Current Treatment Options for Metastatic Renal-Cell Carcinoma: Review of the Literature

Daphne O. Davis, PharmD, BCOP; Megan Hinkley, PharmD, BCOP

BACKGROUND: It is estimated that 63,990 patients will be newly diagnosed with renal cancer in 2017, and 14,400 people will die of this disease. In recent years, the incidence of renal cancer has been on the rise. Despite this, the death rates are declining as the landscape of renal-cell carcinoma (RCC) treatment evolves, with the development of new targeted therapies.

OBJECTIVE: To review the current published literature available for multiple treatment options for patients with metastatic RCC.

DISCUSSION: Sunitinib, pazopanib, axitinib, sorafenib, and bevacizumab plus interferon (IFN)-alpha are considered first-line treatment options for metastatic RCC according to the National Comprehensive Cancer Network guidelines. However, for patients with a good performance status, high-dose interleukin (IL)-2 remains an appropriate treatment option. Temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, is also indicated as a first-line treatment option for patients with poor-risk disease. Any RCC therapy not indicated for the first-line setting remains a valid second-line treatment option. Second-line therapy options also include everolimus, cabozantinib, and nivolumab, which are indicated for use after treatment with an anti–vascular endothelial growth factor tyrosine kinase inhibitor (TKI).

CONCLUSION: The treatment for metastatic RCC has evolved over the past 2 decades. From immunotherapies, such as IFN-alpha, IL-2, and nivolumab, to targeted agents, such as the TKIs and mTOR inhibitors, clinicians have a myriad of options to consider for their patients with this disease. Until a clearer pathway for treatment of metastatic RCC is established, it will be important to keep in mind patient-specific factors such as tolerability and cost when choosing which agents to use for the individual patient.

Treatment Options for Renal-Cell Carcinoma

The treatment of metastatic RCC has evolved significantly since the initial FDA approval of IL-2 in 1992. In addition, the FDA approval in 2015 of the first PD-1 inhibitor, nivolumab, for this disease, has changed the way patients with metastatic RCC are managed, as well as the treatment options available.

Approximately 90% of renal tumors are RCC, and approximately 80% of them are classified as clear-cell tumors. Rare types of RCC include papillary, chromophobe, translocation, and collecting duct tumors. The majority of clear-cell RCCs are associated with loss of function of the VHL gene. This loss of function results in increased VEGF production, leading to increased angiogenesis and tumor-cell proliferation. Another factor in tumor-cell growth, mTOR, of which 2 protein complexes have been identified in humans, are activated in clear-cell RCCs, with mTORC1 being activated in 60% to 85% of clear-cell RCCs. mTOR is involved with cell growth and metabolism regulation, as it functions to promote protein translation.

Dr Davis is Oncology Clinical Pharmacy Specialist, Wake Forest Baptist Medical Center, Winston-Salem, NC; and Dr Hinkley is Clinical Specialist Pharmacist, Oncology, James Cancer Hospital, The Ohio State University, Columbus.
vided patients and clinicians with additional treatment options. Oncologists can now choose from several first-line options for the management of patients with metastatic RCC.

Sunitinib, pazopanib, axitinib, sorafenib, and bevacizumab plus interferon (IFN)-alpha are considered first-line treatment options based on the current National Comprehensive Cancer Network (version 1.2018) guidelines (Table 2).3

However, for patients with a good performance status, high-dose IL-2 remains an appropriate treatment option. The mTOR inhibitor, temsirolimus, is also indicated as a first-line treatment option for patients with poor-risk RCC.3

Any agent not used in the first-line setting remains a valid second-line treatment option. In addition, everolimus is an appropriate second-line treatment option, based on the results of the RECORD-1 study, in which it was used after treatment with an anti-VEGF tyrosine kinase inhibitor (TKI).28,29 With the FDA approval of nivolumab, cabozantinib, and lenvatinib as second-line treatment options, providers may use these novel agents as second-line alternative treatment options (Table 2).

Immunotherapies

Interleukin-2. To determine whether high- or low-dose IL-2 was preferred for the treatment of metastatic RCC, Yang and colleagues compared the use of IL-2, administered intravenously, 720,000 units/kg, every 8 hours, with IL-2 administered intravenously, 72,000 units/kg, every 8 hours.8 The response rates were 21% in the high-dose group and 13% in the low-dose group (P = .048). Patients receiving the high-dose therapy had more side effects (including hypotension, central nervous system disorientation, and thrombocytopenia) than patients receiving low-dose therapy.

A third treatment group included patients who received subcutaneous IL-2 daily, 5 days a week (first week, 250,000 units/kg per dose, then 125,000 units/kg per dose for the next 5 weeks). This group had a lower response rate (10%), which was significantly lower than the high-dose group (P = .033). There were no significant differences in overall survival (OS) between the groups, although patients in the high-dose group who had complete responses did have longer survival.

Patient monitoring during intravenous (IV) administration of IL-2 is of utmost importance, because of the risk for capillary leak syndrome, which can manifest as hypotension, mental status changes, and edema.9

Nivolumab. Nivolumab was the first PD-1 inhibitor to receive FDA approval for the treatment of patients with metastatic RCC, based on promising results in phase 3 clinical trials.5,10 PD-1 is found on activated T-cells; the ligands PD-L1 and PD-L2 are found on tumor cells and on immune cells. Nivolumab and other PD-1 inhibitors block the interaction between PD-1 and PD-L1, which allows for increased anti-tumor immune response.

The CheckMate-025 investigators compared nivolumab with everolimus in a phase 3 study of patients with previously treated, advanced metastatic RCC.10 Patients received IV nivolumab 3 mg/kg every 2 weeks (N = 410) or oral everolimus 10 mg daily (N = 411). The primary end point was median OS: the median OS was 25 months in the nivolumab group and 19.6 months in the everolimus group (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.57-0.93; P = .002). The objective response rate (ORR) was 25% with nivolumab versus 5% with everolimus (odds ratio, 5.98; 95% CI, 3.68-9.72; P < .001). The median progression-free survival (PFS) was similar in both groups—4.6 months versus 4.4 months, respectively (HR, 0.88; 95% CI, 0.75-1.03; P = .11). The benefit of nivolumab was seen regardless of PD-L1 expression.10

The most common side effects associated with nivolumab included fatigue, nausea, and pruritus; grade 3 or 4 adverse events occurred in 19% of patients.10 Grade 3 or 4 adverse drug reactions occurred in 37% of patients receiving everolimus; the most frequently reported adverse events were fatigue, stomatitis, and anemia. This study demonstrated that in patients with previously treated advanced metastatic RCC, nivolumab provided longer OS with fewer side effects when compared with everolimus.10 Because of its mechanism of action, patients receiving nivolumab should be moni-

---

Table 2

<table>
<thead>
<tr>
<th>First-line therapy</th>
<th>Subsequent lines of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>Pazopanib (preferred)</td>
<td>Cabozantinib (preferred)</td>
</tr>
<tr>
<td>Sunitinib (preferred)</td>
<td>Nivolumab (preferred)</td>
</tr>
<tr>
<td>Bevacizumab plus IFN-alpha</td>
<td>Axitinib</td>
</tr>
<tr>
<td>Temsirolimus (for patients with poor prognosis)</td>
<td>Everolimus plus everolimus</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Everolimus</td>
</tr>
<tr>
<td>High-dose IL-2</td>
<td>Pazopanib</td>
</tr>
<tr>
<td>Cabozantinib (for patients with poor and intermediate risk)</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

IFN indicates interferon; IL-2, interleukin-2.

tored on a regular basis for immune-mediated toxicities, such as pneumonitis, colitis, hepatitis, dermatitis, endocrinopathies, or nephritis.

**Targeted Therapy**

**VEGF Inhibitors**

**Sorafenib.** Based on sorafenib’s mechanism of action, which targets multiple kinases involved in the pathways associated with metastatic RCC, the TARGET clinical trial aimed to assess the drug’s effects on PFS and OS in patients with previously treated, advanced clear-cell RCC.\(^{11,12}\) Patients had to have clear-cell RCC that progressed within 8 months of initial systemic therapy. Treatment consisted of the TKI sorafenib, 400 mg, administered orally twice daily (N = 451) versus placebo (N = 452). At the first interim analysis, the median OS was 14.7 months in the placebo group and was not reached in the sorafenib group (HR, 0.72; 95% CI, 0.54-0.94; \(P = .02\)). However, this difference in response did not reach significance based on prespecified O’Brien–Fleming boundaries. A second analysis 6 months later showed a median OS of 15.9 months in the placebo group versus 19.3 months in the sorafenib group (HR, 0.77; 95% CI, 0.63-0.95; \(P = .02\)), which, again, was not a significant difference. The median PFS was 5.5 months with sorafenib versus 2.8 months with placebo (\(P < .001\)).\(^{11,12}\)

Sorafenib led to a disease control rate of 62% versus 37% with placebo. Patients received sorafenib for a median of 23 weeks or placebo for 12 weeks. The most common side effects with sorafenib were diarrhea, rash, fatigue, hand–foot skin reactions, alopecia, and nausea. Hypertension (all grades) was reported in 17% of the sorafenib group; <1% of patients discontinued sorafenib therapy because of hypertension. The discontinuation rates because of side effects were similar in the 2 groups (10% sorafenib vs 8% placebo). The most common reasons for treatment discontinuation were constitutional, gastrointestinal, dermatologic, or pulmonary/upper respiratory tract symptoms. The investigators concluded that sorafenib increases PFS versus placebo in patients with advanced clear-cell RCC who did not respond to first-line therapy.\(^{11,12}\)

**Sunitinib.** Motzer and colleagues compared sunitinib with the then standard-of-care, IFN-alpha, in the treatment of metastatic RCC.\(^{13,14}\) In this randomized, phase 3 study, patients with previously untreated, metastatic RCC received oral sunitinib 50 mg daily for 4 weeks, followed by 2 weeks off, in 6-week cycles, or 3 million units of subcutaneous IFN-alpha, 3 times weekly in week 1; 6 million units 3 times weekly in week 2; and 9 million units 3 times weekly thereafter. The study enrolled 750 patients, with 375 patients in each treatment group. The primary end point was PFS; the secondary end points were ORR, OS, patient-reported outcomes, and safety. The median PFS was 11 months in the sunitinib group versus 5 months in the IFN-alpha group (HR, 0.42; 95% CI, 0.32-0.54; \(P < .001\)).\(^{13,14}\)

Regarding the secondary end points, the ORR was 31% in the sunitinib arm and 6% in the IFN-alpha arm (\(P < .001\)). The median OS was 26.4 months versus 21.8 months, respectively (HR, 0.821; 95% CI, 0.673-1.001; \(P = .051\)).\(^{13,14}\)

Side effects that were more common with sunitinib than with IFN-alpha included grade 3 diarrhea, vomiting, hypertension, and hand-foot syndrome. Laboratory abnormalities seen more often with sunitinib than with IFN-alpha were leukopenia, neutropenia, thrombocytopenia, increased lipase, and increased amylase. Side effects seen more often with IFN-alpha than with sunitinib included grade 3 or 4 fatigue, pyrexia, chills, myalgia, and influenza-like symptoms; lymphopenia was the only significant laboratory abnormality in the IFN-alpha group.

Patient-reported quality of life was assessed using 2 questionnaires, the Functional Assessment of Cancer Therapy (FACT)-General and the FACT-Kidney Symptom Index, and was better in the sunitinib arm than in the IFN-alpha arm (\(P < .001\)).\(^{13,14}\) The results of this study propelled sunitinib to gain FDA approval for the front-line treatment of patients with newly diagnosed metastatic RCC.

**Bevacizumab.** Investigators in the AVOREN clinical trial evaluated bevacizumab plus IFN-alpha-2a versus IFN-alpha-2a alone as first-line treatment for metastatic RCC.\(^{15,16}\) Patients were randomized to bevacizumab 10 mg/kg administered intravenously every 2 weeks plus IFN-alpha-2a, 9 million units administered subcutaneously 3 times weekly, for a maximum of 52 weeks (N = 327), or to IFN-alpha-2a, at the same dose and duration, plus placebo (N = 322).\(^{15,16}\)

The median OS was 23.3 months in the bevacizumab plus IFN-alpha-2a arm and 21.3 months in the placebo plus IFN-alpha-2a arm (unstratified HR, 0.91; 95% CI, 0.76-1.10; \(P = .3360\)). The median PFS was 10.2 months in the bevacizumab arm and 5.4 months in the placebo arm (HR, 0.63; 95% CI, 0.52-0.75; \(P = .0001\)). The ORR was also higher in the bevacizumab arm (31%) than in the placebo arm (13%; \(P < .001\)).\(^{15,16}\)

Adverse events were as had been seen before with IFN-alpha-2a, including fatigue, asthenia, and neutropenia. The adverse events with bevacizumab included proteinuria, hypertension, and bleeding. This trial demonstrated the efficacy of bevacizumab plus IFN-alpha-2a as first-line therapy for the treatment of metastatic RCC.\(^{15,16}\)

In another study similar to the AVOREN clinical...
trial, Rini and colleagues compared the use of bevacizumab plus IFN-alpha with IFN-alpha alone as first-line therapy for the treatment of patients with metastatic RCC.17,18 Patients were randomized to bevacizumab 10 mg/kg administered intravenously every 2 weeks plus 9 million units of IFN-alpha administered subcutaneously 3 times weekly (N = 369), or to IFN-alpha at the same dose and duration (N = 363).17,18

Results showed a median OS of 18.3 months with bevacizumab plus IFN-alpha versus 17.4 months with IFN-alpha monotherapy (unstratified log-rank P = .097). The median PFS was 8.5 months with bevacizumab plus IFN-alpha and with IFN-alpha alone 5.2 months (log-rank P < .0001). The ORR was also improved with the combination, at 25.5% versus 13.1% with IFN-alpha monotherapy (P < .0001).17,18

More patients had grade ≥3 adverse events in the combination arm than in the IFN-alpha monotherapy arm (80% vs 63%; P < .001).18 Patients who received bevacizumab plus IFN-alpha reported significantly more grade 3 hypertension, anorexia, fatigue, and proteinuria than patients who received IFN-alpha alone. This trial showed that bevacizumab plus IFN-alpha improved OS, but not significantly, and the combination therapy resulted in more side effects.17,18

Pazopanib. The FDA approved pazopanib for the treatment of patients with metastatic RCC based on a study that compared it with placebo.19,20 The phase 3 clinical trial COMPARZ compared the efficacy, safety, and tolerability of pazopanib and sunitinib in the first-line setting. The goal was to show the noninferiority of pazopanib to sunitinib. Patients were randomized to oral pazopanib 800 mg daily continuously (N = 554), or to oral sunitinib 50 mg daily for 4 weeks, followed by 2 weeks off (N = 548). The primary end point was median PFS, which was 8.4 months with pazopanib and 9.5 months with sunitinib. The ORR favored pazopanib at 31% versus 25% with sunitinib (P = .03). The median OS was 28.3 months with pazopanib and 29.1 months with sunitinib (HR, 0.92; 95% CI, 0.79-1.06; P = .24).19,20

Side effects seen more frequently with pazopanib were hair-color changes, weight loss, alopecia, increased alanine aminotransferase levels, and increased bilirubin. In contrast, sunitinib was associated with more hand-foot syndrome, mucosal inflammation, stomatitis, hypothyroidism, dysgeusia, dyspepsia, epistaxis, fatigue, leukopenia, thrombocytopenia, neutropenia, and anemia than was pazopanib. The study also assessed health-related quality of life, and found that patients reported significantly less fatigue and foot soreness with pazopanib than with sunitinib. The investigators were able to demonstrate the noninferiority of pazopanib to sunitinib as first-line treatment for metastatic RCC, with a more favorable safety and side-effect profile for pazopanib.19,20

Axitinib. The second-generation VEGF receptor inhibitor axitinib has high affinity for VEGF and low off-target effects, which led to its evaluation against sorafenib for the second-line treatment of metastatic RCC.21,22 The phase 3 trial AXIS randomized patients whose disease progressed with systemic first-line therapy to oral axitinib (N = 361) 5 mg twice daily (which could then be titrated up to 7 mg, then to 10 mg, twice daily, if tolerated) or to oral sorafenib 400 mg twice daily (N = 362). The primary end point was PFS, and the secondary end points were OS, ORR, duration of response, and time to deterioration.21,22

The median PFS was 6.7 months with axitinib and 4.7 months with sorafenib (HR, 0.665; 95% CI, 0.544-0.812; one-sided P < .0001). The ORR was 19% with axitinib and 9% with sorafenib (P = .0001) based on the Independent Review Committee (IRC). Based on the IRC review, the median duration of response was 11 months with axitinib and 10.6 months with sorafenib. At follow-up, the median OS was 20.1 months with axitinib and 19.2 months with sorafenib (HR, 0.969; 95% CI, 0.800-1.174; one-sided P = .3744).21,22

Side effects seen more frequently with axitinib than with sorafenib were diarrhea, hypertension, hypothyroidism, fatigue, decreased appetite, nausea, and dysphonia. Side effects seen more frequently in the sorafenib group than in the axitinib group were alopecia, rash, and palmar-plantar erythrodysesthesia. This study demonstrated that axitinib significantly improved PFS compared with sorafenib, and, as such, axitinib should be considered as second-line therapy for the treatment of patients with metastatic RCC.21,22

Hutson and colleagues evaluated axitinib versus sorafenib as first-line therapy in patients with metastatic RCC.23 Patients received oral axitinib 5 mg twice daily (could be titrated up to 7 mg and 10 mg twice daily; N = 192) or oral sorafenib 400 mg twice daily (N = 96). The median PFS was 10.1 months with axitinib and 6.5 months with sorafenib (stratified HR, 0.77; 95% CI, 0.56-1.05; one-sided P = .038). The ORR was 32% with axitinib and 15% with sorafenib (risk ratio [RR], 2.21; 95% CI, 1.31-3.75, stratified one-sided P = .0006). The median duration of response was not different between axitinib and sorafenib, at 14.7 months and 14.3 months, respectively.23

Side effects more common with axitinib than with sorafenib were diarrhea, hypertension, weight decrease, decreased appetite, dysphonia, hypothyroidism, and upper abdominal pain. In contrast, side effects more common with sorafenib than with axitinib were palmar-plantar erythrodysesthesia, rash, alopecia, and
erythema.\textsuperscript{23} Although it was not compared with sunitinib or with pazopanib, which are often used in the first-line setting for the treatment of metastatic RCC, axitinib did show an improvement in PFS (but not statistically significant) with an acceptable side-effect profile compared with sorafenib.\textsuperscript{23}

**Cabozantinib.** Cabozantinib was approved by the FDA for the treatment of metastatic RCC at the end of April 2016. Because of its multikinase inhibition (including MET, VEGF receptors, and AXL), cabozantinib was compared with everolimus in patients with metastatic RCC whose disease progressed with VEGF receptor inhibition therapy in the METEOR study.\textsuperscript{24,25}

Patients received oral cabozantinib 60 mg daily (N = 330) or oral everolimus 10 mg daily (N = 328). The median PFS was 7.4 months in the cabozantinib arm and 3.8 months in the everolimus arm (HR, 0.51; 95% CI, 0.41-0.62; \(P < .0001\)). The median OS was significantly longer in the cabozantinib group versus the everolimus group at 21.4 months and 16.5 months, respectively (HR, 0.66; 95% CI, 0.53-0.83; \(P = .0026\)). As assessed by an independent radiology review, the ORR was 17% in the cabozantinib group and 3% in the everolimus group (\(P < .0001\)).

Adverse events more frequently associated with cabozantinib than with everolimus were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome, and hypomagnesemia. Everolimus-associated side effects were as seen in other studies, and included anemia, fatigue, hyperglycemia, pneumonitis, and stomatitis. From the results of this study, cabozantinib was approved as another treatment option for patients previously treated for metastatic RCC with an anti-VEGF agent.

**Lenvatinib.** The most recent addition to the metastatic RCC treatment arsenal is the oral multitarget TKI, lenvatinib.\textsuperscript{26} Lenvatinib has activity against VEGF receptors, fibroblast growth factor receptors, platelet-derived growth factor receptors, RET, and KIT. It was studied alone and in combination with everolimus in patients whose disease progressed within 9 months of stopping treatment with a VEGF-targeted treatment. Patients were stratified by hemoglobin and corrected serum calcium, and randomized to the combination of oral lenvatinib 18 mg daily plus oral everolimus 5 mg daily (N = 51), to lenvatinib 24 mg daily (N = 52), or to everolimus 10 mg daily (N = 50) until disease progression, side effects became unmanageable, or withdrawal of patient consent.\textsuperscript{26}

The primary outcome was PFS, which was 14.6 months, 7.4 months, and 5.5 months with the combination, lenvatinib monotherapy, and everolimus monotherapy, respectively (HR, 0.40; 95% CI, 0.24-0.68; \(P = .0005\) for the combination vs everolimus, and HR, 0.61; 95% CI, 0.38-0.98; \(P = .048\) for lenvatinib monotherapy vs everolimus). The ORR was 43% with the combination, 27% with lenvatinib monotherapy, and 6% with everolimus (RR, 7.2; 95% CI, 2.3-22.5; \(P < .0001\) for the combination vs everolimus; RR, 4.5; 95% CI, 1.4-14.7; \(P = .067\) for lenvatinib monotherapy vs everolimus).\textsuperscript{26}

The median duration of response was 13 months with the combination, 7.5 months with lenvatinib monotherapy, and 8.5 months with everolimus. The median OS was 25.5 months, 19.1 months, and 15.4 months, respectively (HR, 0.51; 95% CI, 0.3-0.88; \(P = .024\) for the combination vs everolimus monotherapy, and HR, 0.68; 95% CI, 0.41-1.14; \(P = .12\) for lenvatinib monotherapy vs everolimus monotherapy).\textsuperscript{26}

No significant differences were found between the combination and lenvatinib alone. Adverse events were as reported in other studies for both agents. Patients receiving lenvatinib had more proteinuria, hypertension, and diarrhea, whereas those who received everolimus had more anemia, dyspnea, hypertriglyceridemia, and hyperglycemia. Adverse events were greater in the 2 groups with lenvatinib versus everolimus alone; however, the side effects were manageable with dose reductions. Results of this study showed that the use of lenvatinib in patients with metastatic RCC whose disease progressed with a VEGF inhibitor provided a benefit in survival over everolimus alone.\textsuperscript{26}

**mTOR Inhibitors**

**Temsirolimus.** Temsirolimus alone, IFN-alpha alone, and the combination of temsirolimus plus IFN-alpha were compared in patients with poor-prognosis metastatic RCC.\textsuperscript{27} The phase 3 Global ARCC Trial evaluated 626 patients with treatment-naive, poor-prognosis metastatic RCC. Poor-prognosis required ≥3 of 6 criteria that included serum lactate dehydrogenase >1.5 times the upper limit of normal; hemoglobin less than the lower limit of normal; corrected serum calcium level >10 mg/dL; time from initial diagnosis of RCC to randomization of <1 year; a Karnofsky performance score 60 or 70; or metastases in multiple organs. Patients received treatment based on randomization. Dosing for the IFN-alpha monotherapy group (N = 207) started at 3 million units administered subcutaneously 3 times weekly for week 1, followed by 9 million units 3 times weekly for week 2, and then 18 million units 3 times weekly for week 3, if tolerated.\textsuperscript{27}

Patients receiving temsirolimus monotherapy (N = 209) received IV temsirolimus 25 mg once weekly. Patients in the combination arm (N = 210) received temsirolimus 15 mg IV weekly plus IFN-alpha 3 million units administered subcutaneously 3 times weekly for week 1, followed by 6 million units 3 times weekly from then on.\textsuperscript{27}
Treatment was continued until disease progression or until the patient had intolerable side effects. The primary end point was OS. Secondary end points included PFS, ORR, and clinical benefit rate. The temsirolimus alone group had an HR for death of 0.73 (95% CI, 0.58-0.92; \( P = .008 \)) versus IFN-alpha alone. The combination arm had an HR for death of 0.96 (95% CI, 0.76-1.20; \( P = .70 \)) compared with IFN-alpha alone. The median survival in the IFN-alpha group, temsirolimus group, and combination group was 7.3 months, 10.9 months, and 8.4 months, respectively. The median PFS was 3.1 months for the IFN-alpha group, 5.5 months for the temsirolimus group, and 4.7 months for the combination group, respectively. The ORR was 4.8% in the IFN-alpha group, 8.6% in the temsirolimus group, and 8.1% in the combination group. Clinical benefit, which was defined as objective response or stable disease for ≥24 weeks, was 15.5% in the IFN-alpha group, 32.1% in the temsirolimus group, and 28.1% in the combination group. Adverse effects were as reported in previous studies for the individual agents.27

Patients receiving IFN-alpha had more asthenia, and more grade 3 to 4 adverse events overall. Patients receiving temsirolimus had more rashes, peripheral edema, stomatitis, hyperglycemia, hypercholesterolemia, and hyperlipidemia than patients who received IFN-alpha alone. This study demonstrated the benefit of temsirolimus alone versus IFN-alpha alone based on median OS in patients with poor-prognosis metastatic RCC. The study also showed no benefit with combination therapy, which increased adverse events leading to dose reductions and decreased dose intensity of the medications.27

**Everolimus.** In the RECORD-1 trial, the mTOR inhibitor everolimus was compared with placebo for the treatment of metastatic RCC in patients who did not respond to therapy with a VEGF receptor inhibitor.28,29 Patients were randomized to oral everolimus 10 mg daily (N = 277) or to placebo (N = 139). The primary end point was PFS, and secondary end points included ORR, OS, and safety. At the final follow-up, median PFS was 4.9 months with everolimus and 1.9 months with placebo (HR, 0.33; 95% CI, 0.25-0.43; \( P < .001 \)). In patients randomized to everolimus, the median OS was 14.8 months versus 14.4 months with placebo (HR, 0.87; 95% CI, 0.65-1.15; \( P = .162 \)). Because crossover was allowed, survival results may be confounded, because 80% of patients who received placebo crossed over to receive everolimus.28,29

Common side effects seen with everolimus were stomatitis, rash, fatigue, and diarrhea. Pneumonitis occurred in 8% of patients who received everolimus. This study illustrated the efficacy and safety of everolimus for the treatment of metastatic RCC in patients whose disease progressed with VEGF receptor inhibitor therapy.28,29

**Practical Implications**

At any time during treatment of metastatic RCC, clinical trials are always appropriate for eligible patients. With the FDA approvals of new, oral, targeted therapy options, oncologists were given new options for treating patients.2 However, with the rapid approval of these agents, many were not studied against each other, but were rather compared with the previously used cytokine therapy, IFN-alpha. With each of these agents being studied in the first-line setting, and having similar targets, it can be difficult to determine the correct sequence of anti-VEGF therapy.

Based on the results of clinical trials such as CheckMate-025 with nivolumab and METEOR with cabozantinib, these newer agents will likely replace everolimus as second-line therapy for patients with metastatic RCC.10,24,25

The approval of nivolumab as the first PD-1 inhibitor for the treatment of patients with metastatic RCC changed the treatment landscape of metastatic RCC again.

Side effects of anti-VEGF therapy, such as hypertension, diarrhea, thyroid dysfunction, hand-foot syndrome, and changes in liver function, can assist providers in determining the most ideal therapy, because these side effects vary between agents. The COMPARZ trial, which evaluated sunitinib versus pazopanib, provided a direct comparison of 2 first-line TKI therapies. While noting differences in the incidence of side effects, investigators in COMPARZ concluded that pazopanib was noninferior to sunitinib.19,20

In addition, axitinib was compared with sorafenib in the first- and second-line settings. When assessed in the first-line setting, axitinib did show an improvement in PFS, with an acceptable side-effect profile, compared with sorafenib.21 However, neither axitinib nor sorafenib were compared with sunitinib or pazopanib (2 TKIs often considered preferred first-line agents) in large randomized clinical trials.

Axitinib and sorafenib were also compared as second-line treatment options in the AXIS trial. According to results from the AXIS trial, axitinib demonstrated an improvement in PFS with a similar toxicity profile when compared with sorafenib, helping to solidify the role of axitinib as a second-line therapy.21,22
The approval of nivolumab as the first PD-1 inhibitor for the treatment of patients with metastatic RCC changed the treatment landscape of metastatic RCC again. Nivolumab, which may be used in the second-line setting after treatment with an anti-VEGF therapy, demonstrated a 25% ORR versus a 5% ORR with everolimus. Nivolumab offers a viable treatment option that can provide a sustained response for patients; it showed a median OS of 25 months in the CheckMate-025 trial.10

Rare side effects associated with nivolumab include immune-mediated hepatitis, nephritis, pneumonitis, and colitis. Although nivolumab is administered intravenously every 2 weeks, it has been a revolutionary treatment option for patients with metastatic RCC.

Conclusion

The treatment for patients with metastatic RCC has evolved over the past 2 decades, from immunotherapies, such as IFN-alpha, IL-2, and nivolumab, to targeted agents, such as the TKIs and mTOR inhibitors, providing clinicians a myriad of options to consider for their patients. Until a clearer pathway for the treatment of this disease is established, it will be important to keep in mind patient-specific factors, such as tolerability and cost, when choosing which agents to use for the treatment of an individual patient.

Author Disclosure Statement

Dr Davis and Dr Hinkley have no conflicts of interest to report.

References