclusions. Such information will also allow third-party payers to understand the value that they are providing to their members.