ARTICLE TITLE: Treatment of Renal Cell Carcinoma: Current Status and Future Directions

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After reading the article “Treatment of Renal Cell Carcinoma: Current Status and Future Directions,” the learner should be able to:

1. Describe the role of cytoreductive nephrectomy and metastatectomy in treatment of metastatic renal cell carcinoma.
2. Review current recommendations and supporting evidence for targeted therapies and immunotherapies in first-line and second-line treatment of metastatic renal cell carcinoma.

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Treatment of Renal Cell Carcinoma: Current Status and Future Directions

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Abstract: Over the past 12 years, medical treatment for renal cell carcinoma (RCC) has transitioned from a nonspecific immune approach (in the cytokine era), to targeted therapy against vascular endothelial growth factor (VEGF), and now to novel immunotherapy agents. Multiple agents—including molecules against vascular endothelial growth factor, platelet-derived growth factor, and related receptors; inhibitors of other targets, such as the mammalian target of rapamycin and the MET and AXL tyrosine-protein kinase receptors; and an immune-checkpoint inhibitor—have been approved based on significant activity in patients with advanced RCC. Despite these advances, important questions remain regarding biomarkers of efficacy, patient selection, and the optimal combination and sequencing of agents. The purpose of this review is to summarize present management and future directions in the treatment of metastatic RCC.

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Keywords: clinical trials, immunotherapy, programmed death 1 (PD-1), renal cell carcinoma, targeted agents, vascular endothelial growth factor (VEGF)

Practical Implications for Continuing Education

> The role of perioperative systemic treatment for localized renal cell carcinoma continues to be under active research. Dose intensity, patient selection and time on treatment may be key factors according to recent completed trials, but the standard of care has not changed yet.

> The recent approvals of nivolumab, cabozantinib, and lenvatinib/everolimus have changed the treatment landscape for refractory renal cell carcinoma. Nonetheless, the optimal treatment sequencing is unknown, and better biomarkers that help individualized treatment choices are still lacking.

> Future treatment strategies for advanced clear-cell renal cell carcinoma include new kinase inhibitors, the use of established drugs for new indications, and the combination regimens with checkpoint inhibitors and targeted therapies.

> Systemic treatment options for nonclear cell renal cell carcinoma remain limited. Immunotherapy is being tested with interesting preliminary results, and personalized treatment based on each tumor’s unique genomic alterations is driving future biomarker-based studies.

Introduction

Kidney cancer is among the 10 most common cancers in both men and women, representing 3.7% of all new cancer cases, and it is estimated that 63,990 people will be diagnosed in 2017 in the United States. Renal cell carcinoma (RCC) is the most common form of kidney cancer and is responsible for up to 85% of cases; it is more frequent in men than in women (ratio, 1.7:1), and most people are older, with an average age of 64 years. Although the 5-year relative survival rates at diagnosis have shown some improvement, the overall prognosis is still poor, particularly for patients who present with high-stage disease.
Over the past 12 years, medical treatment for RCC has transitioned from a nonspecific immune approach (in the cytokine era), to targeted therapy against vascular endothelial growth factor (VEGF), and now to novel immunotherapy agents.3,6 The purposes of this review are to summarize the systemic treatment for localized and metastatic RCC (mRCC), address the current practices and challenges with these novel therapies, and explore the next steps in the management of this disease.

Molecular Pathology of RCC
According to the pathological classification by the International Society of Urological Pathology Vancouver Consensus Statement, RCC includes a heterogeneous group of cancers with different histologic, molecular, and genetic alterations.7 Clear cell, types I and II papillary, and chromophobe are the most common solid RCCs and account for 80% to 85% of all renal tumors.8

Clear cell RCC (ccRCC) is the most common subtype of RCC, occurring in 70% to 75% of cases, and is strongly associated with alterations in the von Hippel-Lindau (VHL) gene.9 This is a 2-hit tumor-suppressor gene in which, typically, the first allele is inactivated through an intragenic mutation, and the second is deleted as part of large deletion.10 In the tumor cell, the inactivation of VHL leads to increased activity of the hypoxia-induced factor (HIF) and ultimately to overexpression of VEGF and platelet-derived growth factor (PDGF).11,12 The HIF activity may also be increased via the mammalian target of rapamycin (mTOR) pathway (Fig. 1).13 Understanding the role of the VHL protein in tumor-cell pathogenesis has contributed to the significant progress made in the medical management of RCC with the development of targeted therapy. Multiple agents against VEGF, PDGF, related receptors and inhibitors of mTOR, and the MET and AXL tyrosine-protein kinase receptors, have been approved based on significant activity in RCC and are described in the sections below. The nonclear cell subtypes account for approximately 25% of the cases and are discussed in more detail below (see Nonclear Cell RCC).

The Role of Systemic Therapy for Localized Disease
Predicting the Risk of Recurrence
Tumor stage (TNM), defined by the anatomic involvement of disease, is recognized as one of the strongest prognostic factors in the clinical outcome of patients with RCC, as described in the eighth edition of the American Joint Commission on Cancer (AJCC) Cancer Staging Manual.14

FIGURE 1. Therapeutic Biologic Pathways for Targeted Therapies in Renal Cell Carcinoma. 4E-BP1, 4E binding protein-1; AKT, protein kinase B; FKBP, forkhead binding protein; elf-4E, eukaryotic initiation factor-4 subunit E; FGF, fibroblast growth factor; HIF, hypoxia-inducible factor; IL-8, interleukin-8; mLST8, mammalian lethal with SEC13 protein B; mTORC1, mammalian target of rapamycin complex 1; P70S6K, P70S6 kinase; PDGFR, platelet-derived growth factor receptor; P, phosphorous; PI3K, phosphoinositide 3-kinase; Pro, proline; PTEN, phosphatase and tensin homolog; Ub, ubiquitin; VEGFR, vascular endothelial growth factor receptor; VHL, von Hippel-Lindau. Source: This figure has been reproduced with permission from David Schumick, Cleveland Clinic Foundation.
Indeed, patients with stage I disease have a 5-year recurrence-free survival of >92%, whereas the risk of recurrence for those with stage II and III disease is up to 40%.15,16

Because surgical resection of RCC remains curative for a proportion of patients with localized disease, several models have been developed to predict outcomes after surgery. One score, the SSIGN, was developed at the Mayo Clinic (also known as the Leibovich score) and classified patients with ccRCC into low-risk, intermediate-risk, or high-risk categories, according to stage, tumor size, nuclear grade, and the presence of tumor necrosis.17,18 This score has been externally validated in different institutions, and the prognostic accuracy (Harrel concordance)19 index ranged between 0.78 and 0.86.20,21

The University of California Los Angeles Integrated Staging System (UISS) defines low-risk, intermediate-risk, and high-risk prognostic groups based on stage, Fuhrman nuclear grade, and Eastern Cooperative Oncology Group performance status. The UISS score has been developed for the classification of patients with both localized and advanced disease,22,23 with an accuracy index ranging between 0.79 and 0.86.24 These prognostic scores are established and continued to be used for balancing and comparing groups of patients in clinical studies, but they are less useful for individualized prediction of risk, because there is no approved therapy based on any of these scores to date.

With the development of multigene assays in cancer, analyses of the association between different gene signatures and clinical outcomes have been explored to provide further information beyond traditional clinicopathologic parameters. Successful examples include the validated 16-gene assay—using RNA obtained from reverse transcription—to predict recurrence after surgery in high-risk patients25,26; and the 4-gene signature to predict prognosis in ccRCC.27 The incorporation of gene-based prognostic tools into routine clinical practice, however, awaits further study.

**Adjuvant Studies**

Historically, the choice of therapies tested in an adjuvant setting has been guided by existing evidence of efficacy against metastatic disease.15 In the pretargeted therapy era, cytokine-based immunotherapy with interferon-α (IFN-α) and interleukin-2 (IL-2), either alone or in combination, were the standard of care for the treatment of advanced RCC, despite their known significant toxicity and modest overall response rates (ORRs) (range, 5%-31%).6 Several adjuvant trials were conducted with IFN-α28-32 and IL-2,31-34 as well as with other immune therapies, such as autologous irradiated tumor cells,35,36 bacillus Calmette-Guerin,35,36 and tumor-derived heat-shock protein (gp96),37 but all failed to improve disease-free survival (DFS) or overall survival (OS). In addition, although the phase 3 study investigating the autologous renal tumor cell vaccine in patients with pathologic T2 or greater (≥pT2) N0-N3 M0 RCC met the primary endpoint of PFS, it failed to show a survival benefit at 5 and 10 years.38,39 Plus, that study had some methodological problems, and the development of this immunotherapy agent was ultimately discontinued.40

Other classes of agents, including hormone therapies (tamoxifen,31 primostat,35 medroxyprogesterone,41 chemotherapy (5-fluorouracil,31 doxorubicin in combination with gemcitabine,42 and radiotherapy,43 also failed to provide any clinical benefit.

**Any Role for Adjuvant Therapy?**

There are currently 7 large, multicenter, placebo-controlled, phase 3 clinical trials that explore the role of adjuvant systemic treatment in RCC (Table 1).15,44-51 ARISER was the first study to investigate the addition of a targeted agent, girentuximab, a chimeric immunoglobulin G1 (IgG1+) monoclonal antibody to carbonic anhydrase IX, in the adjuvant setting.45,52 This phase 3 study randomized 864 patients with ≥pT1b N0 M0 ccRCC who underwent partial or radical nephrectomy to receive either weekly girentuximab or placebo for a total of 24 weeks (Table 1). Compared with patients randomized to the placebo arm, those who received girentuximab had no significant advantage in DFS (hazard ratio [HR], 0.97) or OS (HR, 0.99). Similar to prior agents, girentuximab did not meet the primary endpoint of DFS, and further investigation of this agent was discontinued.

Since then, the scientific community has been waiting for results from the multiple trials with antiangiogenic therapies and mTOR inhibitors, known active drugs in the advanced setting (Table 2).78-82 The phase 3 study ASSURE was the first study to be reported.46 In total, 1943 patients who had intermediate-risk or high-risk (≥pT1b) tumors with any histology (80% clear cell) were randomized to receive 1 year of sorafenib (400 mg twice per day), sunitinib 50 mg daily (4-weeks-on/2-weeks-off [4/2] schedule), or placebo.

Importantly, the starting dose of sorafenib and sunitinib had to be reduced after 45% and 44% of patients discontinued treatment because of adverse events (AEs), respectively. Despite the dose reduction, 62% of patients who received sorafenib and 71% of those who received sunitinib reported grade ≥3 AEs, most frequently hypertension (17% and 16%, respectively), hand-foot syndrome (33% and 15%, respectively), and rash (15% and 2%, respectively); a total of 5 toxic deaths were observed, all in the tyrosine kinase inhibitor (TKI) arms. This primary analysis of ASSURE showed no significant differences in median DFS, which
was 5.8 years for sunitinib (HR, 1.02), 6.1 years for sorafenib (HR, 0.97), and 6.6 years for placebo. In a recent ad-hoc analysis of the high-risk population in the ASSURE trial (n = 1069 patients), defined as those with pT3, pT4, or lymph node-positive disease, there was no difference in the 5-year survival rate (HR, 0.94 for sunitinib vs placebo; HR, 0.90 for sorafenib vs placebo), and the dose intensity of therapy did not affect outcomes.53

After the disappointing results from ASSURE, the second completed trial with sunitinib (S-TRAC) was unveiled.48 That study randomized 615 patients with high-risk ccRCC to receive either 1 year of sunitinib 50 mg daily or placebo on a 4/2 schedule. Similar to the prior study, dose reductions or interruptions because of AEs were allowed and occurred in 34.3% and 46.4% of patients in the sunitinib arm, respectively, compared with 2% and 13.2% of those in the placebo arm, respectively. Importantly, however, all patients started at the 50-mg dose of sunitinib. The most common grade 3 and 4 AEs were hand-foot syndrome (16%), hypertension (7.8%), and neutropenia (8.5%). Furthermore, 44.4% of patients in the sunitinib group did not complete therapy compared with 30.6% of those in the placebo group. The efficacy analysis showed a significant difference in median DFS of approximately 1.2 years: the median DFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group (HR, 0.76; 95% confidence interval [CI], 0.59-0.98; P = .03). Of note, DFS was not prolonged on the basis of investigator review. At the time of publication, the median OS was not reached in either group, and the HR for the comparison was 1.01.

Results were recently presented from a different phase 3 study (PROTECT) investigating pazopanib in patients with locally advanced RCC postnephrectomy.47 In total, 1538 patients were randomly assigned to receive either pazopanib or placebo for 1 year. The starting dose was 800 mg and, after treatment of 403 patients, was lowered to 600 mg to improve tolerability; and the primary endpoint was changed to DFS with pazopanib (600 mg). The primary analysis showed no difference in DFS with pazopanib 600 mg (HR, 0.86; 95% CI, 0.70-1.06; P = .16). Interestingly, there were differences in DFS of 31% and 20% in favor of patients who received pazopanib 800 mg (HR, 0.69; 95% CI, 0.51-0.94) and in all patients who received pazopanib (HR, 0.80; 95% CI, 0.68-0.95), respectively, which were secondary endpoints of the study. A secondary analysis of pazopanib trough concentrations and DFS also demonstrated a positive association between higher drug concentration and longer DFS (HR, 0.58; 95% CI, 0.42-0.82; P = .002).54 The details of the safety profiles in the 600-mg and 800-mg pazopanib groups have not been published in detail yet but were similar, and the most common AE leading to treatment discontinuation was liver function test elevation.

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**TABLE 1. Randomized Phase 3 Trials Evaluating the Benefit of Adjuvant Targeted Therapies in Renal Cell Carcinoma**

| ACRONYM | REFERENCE | STATUS | INTERVENTION | HISTOLOGY | ENDPOINTS | SAMPLE SIZE | ELIGIBILITY | HISTOLOGY | INTERVENTION | HISTOLOGY | ENDPOINTS | MEDIAN, Y | TEST | PLACEBO | HR (95% CI) |
|---------|-----------|--------|--------------|-----------|-----------|-------------|-------------|-----------|--------------|-----------|-----------|-----------|-------|---------|-------------|
| ARISER  | Belldegrun 2013 | Completed | Girentuximab (6 mo) | Clear cell | DFS, OS | 864 | pT1b grade 3-4, NxM0 | Any | DFS | Clear cell | NA | 6.95 | NR | 0.97 |
| ASSURE | Haas 2016 | Completed | Sorafenib or sunitinib (1 y) | Any | DFS | 1943 | pT1b grade 3-4, NxM0 | Any | DFS (PAZ 600) | Clear cell | NA | 6.1 vs 5.8 | 0.97 vs 1.02 |
| PROTECT | Motzer 2017 | Completed | Pazopanib (1 y) | Clear cell | DFS (PAZ 600) | 1538 | pT2N0M0 or pTxN1M0 | Clear cell | DFS | Clear cell | NA | 615 | 5.6 | 0.76 |
| S-TRAC | Ravaud 2016 | Completed | Sunitinib (1 y) | Clear cell | DFS | 615 | pT2N0M0 or pT1bM0 | Clear cell | DFS | Clear cell | NA | 120 | 6.8 | 0.97 |
| SORCE | Medical Research Council 2007 | Completed | Sorafenib (1 y) or (3 y) | Clear cell | DFS | 1420 | pT1b grade 3-4, NxM0 | Any | DFS | Clear cell | NA | 502 | 6.9 | 0.76 |
| ATLAS | SFJ Pharmaceuticals, Inc 2012 | Active, not recruiting | Axitinib (3 y) | Clear cell | DFS | 592 | pT2N0M0 or pT1bM0 | Clear cell | DFS | Clear cell | NA | 1218 | 6.5 | 0.97 |
| EVEREST | Southwest Oncology Group 2010 | Active, not recruiting | Everolimus (1 y) | Clear cell | DFS | 1218 | pT1b grade 3-4, NxM0 | Clear cell | DFS | Clear cell | NA | 1218 | 6.5 | 0.76 |
What can we learn from these data? First, S-TRAC is a proof of concept that adjuvant treatment with an effective anti-RCC drug may prolong DFS, at least for patients with clear cell histology and a higher risk for recurrence, when compared with the patient population enrolled in the ASSURE study. Second, the dose intensity of drugs may play a role in the adjuvant setting, as evidenced by the risk reduction in DFS observed in the pazopanib 800-mg group, and not in the pazopanib 600-mg group, and confirmed in the secondary analysis on the correlation between pazopanib concentration and DFS (HR, 0.58; P < .002).54 Furthermore, while the median duration on treatment with sunitinib was similar in both S-TRAC and ASSURE (49.6 vs 48 weeks, respectively), the sunitinib relative median dose intensity in S-TRAC was 88.4% (median daily dose, 1285 mg) compared with 71.4% (median daily dose, 1000 mg) in the ASSURE study, emphasizing the importance of dose intensity in the adjuvant setting.46,48

Third, the benefit must be well balanced with tolerability. In both studies, the treatment duration of 1 year exposed patients to potential risk; and, in S-TRAC, the time of DFS gained was only slightly greater than the time spent on treatment. Finally, it is still unclear whether prolonging DFS has any real impact on OS. The results from the SORCE,52 ATLAS,53 and EVEREST54 trials will help us better define the role of targeted therapy in the adjuvant setting. The patients included in these trials are being treated with sorafenib, axitinib, or everolimus for 3 years, the ATLAS study includes only those who have tumors with clear-cell histology subtype, whereas the EVEREST and SORCE studies include those who have tumors with any histology.

With the advent of novel immunotherapy agents, the future of RCC adjuvant therapy may likely include these strategies in the equation. On the basis of data from the advanced setting with nivolumab (CheckMate-025),55 programmed death 1 (PD-1)/PD-1 ligand 1 (PD-L1) inhibitors may induce durable responses with a better toxicity profile compared with standard-of-care drugs (see “What is Beyond VEGF Pathway Inhibition?,” below). The adjuvant phase 3 trial (IMmotion010; National Clinical Trials [NCT] identifier NCT03024996)56 exploring 1 year of avelozolimab, a checkpoint inhibitor of PD-L1, was recently launched and is actively recruiting patients. Other clinical trials exploring PD-1 inhibitors nivolumab (NCT02575222, NCT03055013) and pembrolizumab (NCT03142334, NCT02212730) and the combination of different immunotherapy agents (NCT02762006, NCT03138512) are also being studied in the neoadjuvant and perinephrectomy setting.

### Systemic Therapy for Metastatic Disease

#### Clear Cell RCC

**Contemporary prognostic models**

Approximately 30% of patients present with de-novo, metastatic disease; and one-third of patients who are treated for localized RCC with curative intent have a relapse in distant sites.3,57 Of note, the latency from diagnosis to metastasis in kidney cancer is relatively variable, with some late recurrences.

In mRCC, several clinical factors have been associated with a reduced OS and integrated into different risk prognostic models.58 These models categorize patients according to expected outcomes and help in patient counseling, risk stratification, and therapy selection.5

The group at Memorial Sloan Kettering Cancer Center (MSKCC)59 developed one of the most used prognostic models used in the era of traditional immunotherapy studies, including: performance status (<80%), high levels of serum lactate dehydrogenase (>1.5 times the upper limit of normal), low hemoglobin level (below the lower limit of normal), high level of corrected serum calcium (>10 mg/dL), and shorter time from initial RCC diagnosis to the start of systemic therapy (<1 year). Patients were stratified into 3 risk categories according to the number of risk factors: favorable (0 factors), intermediate (1-2 factors), and

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**TABLE 2. Summary of Randomized Trials Evaluating the Benefit of Targeted Therapies in Front-Line Renal Cell Carcinoma**

| TEST AGENT       | REFERENCE          | COMPARATOR | SAMPLE SIZE | PFS MEDIAN, MO | COMPARATOR | HR (95% CI) | OS MEDIAN, MO | COMPARATOR | HR (95% CI) |
|------------------|--------------------|------------|-------------|----------------|------------|------------|---------------|------------|------------|
| Sunitinib        | Motzer 200778      | IFN-α      | 750         | 11.0           | 5.0        | 0.54       | 26.4          | 21.8       | 0.82       |
| Bevacizumab + IFN-α | Escudier 200779 | IFN-α + placebo | 649       | 10.2           | 5.4        | 0.63       | 23.3          | 21.3       | 0.34       |
| Pazopanib        | Stemberg 201080    | Placebo    | 435         | 9.2            | 4.2        | 0.46       | 22.9          | 20.5       | 0.91       |
| Pazopanib        | Motzer 201381      | Sunitinib  | 110         | 8.4            | 9.5        | 1.05       | 28.4          | 29.3       | 0.91       |
| Temsirolimus     | Hudes 200752       | IFN-α      | 626         | 5.5            | 3.1        | NR         | 10.9          | 7.3        | 0.73       |

HR, hazard ratio; IFN-α, interferon-α; NR, not reported; OS, overall survival; PFS, progression-free survival.
Role of Surgery in the Advanced Setting
Cytoreductive nephrectomy

The importance of nephrectomy in metastatic disease has been demonstrated in historical series, including 2 randomized trials that demonstrated an OS advantage, conducted in the cytokine era. In the Southwest Oncology Group trial of 246 patients with mRCC of any histology who received treatment with IFN-α, the addition of cytoreductive nephrectomy (CN) improved OS from 8 to 11 months. Similarly, a smaller European study reported by Mickisch et al on behalf of the European Organization for Research and Treatment of Cancer (EORTC) assigned 83 patients with mRCC to either combined CN and IFN or IFN alone. In that study, the addition of CN more than doubled the median OS from 7 to 17 months in favor of the group of patients allocated to the combination strategy.

Conversely, in the contemporary era of targeted therapy, there has been a decreasing utilization rate of CN, probably because of the absence of contemporary randomized studies. Of note, there are several retrospective analyses available; and a recent systematic review and meta-analysis, including 12 articles with almost 40,000 patients, has identified an OS benefit (HR, 0.46; 95% CI, 0.32-0.64) for patients who undergo CN. At the same time, some patients do poorly after surgery, and some factors like poor-risk group (MSKCC criteria), poor performance status (<80%), liver metastasis, or retroperitoneal or supradiaphragmatic adenopathies have been associated with poor outcomes and might help with patient selection.

To address the limitations associated with the retrospective nature of contemporary data, 2 ongoing phase 3 clinical trials are addressing the role and timing of CN. The CAR-MENA trial uses a design similar to that of the Southwest Oncology Group and EORTC studies to randomize patients with RCC of any histology to either sunitinib as first-line therapy or CN followed by sunitinib. The second phase 3 study (SURTIME), also being conducted by the EORTC, investigates the timing of CN by randomizing patients with ccRCC to undergo either immediate CN followed by sunitinib or delayed surgery after sunitinib.

Currently, ideal candidates for CN include patients with good performance status, no symptoms or mild symptoms from the disease, and low metastatic burden outside the primary tumor, for which surgery can offer a significant reduction of tumor burden.

Surgical resection of metastatic disease

In selected patients with mRCC and indolent disease, surgical resection of metastatic sites (metastasectomy) has been shown to be feasible and effective. In the pre-TKI era, a retrospective analysis of 278 patients with mRCC reported that the 5-year OS rate was higher in patients who...
underwent curative-intent metastasectomy (44%) compared with those who underwent noncurative metastasectomy (14%) and those who received nonsurgical treatment (11%). Metastases were most commonly resected from the lung, brain, bone, and soft tissue. The predictors of prolonged survival at 5 years included a DFS interval from nephrectomy to the detection of metastatic disease greater than 1 year (55% vs 9%; \( P < .0001 \)), with a single site of disease (54% vs 29%; \( P < .001 \)), and age younger than 60 years (49% vs 35%; \( P < .05 \)).

A contemporary study also evaluated the impact of metastasectomy in 887 patients who underwent nephrectomy for RCC and who subsequently developed multiple metastases.77 The most common sites were the lungs (52%) and bones (12%), and approximately two-thirds (75%) of the patients had 3 or more metastatic sites. Fourteen percent of patients (n = 125) underwent complete surgical resection of all metastatic lesions. With a median follow-up of 3.1 years, complete metastasectomy was associated with prolongation of cancer-specific OS (4.8 vs 1.3 years; \( P < .001 \)). Of note, complete resection remained predictive of prolonged survival regardless of the number of metastatic lesions (\( P < .001 \)) and for patients with synchronous (\( P < .001 \)) and asynchronous (\( P = .002 \)) disease. While surgical management needs further validation in prospective studies, the results from these studies and our reports make this strategy a consideration for selected patients.

First-line options

After the discovery of \( VHL \) mutations and the activation of VEGF, PDGF, and other genes involved in angiogenesis, cell growth, and survival, several targeted therapies have successfully been developed and have improved the clinical outcomes of patients with mRCC (Fig. 1).3 The multitypered, small-molecule TKI drugs against the VEGF receptors (VEGFRs), PDGF receptors (PDGFRs), and other kinases (sunitinib and pazopanib); the monoclonal antibody that inhibits VEGF (bevacizumab); and the mTOR inhibitor temsirolimus for the poor-risk group are the recommended options for patients who have previously untreated mRCC with predominantly clear-cell histology, with Level I evidence (Table 2). All therapies were compared with the standard of care of the time (IFN-\( \alpha \)),78-80 except pazopanib, which, after having shown superiority to placebo, was compared with sunitinib in 2 phase 3 studies, COMPARZ and PRISCES.81-83 Although, in the noninferiority trial COMPARZ, pazopanib was shown to have similar efficacy to sunitinib, and quality-of-life (QoL) data favored pazopanib; the PRISCES study demonstrated a significant patient preference for pazopanib over sunitinib, with QoL and safety identified as significant influencing factors.

With the aforementioned agents, the median PFS improved from 5.5 to 11 months, and the median OS improved from 23 to 26 months, in favor of the experimental arms.78,79,82 Both outcomes were shorter with temsirolimus compared with TKIs, which was investigated mainly in the poor-risk population with expected worse parameters.82

Despite different mechanisms of action, the toxicity profile (any grade 3 or 4) of these therapies shared some similarities, with fatigue/asthenia (grade 3, 33%-65%; grade 4, 7%-10%), anorexia (grade 3, 22%-37%; grade 4, 2%-3%), nausea (grade 3, 26%-52%; grade 4, 1%-3%), and diarrhea (grade 3, 20%-63%; grade 4, 1%-5%) among the most frequent AEs reported. Medullary toxicities, including anemia (grade 3, 31%-71%; grade 4, 2%-4%), leukopenia (grade 3, 37%-78%; grade 4, 1%-5%), and thrombocytopenia (grade 3, 41%-65%; grade 4, 4%-8%) were common with sunitinib/pazopanib,78,80,81 whereas bleeding (grade 3, 33%; grade 4, 3%) was common with bevacizumab,79 and rash (grade 3, 47%; grade 4, 4%) and dyspnea (grade 3, 28%; grade 4, 9%) were frequent with temsirolimus.82 Hypertension (grade 3, 24%-40%; grade 4, 4%-9%) was frequent with all VEGF inhibitors.

Two novel TKIs, axitinib and tivozanib, have also been tested in the front-line setting but failed to improve clinical outcomes compared with the standard-of-care sorafenib in 2 large, multicenter, randomized, phase 3 trials.84,85 In the first phase 3 study, 288 patients with treatment-naive, metastatic ccRCC were randomly assigned (2:1) to receive axitinib or sorafenib, and the primary endpoint was PFS, which was assessed by an independent review. The results of the trial were presented at first data cutoff; axitinib versus sorafenib yielded numerically (but not statistically) longer median PFS (10.1 vs 6.5 months, respectively; HR, 0.77; 95% CI, 0.56 [one-sided]; \( P = .038 \)) and higher response rates (32% vs 15%, respectively; \( P < .001 \)).84 The updated OS results were published more recently and showed no difference between the 2 groups (27.1 vs 23.3 months, respectively; HR, 0.99; 95% CI, 0.73 [one-sided]; \( P = .49 \)).86

The third-generation tivozanib has also been compared with sorafenib in 517 patients with treatment-naive, metastatic ccRCC in a phase 3 study.85 The primary endpoint of this trial was PFS, as assessed by independent review. At the data cutoff, patients assigned to tivozanib had prolonged PFS compared with those assigned to sorafenib (11.9 vs 9.1 months; HR, 0.80; 95% CI, 0.63-0.99; \( P = .04 \)). However, the final OS showed a trend toward longer survival on the sorafenib arm than on the tivozanib arm (29.3 vs 28.8 months; HR, 1.24; 95% CI, 0.95-1.62; \( P = .105 \)). On the basis of these results, the agent did not get approved by the US Food and Drug Administration (FDA), and there is a pending, tentative approval of tivozanib in the European region.

Alternative regimen and scheduling of sunitinib

Although the antiangiogenic TKIs can produce objective responses and extend PFS and OS in patients with advanced
RCC, they are not curative, thus their benefits must be weighed against the burden of treatment. To balance the clinical benefit with the toxicity of these agents, alternative ways to deliver these drugs have also been evaluated. A retrospective analysis (RAINBOW) reported by Bracarda et al. evaluated 208 consecutive patients with previously untreated mRCC who started sunitinib on a 4/2 schedule, switched to a 2-weeks-on/1-week-off (2/1) schedule for toxicity, and used a second group of 211 patients who were treated on the 4/2 schedule for external control. In the group that changed from the 4/2 to the 2/1 schedule, grade 3 and 4 AEs were significantly reduced from 45.7% to 8.2% (P < .001) after switching to the 2/1, including fatigue, hypertension, hand-foot syndrome, and thrombocytopenia. Currently, multiple phase 2 studies are prospectively investigating a sunitinib 2/1 schedule.88,89

The option of treatment breaks has also been explored with sunitinib in a phase 2 study by Ornstein et al. In total, 37 patients with previously untreated mRCC received 4 cycles of sunitinib (50 mg on a 4/2 regimen). Patients who had a reduction of 10% or more in tumor burden were eligible to hold sunitinib until an increase of 10% or more in tumor burden was observed; they resumed sunitinib for 2 cycles if they had an increase of 10% or more in tumor burden and held it again if they had another reduction in tumor burden of 10% or more. The primary endpoint was feasibility, which was defined as the proportion of eligible patients who underwent intermittent therapy. Of 37 patients enrolled, 20 were eligible for intermittent therapy, and 100% entered the intermittent phase, with an ORR of 46% after 4 cycles of therapy. Most patients exhibited a stable, saw tooth pattern, stayed off sunitinib for a median of 8.3 weeks, and had an observed median PFS and OS of 22.4 months (95% CI, 5.4-37.6 months) and 34.8 months (95% CI, 14.8 months to not applicable), respectively.

Of note, a European phase 2/3 clinical trial is randomizing patients to a conventional 4/2 regimen sunitinib arm and a treatment arm of sunitinib with preplanned treatment breaks; it aims to compare the efficacy and tolerability of sunitinib between the 2 strategies.91 Thus emerging data support the consideration of alternate strategies to administer sunitinib that may preserve efficacy and reduce toxicity. Such strategies likely apply to other targeted therapies as well.

**What is beyond VEGF pathway inhibition?**

Cytokine-based immunotherapies like IFN-α and IL-2 have proven to be an effective therapeutic modality for a small subset of patients with mRCC. High-dose IL-2 therapy was approved by the FDA based on the pooled results from 7 phase 2 studies conducted in multiple institutions.92 Patients from these studies were continually monitored for toxicity and clinical outcomes; the most recent ORR was 15%, and complete responses were observed in 7% of patients.93 Unfortunately, a majority of patients fails to achieve a long-term disease control, and novel immunotherapy strategies are being developed with interesting clinical data among tumors with higher immunogenicity, including RCC (Table 3).82,94-102

One of these strategies included IMA901, which is the first therapeutic vaccine consisting of multiple tumor-associated peptides (9 different class I human leucocyte antigens [HLA] [HLA-A*02] and 1 class II HLA), which were confirmed as naturally present in human cancer tissue.103 IMA901 was studied in a multicenter, randomized, phase 2 study (IMA901-202), in combination with granulocyte-macrophage–colony-stimulating factor with or without cyclophosphamide, in 68 patients with refractory mRCC. The primary endpoint of the study was defined as the disease control rate after 26 weeks of treatment, and secondary endpoints included PFS and OS. Analysis of the primary efficacy variable showed a disease control rate of 24.6% (95% CI, 14.5%-37.3%) at 6 months, and the median PFS was 3.3 months. Importantly, although the median OS was 19.8 months for all second-line patients who received treatment with cytokines, the time of data cutoff, the median OS was not reached (>26 months) for patients who received cyclophosphamide.103 The median OS obtained with IMA901 compared favorably to that obtained in studies with sunitinib104 and sorafenib,105 and the decision was to move forward with a confirmatory trial (IMPRINT).95 That phase 3 study randomized 339 HLA-A*02-positive patients (of 1171 screened patients who had metastatic ccRCC) to receive either sunitinib plus IMA901 (with granulocyte-macrophage–colony-stimulating factor and cyclophosphamide) or sunitinib alone. With a median follow-up of 33.3 months, the vaccine therapy did not improve OS (primary endpoint) when added to sunitinib as first-line treatment (HR, 1.34; 95% CI, 0.96-1.86).

The understanding of the importance of dendritic cells in stimulating cell-mediated immunity by the efficient presentation of antigens to both CD4-positive and CD8-positive lymphocytes led to the development of rocapuldencel-T (AGS-003), an autologous product prepared from matured, monocyte-derived dendritic cells transfected with amplified tumor RNA plus synthetic CD40 ligand RNA.22 In a single-arm, open-label, phase 2 trial, AGS-003 was studied in combination with sunitinib in 21 patients who had intermediate-risk or poor-risk RCC.106 The primary endpoint was the complete response rate, and secondary endpoints included OS, PFS, and safety. Approximately 62% of patients experienced a clinical benefit (9 had partial responses, and 4 had stable disease), but there were no complete responses, and enrollment was terminated early. Nonetheless, the median PFS from registration was 11.2 months...
(95% CI, 6.0–19.4 months), the median OS was 30.2 months (95% CI, 9.4–57.1 months), and no significant AEs attributed to AGS-003 were observed.

These promising OS results were approximately 2 times longer than those reported in other studies using front-line TKIs, and the decision was to continue the development of this agent. A confirmatory, phase 3 study (ADAPT) randomized patients with newly diagnosed, advanced RCC to receive the combination of AGS-003 plus standard therapy versus standard therapy alone on a 2:1 basis. The study completed accrual of 462 patients with the goal of collecting 290 events for the primary endpoint of OS; and the standard-of-care agent primarily consisted of sunitinib. Recently, the Independent Data Monitoring Committee for the ADAPT trial recommended halting the study after a futility analysis, and the publication of this negative study is pending.96

Another immunotherapy strategy is to inhibit the interaction between immune cells and tumor cells, thus inhibiting immune tolerance. The receptors involved in this interaction include cytotoxic T-lymphocyte–associated protein-4 (CTLA-4), PD-1 receptors expressed in activated T cells, and PD-L1 and PD-L2 receptors, which are expressed on immune cells and tumor cells (Fig. 2).107,108

Because nivolumab, a fully human monoclonal IgG4 antibody specific for PD-1, has demonstrated a survival benefit in patients with mRCC (see “Second-line options and beyond,” below), several other checkpoint inhibitors are being tested as single agents (such as T-cell agonists, T regulatory antagonists, and vaccines) or combined with other therapies.55 Interestingly, there are preclinical data suggesting synergy between angiogenesis inhibition and immune system activation as well as different ways of stimulating the immune system.94,109-112

After the publication of data from early trials with promising ORRs (range, 40%-55%) and manageable AEs, several large phase 3 trials are being conducted in the front-line setting (Table 3).

In the next 3 years, we will know much more about the synergy between different agents with specific mechanisms of action, when the results from the clinical studies with CTLA-4 (ipilimumab), PD-1 inhibitors (nivolumab, pembrolizumab), and PD-L1 inhibitor (atezolizumab, avelumab) with antiangiogenic drugs (lenvatinib, axitinib, sunitinib, and bevacizumab) will be presented (Table 3).96-102 In addition, a phase 1 trial investigating the triple regimen of cabozantinib with ipilimumab and nivolumab (NCT02496208) is ongoing, and a phase 3 trial studying the combination of epacadostat (a potent oral inhibitor of indoleamine 2,3-dioxygenase) with pembrolizumab (NCT pending) is being planned to launch later this year.

Second-line options and beyond

Until 2015, recommendations for second-line treatment of advanced RCC after prior treatment with a TKI were based on 2 phase 3 trials, with everolimus (RECORD-1, 2008) and axitinib (AXIS, 2011) (Table 4).55,116-123

RECORD-1 was a randomized, placebo-controlled, phase 3 study investigating the efficacy of everolimus, an oral mTOR inhibitor, or placebo in 410 patients who had advanced RCC with a clear-cell component and were refractory to antiangiogenic therapy. Although one prior line of VEGFR-directed treatment was required (sunitinib, 46%; sorafenib, 28%), approximately 26% of patients had received both sunitinib and sorafenib. The median PFS was 4.0 months in the everolimus group compared with 1.9 months in the placebo group (HR, 0.30; 95% CI, 0.22-0.40), and the confirmed ORR was 1% in patients who received everolimus and zero in the placebo group. In the updated analysis, the median OS was 14.8 months for patients allocated to everolimus and 14.4 months for those allocated to placebo (HR, 0.87; P = .162).117 The proportion of significant AEs was low, and the most common events were stomatitis, rash, fatigue/asthenia, and diarrhea. In total, 13% of patients who received everolimus discontinued treatment for AEs.

Axitinib is a second-generation oral inhibitor of VEGFR with 50 to 450 times greater affinity than that of the first class of VEGF inhibitors. In the AXIS trial, axitinib was...
compared with sorafenib as second-line treatment in 723 patients with metastatic ccRCC.\textsuperscript{118} More than one-half of patients (54%) had received sunitinib, and one-third had received cytokines, before enrollment. The median PFS was 6.7 months for the axitinib group and 4.7 months for the sorafenib group (HR, 0.67; 95% CI, 0.54-0.81), and the ORR was 19.4% versus 9.4% ($P < .001$), in favor of axitinib.

Interestingly, the preplanned subgroup analysis showed a significant superiority of axitinib over sorafenib both in the subgroup that received previous sunitinib (HR, 0.74; 95% CI, 0.57-0.96) and in the subgroup that received previous cytokine treatment (HR, 0.46; 95% CI, 0.32-0.67), and the difference was greater for the cytokine subgroup. The updated results showed no difference in OS between the 2 groups, and treatment-induced hypertension was identified as a favorable prognostic factor for survival in patients treated with axitinib (20.7 vs 12.9 months; $P = .012$) and sorafenib (20.2 vs 14.8 months; $P = .002$).\textsuperscript{124} In this analysis, reported AEs were those generally expected for this class of agents, with hypertension (40%), nausea (32%), and

![FIGURE 2. Mechanism of Action of Immunotherapy Modalities. ADC, antibody-drug conjugate; BiTE, bispecific T-cell engager antibody; CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; mAb, monoclonal antibody; MHC, major histocompatibility complex; PD1, programmed cell death 1 ligand 1; TCR, T-cell receptor. Source: Reproduced and modified with permission from Macmillan Publishers Ltd: Batlevi CL, Maatsuki E, Brentjens RJ, Younes A. Novel immunotherapies in lymphoid malignancies. Nat Rev Clin Oncol. 2016;13:25-40.108](image)

### TABLE 4. Summary of Approved Drugs for Refractory, Advanced, Clear-Cell Renal Cell Carcinoma

| DRUG               | REFERENCE                  | COMPARATOR   | SAMPLE SIZE | RISK GROUPS                  | PFS, MO | OS, MO | ORR, % | TOXICITY GRADE > 3, % |
|--------------------|----------------------------|--------------|-------------|------------------------------|---------|--------|--------|-----------------------|
| Everolimus         | Motzer 2008,\textsuperscript{116} 2010\textsuperscript{117} | Placebo      | 410         | 56% Int/15% poor (MSKCC)     | 4.0     | 14.8   | 1      | 45                    |
| Axitinib           | Rini 2011\textsuperscript{118} | Sorafenib    | 723         | 37% Int/33% poor (MSKCC)     | 6.7     | 20.3   | 19.4   | 67                    |
| Cabozantinib       | Choueiri 2015\textsuperscript{119} 2016\textsuperscript{120} | Everolimus   | 658         | 45% Int/14% poor (MSKCC)     | 7.4     | 21.4   | 17     | 68                    |
| Nivolumab          | Motzer 2015\textsuperscript{121} | Everolimus   | 821         | 49% Int/16% poor (MSKCC)     | 4.6     | 25     | 25     | 19                    |
| Lenvatinib/everolimus | Motzer 2016,\textsuperscript{121,122} | Lenvatinib alone and everolimus alone | 153 | 64% Int/20% poor (IMDC) | 12.8 | 25.5 | 35 | 71 |

Int, intermediate-risk group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; poor, poor-risk group.
dysphonia (31%) occurring more frequently in patients allocated to axitinib; whereas skin rash (32%), hand-foot syndrome (27%), and alopecia (32%) were more commonly observed with sorafenib therapy.

Acknowledging data that suggest different optimal axitinib exposure among patients with mRCC, individualized dose titration of axitinib has been investigated. In a multicenter phase 2 study, 213 patients with treatment-naive mRCC were enrolled, of whom 112 were randomly assigned either to the individualized axitinib dose titration group or to the placebo titration group. With a median follow-up of 26.5 months, higher ORRs were observed with dose titration compared with standard axitinib dosing (54% vs 34%, one-sided \( P = .019 \)), validating this concept of dose intensity.\(^{125,126} \) This strategy is being assessed with axitinib in patients with mRCC who are refractory to checkpoint inhibitors.\(^{127} \)

In November 2016, the treatment landscape for refractory disease dramatically changed with the results of 3 randomized clinical trials, leading to the approval of nivolumab\(^{55} \) and cabozantinib\(^{119} \) and reports on the combination of lenvatinib/everolimus\(^{121} \) (len/eve) (Table 4). While all studies enrolled patients with ccRCC and used everolimus as the standard comparator arm, there were important differences among the investigational drugs that deserve further detail.

On the basis of data showing an upregulation of MET and AXL after chronic treatment with VEGFR inhibitor,\(^{128} \) cabozantinib, a TKI of VEGFRs, MET, and AXL, was tested in a phase 1 study in heavily pretreated patients with mRCC.\(^{129} \) The preliminary results suggested that cabozantinib was able to overcome the mechanism of resistance to antiangiogenic therapies. Thus, a confirmatory, randomized, open-label, phase 3 study (METEOR) of cabozantinib versus everolimus was conducted in 658 patients who had progressive ccRCC after treatment with a VEGFR TKI.\(^{119} \) The median PFS was 7.4 months with cabozantinib and 3.8 months with everolimus (HR, 0.58; 95% CI, 0.45-0.75), and the ORR was 21% versus 5%, respectively (\( P < .001 \)). The final OS analysis was published more recently and was 21.4 months for patients allocated to cabozantinib and 16.5 months for patients who received everolimus (HR, 0.66; 95% CI, 0.53-0.83).\(^{120} \) Dose reductions were almost 3 times more frequent with cabozantinib than with everolimus (60% vs 25%, respectively), but the incidence of grade 3 and 4 AEs was similar for both groups (68% vs 58%, respectively), and approximately 10% of patients in each group discontinued treatment because of side effects. The most common significant AEs observed with cabozantinib were hypertension, diarrhea, and fatigue; whereas, with everolimus, the most common grade 3 and 4 AEs were anemia, fatigue, and hyperglycemia.

Of note, cabozantinib was also tested in the front-line setting in a small, randomized, phase 2 trial comparing it with sunitinib (CABOSUN) in 157 patients who had intermediate-risk/poor-risk (IMDC criteria), previously untreated mRCC.\(^{130} \) A longer PFS (8.2 vs 5.6 months; HR, 0.66; 95% CI, 0.46-0.95) was demonstrated in favor of the cabozantinib arm.

These results are not definitive and deserve further investigation, mainly because of the limitations inherent to phase 2 studies (such as the highly selected population and the rate of false-positive results, whereby PFS is lengthened but OS is not).\(^{131} \) Nevertheless, a hypothesis has been generated that MET and AXL inhibition may provide additional clinical benefit to VEGFR inhibition in RCC.

The importance that checkpoint-inhibition pathways have on immune surveillance has led to the rapid development of agents capable of blocking these targets, as presented before (Figure 2). Nivolumab (a PD-1 inhibitor) was the first checkpoint inhibitor to be investigated in a randomized, phase 3 trial (CheckMate-025) in a comparison with everolimus among 821 patients with advanced RCC who had received one or two prior lines of therapy.\(^{55} \) The study showed a longer OS in favor of nivolumab (HR, 0.73; 95% CI, 0.57-0.93) of about 6 months (25.0 vs 19.6 months; \( P = .002 \)), which was independent of PD-L1 status, and a survival benefit was observed for both the PD-L1 expression < 1% (HR, 0.77; 95% CI, 0.6-0.97) and PD-L1 expression ≥ 1% (HR, 0.79; 95% CI, 0.53-1.17) groups. The ORR was greater with nivolumab than with everolimus (25% vs 5%; \( P < .001 \)), and there was no difference in PFS (4.6 vs 4.4 months, respectively; HR, 0.88; \( P = .11 \)). Because PD-L1 status was not predictive of response to nivolumab, this biomarker is not useful to select patients with ccRCC for this agent. The safety profile was very favorable for the nivolumab group, with less than 20% of significant AEs (grade 3 and 4) compared with 37% in the everolimus group; QoL was also improved with nivolumab.

Lenvatinib is an oral TKI that targets multiple kinases, including VEGFR1, VEGFR2, and VEGFR3; fibroblast growth factor receptor 1 (FGFR1), FGFR2, FGFR3, and FGFR4; PDGFR-\( \alpha \); RET; and KIT.\(^{121} \) To explore the potential synergistic effect with dual inhibition of VEGFR and mTOR pathways in RCC, the combination of len/eve was investigated in a small, phase 2 study in which patients who progressed on a single prior antiangiogenic therapy were allocated at a 1:1:1 ratio to either everolimus 10 mg (\( n = 50 \)), lenvatinib 24 mg (\( n = 52 \)), or the combination len/eve 18 mg/5 mg (\( n = 51 \)). The investigator-assessed median PFS was 5.6 in the everolimus arm compared with 9.0 months in the lenvatinib arm (HR, 0.61; 95% CI, 0.38-0.98), and it was 12.8 months in the len/eve arm (HR, 0.40; 95% CI, 0.24-0.68).\(^{122} \) Although, at the primary data
In a single-arm, phase 2 study, which has been completed, dual oral FGFR and VEGFR inhibitors being investigated have failed 2 or 3 prior systemic regimens; and brivanib, a 7.9 months for first-line everolimus and 10.7 months for PFS with first-line everolimus compared with first-line patients with mRCC. The primary endpoint was to assess the best sequence strategy, and head-to-head comparisons are usually characterized by resistance to systemic regimens may favor sunitinib, as discussed above.

With the advent of multiple active drugs for the treatment of advanced RCC, one would wonder whether the sequence TKI-TKI would be better than the alternative TKI-mTOR inhibitor. The phase 3 trial INTORSECT was one of the first to help answer that question by comparing the efficacy of sorafenib and temsirolimus as second-line therapy in 512 patients with mRCC who progressed on sunitinib. The median PFS in the sorafenib and temsirolimus arms were 3.9 and 4.3 months, respectively; and there was a significant OS difference in favor of sorafenib (HR, 1.31; 95% CI, 1.05-1.63; P = .01). Although sorafenib is not considered an optimal second-line therapy, the study supported the TKI-TKI sequence. After INTORSECT, the studies METEOR, CheckMate-025, and len/eve all showed superiority of the experimental drugs against everolimus; and mTOR inhibition has lost influence in the clinical decision process. Conversely, genomic analysis may help identify those tumors with mutations in the TSC/mTOR genes, which are associated with response to mTOR inhibitors in this setting, according to different retrospective studies.

What is the ideal treatment sequence?

While the selection of FDA-approved therapies is based on randomized clinical trials, there are no good data on the best sequence strategy, and head-to-head comparisons are generally lacking. Still, we may use indirect data from published studies to help us in the clinical decision process. Because the VEGF and mTOR pathways are important targets in RCC, and there was no direct comparison between a TKI and mTOR inhibitor for the first-line setting, a randomized, noninferiority, phase 2 trial (RECORD-3) compared with sorafenib in patients who have failed 2 or 3 prior systemic regimens; and brivanib, a dual oral FGFR and VEGFR inhibitor being investigated in a single-arm, phase 2 study, which has been completed, and results are awaited.

Nonclear Cell RCC

Non-clear cell RCCs (nccRCCs) represent a heterogeneous group of diseases with distinct molecular characteristics, histologies, and clinical outcomes and account for up to 25% of all RCCs. nccRCC includes, but is not limited to, papillary RCC, chromophobe RCC, collecting-duct carcinoma, renal medullary carcinoma, and carcinoma associated with Xp11.2 translocation. Once metastatic, nccRCC histologies are usually characterized by resistance to systemic...
therapies that are active against ccRCC, but the general approach is to use the same options that are used for tumors with clear cell histologies.

The best data are based on 2 randomized, phase 2 clinical trials comparing sunitinib with everolimus (ASPN and ESPN), with a total of 176 patients (55% papillary RCCs). A third randomized, phase 2 study (INTORSECT) included 10% of patients with nccRCC. Overall, PFS was longer for the sunitinib arm in all studies (8.3 vs 5.6 months, 6.1 vs 4.1 month, and 10.7 vs 7.9 months, respectively), and OS was longer for the sunitinib arm in ESPN and INTORSECT (16.2 vs 14.9 months and 32 vs 22 months, respectively). Thus, the default standard of care for nccRCC is VEGF-targeting agents, although clinical trials are strongly encouraged given the generally poor outcomes to date.

The Cancer Genomic Atlas Research Network reported that MET alterations are strongly associated with hereditary papillary type 1 RCC and sporadic papillary RCC. Responses with c-MET–targeted agents, such as foretinib, have been reported, and other trials of Met inhibitors in nccRCC are in progress. Cytotoxic chemotherapy has also been tested and has produced some clinical responses, especially for collecting-duct RCC and renal medullary carcinoma.

Immunotherapy with the checkpoint inhibitor nivolumab has become an established modality in ccRCC. However, clinical trials with nivolumab have excluded patients without a clear-cell component. In a study of 101 patients with nccRCC, PD-L1 was expressed in 10.9% and was more common in the papillary (30%) and translocation (20%) subtypes. Patients who had tumors with PD-L1 expression appeared to have worse outcomes (P = .08), but that may have been because of higher tumor stage and grade. Data from prospective studies investigating the activity of checkpoint inhibitors specifically for this tumor subtype are missing. Rather, in a phase 1a clinical trial investigating the safety of atezolizumab in mRCC, only 1 immune-related response was seen in the subgroup of patients with nccRCC (n = 7; 14%). Recently, the results from a multicenter retrospective study with nivolumab in 23 patients with refractory nccRCC were presented. After a median follow-up of 6.5 months, the median PFS was 4.2 months, and the median OS was not reached. Among 21 patients who were eligible for response, the ORR was 29%, and most frequent AEs occurred in less than 15% of patients. Multiple clinical studies with anti-VEGF therapies and immune-checkpoint inhibitors, either as single agents or in combination, are ongoing in this population.

Future Directions

The treatment landscape for RCC is changing with the introduction of next-generation VEGF-targeted therapies, immunotherapy agents, and combination regimens. Preclinical research has demonstrated a role of VEGF in suppressing tumor-directed immune responses, thus inhibiting the suppressive state in the tumor microenvironment—an attractive strategy to combine with checkpoint inhibitors. This successful synergy has been confirmed in phase 1 and 2 studies with axitinib-pembrolizumab, axitinib/avelumab, lenvatinib-pembrolizumab, and bevacizumab-atezolizumab. The ORR ranged between 32% and 67%, and AEs were manageable in all these studies, in contrast to studies in other combinations with different TKIs (pazopanib/sunitinib) plus immunotherapy, which did not move forward because of unacceptable toxicity. Although preliminary, the above-mentioned results are encouraging and have led to larger, confirmatory, phase 3 trials (Table 3), which are now actively accruing patients.

In addition, different novel immune therapies beyond checkpoint inhibitors are being investigated, including T-cell agonists, tumor vaccines, T-regulatory antagonists, and adoptive cell therapy. Patient selection to increase response to a specific agent is still a major challenge, and better biomarkers and predictive models are needed. The growing knowledge of molecular RCC subtypes with next-generation sequencing is the first step toward developing RCC-specific genomic signatures and guiding therapy selection, thereby moving toward precision medicine.

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