Personalizing First-Line Management of Metastatic Renal Cell Carcinoma: Leveraging Current and Novel Therapeutic Options

Kelly N. Fitzgerald, MD,1 and Chung-Han Lee, MD, PhD1

ABSTRACT

The treatment of metastatic renal cell carcinoma (RCC) has been revolutionized by advances in immunotherapeutic and targeted agents. Therapeutic approaches to RCC in these categories have recently evolved to include immune checkpoint inhibitors, novel vascular endothelial growth factor receptor–targeting tyrosine kinase inhibitors, and combinations of those agents. Multiple regimens within each category have been approved for use in the first-line treatment of clear cell and non–clear cell RCC. However, few of these regimens have been directly compared, leading to a new clinical challenge for physicians: how to select a first-line treatment regimen for an individual patient from among multiple approved options. In the modern era of RCC management, the initial treatment selection therefore becomes highly personalized and depends on numerous patient-specific factors, including histopathologic and clinical features of the disease, comorbid conditions, and psychosocial and economic factors. This review details current first-line treatment options for the management of metastatic RCC and proposes a framework whereby treatment selection can be optimized for individual patients.

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Background

Renal cell carcinoma (RCC) is the eighth most common malignancy in the United States; in 2020 alone, approximately 74,000 new cases of RCC were diagnosed and approximately 15,000 deaths were reported.1 Historically, treatment options for advanced RCC have been severely limited. Although RCC has long been recognized to be responsive to immune-stimulatory agents, only IL-2 and IFN-α were approved for advanced RCC until 2005.2,3 However, between 2005 and 2010, new targeted approaches were identified, directed at the VEGFR and mTOR pathways.4–10 Immunotherapeutic and targeted approaches have more recently evolved to include immune checkpoint inhibitors, novel VEGFR-targeting tyrosine kinase inhibitors (TKIs), and combinations of those agents. Multiple agents within each category have been approved for use in the first-line treatment of clear cell (cc) and non–clear cell (ncc) RCC.

This rapid expansion of systemic treatment options for the management of advanced RCC has given rise to a new clinical challenge for physicians: how to choose from among the multiple approved treatment options. This review discusses current standards of care in the systemic treatment of advanced RCC and describes an approach to personalizing patient care in the modern era. We begin with a summary of the approved regimens for the first-line management of RCC and conclude with a discussion of patient and disease characteristics that may guide an individualized approach to first-line treatment selection.

Risk Stratification

Understanding a patient’s RCC risk category, or their risk of early cancer mortality, is critical for selecting a first-line therapy, because data from pertinent trials are stratified by patient risk category. The most widely adopted risk stratification systems include the Memorial Sloan

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Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC) models. The MSKCC stratification system incorporates 5 prognostic factors (Karnofsky performance status <80%, serum lactate dehydrogenase >1.5 times the upper limit of normal, hemoglobin less than the lower limit of normal, corrected serum calcium >10 mg/dL, and time from diagnosis to systemic therapy <1 year) divided into 3 risk categories separated by at least 6 months of overall survival (OS) time. Importantly, the MSKCC system was developed before the modern era of TKI and immunotherapy, and therefore median OS for each risk category was lower than what is currently expected. Categories include favorable risk (no risk factors present; median OS, 20 months), intermediate risk (1 or 2 risk factors present; median OS, 10 months), and poor risk (≥3 risk factors present; median OS, 4 months).11 Similarly, the IMDC stratification system, which was developed in the TKI era, incorporates 6 clinical criteria (anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky performance status, and time from diagnosis to treatment) to stratify patients as having favorable, intermediate, and poor risk.12 Both the MSKCC and IMDC risk stratification methods were subjected to more recent validation in cohorts of patients receiving VEGFR-targeting TKI therapy; therefore, despite evolving treatment paradigms, they remain in use and are believed to reflect the underlying biology of RCC tumors.13 Risk category guides recruitment cohorts and statistical analytic design for some clinical trials in RCC, leading to some differences in first-line treatment regimen approvals for favorable versus intermediate/poor risk groups. For the remainder of this review, regimens discussed are approved for all risk groups unless specifically noted otherwise.

Immunotherapy

The availability of novel immune checkpoint inhibitors has revolutionized the treatment of patients with RCC. High-dose IL-2 remains listed as a treatment option NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer for select fit patients with ccRCC, but it is not widely used and should not be considered for use over immune checkpoint inhibitors.14 More recently, monoclonal antibodies targeting immune checkpoint molecules were found to be more tolerable and more efficacious than cytokine therapies. Commonly used agents in RCC include the PD-1 inhibitors pembrolizumab and nivolumab and the CTLA-4 inhibitor ipilimumab. In the first-line setting, the combination of ipilimumab and nivolumab (ipi/nivo) is the only preferred treatment option for ccRCC using immunotherapy alone in the NCCN Guidelines Kidney Cancer.15 In patients with nccRCC, PD-1 inhibitor monotherapy with pembrolizumab and nivolumab can be considered in patients who have relative contraindications to TKI; however, the efficacy is limited.14

Nivolumab With Ipilimumab

In April 2018, combination ipi/nivo was approved for first-line treatment of intermediate- and poor-risk patients. This approval was based on the results of the CheckMate 214 study, in which all patient risk groups were enrolled, but co-primary endpoint statistical analytic design was based on enrollment of intermediate/poor risk only. Among this subgroup, the ipi/nivo combination showed significantly superior OS and overall response rate (ORR) to sunitinib, although it did not meet its prespecified threshold of significance for progression-free survival (PFS). A total of 1,096 patients were randomized to receive either sunitinib, 50 mg orally once daily for 4 weeks (6-week cycle) or nivolumab (3 mg/kg body weight) plus ipilimumab (1 mg/kg) intravenously every 3 weeks for 4 doses, followed by nivolumab (3 mg/kg) every 2 weeks. Median OS was not reached with ipi/nivo versus 26.0 months with sunitinib (hazard ratio [HR] for death, 0.63; P<.001). The ORR was 42% versus 27% (P<.001), and PFS was 11.6 versus 8.4 months, respectively (HR for disease progression or death, 0.82; P=.03, not significant per the prespecified 0.009 threshold).15 Notably, at 42-month extended follow-up, median OS remained significantly improved in the ipi/nivo versus sunitinib arms (for intermediate/poor-risk patients, 48.1 vs 26.6 months, respectively; HR, 0.65; 95% CI, 0.54–0.78).16

Toxicity and Decision-Making

The potential for long-term durability of response makes ipi/nivo a preferred regimen in patients for whom the risk of toxicity is acceptable. However, it must be noted that TKI/immunotherapy regimens were developed later than ipi/nivo, and therefore it remains to be seen whether any of these regimens (discussed later) may yield a similar rate of long-term response. Ipi/Nivo can also be considered for patients who are not candidates for TKI therapy.

The potential for immune-related adverse effects (irAEs) is an important consideration for ipi/nivo as a potential first-line treatment option. irAEs can involve inflammatory insult to any organ system and can range from mild and transient to permanent or life-threatening. Immune-mediated colitis, hepatitis, pancreatitis, inflammatory endocrinopathies including adrenalitis and hypophysitis, pneumonitis, myocarditis, and encephalitis can all lead to permanent morbidity or mortality; grades 3–4 toxicity is observed in 38% to 46% of patients who receive ipi/nivo.17 This risk for autoinflammatory events also raises concern about the safety of these agents in patients with underlying autoimmune disease. Grades 3–4 treatment-related adverse effects (trAEs) occurred in 46% of patients receiving ipi/nivo, leading to treatment discontinuation in 22%.17 However, some patients who discontinue treatment have not required further systemic
therapy. Among intermediate/poor-risk patients receiving either ipi/nivo or sunitinib in another study, 18% and 5%, respectively, were surviving treatment-free at 42-month follow-up, and mean treatment-free survival was 6.9 versus 3.1 months, respectively.\(^{18}\)

Furthermore, treatment failure rate is an important consideration for patients with major disease burden in whom impending organ crisis or excessive symptoms related to disease burden are a concern. The reported response rate of 42% for ipi/nivo is inferior to rates reported for TKI/immunotherapy combinations described later. This implies that ipi/nivo may be a riskier approach in patients in whom immediate response is necessary.

**Tyrosine Kinase Inhibitors**

Antiangiogenic TKIs that inhibit VEGFR have transformed management of RCC, and single-agent TKI therapy may be appropriate for those who wish to avoid the potential toxicities of immunotherapy-based regimens and/or prefer the convenience of orally administered treatments.\(^{19}\) ccRCC is generally characterized by von Hippel-Lindau (VHL) gene inactivation and downstream upregulation of hypoxia-inducible factors (HIFs), allowing tumor angiogenesis and cell proliferation. Numerous VEGFR-targeting TKIs have been explored for use in RCC; agents that have been approved for use in the first-line setting, either alone or in combination with immunotherapy, include sunitinib, pazopanib, axitinib, lenvatinib, and cabozantinib. Additional TKIs have been approved for use in later lines of treatment, including sorafenib and tivozanib for ccRCC and erlotinib for papillary RCC.\(^{20–22}\)

Among these, cabozantinib is the only TKI monotherapy listed as a preferred option in the NCCN Guidelines for ccRCC (for intermediate/poor risk only).\(^{14}\) Its approval in this setting is based on the results of the CABOSUN trial, in which patients with intermediate/poor-risk ccRCC were randomized to receive cabozantinib or sunitinib monotherapy; cabozantinib was found to have a PFS advantage of 8.6 months versus 5.3 months for sunitinib (HR, 0.48; 95% CI, 0.31–0.74; \(P=0.008\)).\(^{23}\) VEGFR-targeting TKIs have also been explored in nccRCC. Sunitinib and cabozantinib remain the only preferred treatment options for first-line management of nccRCC in the NCCN Guidelines for Kidney Cancer.\(^{14}\) Approval for sunitinib was based on the results of the ASPEN trial,\(^{24}\) which showed a PFS advantage to sunitinib over everolimus in patients with metastatic nccRCC, and approval for cabozantinib was based on the results of a large multicenter retrospective cohort study of 112 patients with nccRCC who received cabozantinib,\(^{25}\) showing a median PFS of 7.0 months (95% CI, 5.7–9.0 months) and a tolerable adverse effect profile (supplemental eTable 1, available with this article at JNCCN.org).

**Toxicity and Decision-Making**

Although TKI monotherapy is rarely used in the first-line setting for ccRCC, cabozantinib monotherapy may still be a preferable approach in patients with relative contraindications to immunotherapy. Nevertheless, TKI-related adverse effects must be considered. Although the complete adverse effect profile differs for each TKI by its spectrum of kinase targets (Figure 1), some toxicities are shared by all members of the class, including skin rash, hypertension, hepatotoxicity, gastrointestinal toxicity (anorexia, nausea, vomiting, diarrhea, and/or constipation), and mucocutaneous toxicity (hand-foot syndrome, oral ulcers, anogenital ulcers, rectal fistulae). In the CABOSUN trial,\(^{23}\) grades 3–4 trAEs occurred in 67% of the cabozantinib group and 68% of the sunitinib group; similarly, grades 3–5 trAEs were seen in 78% of sunitinib-treated patients in the ASPEN study.\(^{24}\)

Furthermore, mechanisms of resistance are a concern with the use of TKIs. Proposed mechanisms of resistance include, among others, (1) redundancy of tumor-derived proangiogenic factors, (2) upregulation of antiapoptotic effector molecules in host endothelial cells, and (3) heterogeneous vascular dependence of tumor cell populations.\(^{26}\)

**Combination Therapy: TKIs With Immunotherapy**

Regimens incorporating VEGFR-targeting TKIs and PD-1 inhibitors (ie, TKI/immunotherapy) have been developed as a strategy for inducing a synergistic immune antitumor response. Several TKI/immunotherapy regimens are approved for first-line treatment of ccRCC; these regimens may be preferred in patients who are candidates for both TKI and immunotherapy drugs and in whom rapid disease shrinkage is needed due to symptoms or impending visceral crisis.

VEGFR blockade seems to independently modulate the antitumor immune response; however, the mechanisms of this phenomenon, and their implications in the clinical context of immunotherapy, are not fully elucidated and remain controversial. Nevertheless, preclinical discoveries provide a biologic rationale for the addition of VEGFR-targeting TKIs to anti–PD-1 agents (Figure 2).

Three combination regimens, including axitinib + pembrolizumab (axi/pembro), cabozantinib + nivolumab (cabo/nivo), and lenvatinib + pembrolizumab (lenva/pembro), are approved for the first-line treatment of metastatic ccRCC. All 3 regimens have been evaluated with randomized phase III clinical trials and have been shown to have efficacy superior to that of sunitinib (Table 1).

**Toxicity and Decision-Making**

TKI/Immunotherapy combination therapies offer an appealing option for first-line treatment of ccRCC because of their multimodality approach with biologic
rationale and the lower risk of permanent or life-threatening autoimmune adverse effects than that of ipi/nivo. However, chronic predictable toxicities are associated with ongoing TKI therapy. Thus, the risk of toxicity must be considered when selecting TKI/immunotherapy combination therapy; the toxicity profile of these regimens reflects the possible adverse effects of TKI or immunotherapy monotherapy described earlier. Furthermore, overlapping toxicities such as diarrhea and hepatotoxicity can compound the severity of these symptoms and can create a diagnostic challenge in their diagnosis and management. Any adverse effect occurred in >99% of patients receiving each of the 3 regimens described earlier. Grade ≥3 adverse effects were seen in 75.8% of patients receiving axi/pembro, 75.3% receiving cabo/nivo, and 82.4% receiving lenva/pembro.

### Classifying the Patient With RCC

Although the treatments described earlier represent a decade of advancements in therapeutic options for metastatic RCC, this wealth of treatment options presents a challenge in selecting a first-line regimen. However, numerous factors can guide treatment selection (Figure 3).

#### Histology and Genetics

Accurate understanding of a patient’s histologic subtype is important to guide first-line management decisions. The most commonly recognized histologic categories of RCC and the respective frequencies of each category include the following: clear cell (80%), papillary (11%–14%), chromophobe (4%–5%), or collecting duct (<1%) RCC subtypes or RCC not otherwise specified (<1%). The relative rarity of nccRCC compared with ccRCC, and its exclusion from most large randomized clinical trials, has led to a paucity of approved therapies for nccRCC. Sunitinib and cabozantinib are approved for first-line treatment of nccRCC, as discussed earlier. However, enrollment in a clinical trial may be preferable for patients with nccRCC. Ongoing clinical trials in the Unites States for first-line treatment of nccRCC include NCT04704219 (pembrolizumab + lenvatinib), NCT03635892 (nivolumab + cabozantinib), and NCT04413123 (cabozantinib + nivolumab and ipilimumab).
Understanding of the genomic features underlying each patient’s disease also guides initial management decisions. Specifically, the physician must decide whether referral to a genetics service is needed and whether VHL disease is present, for which specific treatment is indicated. Several RCC-associated genetic cancer syndromes have been identified. Therefore, hereditary RCC gene panel testing and cancer genetics referral are recommended for patients who meet any one or more of the following criteria: (1) close relative with a known pathologic/likely pathogenic variant in a cancer susceptibility gene, (2) at least one first- or second-degree relative with RCC, (3) RCC diagnosed at age ≤46 years, (4) bilateral or multifocal renal tumors, or (5) meets specific clinical or pathologic criteria for a hereditary RCC syndrome. For patients with confirmed VHL disease, HIF-2α inhibitor belzutifan is recommended for first-line treatment based on the results of a recently reported phase II clinical trial showing an ORR for belzutifan of 49% (95% CI, 32%–62%) and a tolerable adverse effect profile. Genetic testing can also help first-line therapy selection if it leads to clarification of RCC histologic subtype.

**Figure 2.** Mechanisms of VEGFR blockade modulation of antitumor immunity. (1) VEGFR-targeting TKIs act directly on the cancer cell by inhibiting downstream cascade functions of VEGFR. VEGFR is expressed on RCC cells; when activated, it functions to activate PI3K and RAS signaling, which lead to numerous downstream events, including the activation of mTOR, leading to increased cell growth, protein synthesis, and HIF-1 production. (2) VEGFR activation induces proliferation and infiltration of MDSCs. Blockade has been shown to reduce the suppressive capacity of MDSCs. (3) VEGF/VEGFR binding significantly reduces the cytotoxic activity of T cells and inhibits TCR-dependent activation of T cells. (4) Treg cells are immunosuppressive and can suppress or downregulate induction and proliferation of effector T cells. The expression of VEGF has been shown to be positively associated with intratumoral Treg cells. (5) Signaling via the VEGF–VEGFR1 axis impairs dendritic cell maturation. (6) eNOS activity in solid tumors has been shown to impair invasion and antitumor activity of tumor-infiltrating lymphocytes. (7) Signaling cascades downstream of VEGFR activation lead to increased mTOR activity. mTOR promotes cancer cell growth through numerous mechanisms and also increases cellular production of VEGF.

Abbreviations: HIF-1, hypoxia-inducible factor 1; MDSC, myeloid-derived suppressor cell; RCC, renal cell carcinoma; TCR, T-cell receptor; TKI, tyrosine kinase inhibitor; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Disease Location and Burden
The distribution and size of metastases and the subsequent potential for organ crisis can also guide the choice of systemic therapy. An initial decision must be made in collaboration with medical, surgical, and radiation oncology teams regarding whether site-directed therapy should precede systemic therapy. Generally, brain metastases, cord-threatening spinal lesions, or symptomatic metastases warrant urgent intervention; should surgery or radiation be indicated, TKI therapy may be delayed due to the risk of radionecrosis or perioperative complications.

Furthermore, when selecting an initial therapy for patients with a large disease burden, the risk of primary progression of disease must be considered. As discussed earlier, the ORR for ipi/nivo was 42% in CheckMate 214; conversely, the ORR for TKI/immunotherapy regimens described earlier ranged from 55.7% to 71%. In patients with impending organ crisis, a regimen with lower risk of primary progression of disease may be preferable.

Likewise, in asymptomatic patients with minimal disease burden, several initial management options exist. First, in individuals with slow-growing disease, management with active surveillance may be preferable and has been shown to be a safe approach in select patients based on a recently reported prospective observational study. In addition, although support for a survival benefit of cytoreductive nephrectomy in the metastatic setting is mixed, this may be considered in select patients with limited disease burden. The best candidates for nephrectomy are intermediate-risk patients with limited metastatic burden and low perioperative risk.

The location of metastases may also guide therapy. In patients with bone metastases, which are generally challenging to treat with systemic therapies and may portend a worse prognosis, cabozantinib-containing regimens may be preferred due to their apparent efficacy based on a retrospective analysis. The blood–brain barrier penetration of TKIs is not well characterized. Multiple retrospective studies and case series have suggested efficacy of cabozantinib for RCC brain metastases, whereas few data have been reported for axitinib and lenvatinib in this setting. However, only one prospective study has evaluated the efficacy of a VEGFR TKI in RCC with brain metastases. This was a phase II study evaluating sunitinib efficacy in patients with untreated brain metastases, and, among 16 evaluable patients, the central nervous system response rate was 0%: 31% of patients had stable disease. Conversely, patients with brain metastases are included in the CLEAR trial, in which OS benefit was demonstrated in intermediate/poor risk patients only. Grades 3–4 trAEs are a representative list and not comprehensive for all grades 3–4 trAEs that occurred in the study.

Table 1. Preferred Combination TKI/Immunotherapy Regimens for Metastatic RCC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
<th>Comparison</th>
<th>Phase III Trial</th>
<th>Primary Endpoints</th>
<th>PFS</th>
<th>OS</th>
<th>Most Frequent Grade 3–4 trAEs</th>
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<tbody>
<tr>
<td>Axitinib/</td>
<td>Axitinib, 5 mg PO bid, pembrolizumab, 200 mg IV q3w</td>
<td>Sunitinib, 50 mg PO daily, 4 wk on, 2 wk off</td>
<td>KEYNOTE 426 and extended follow-up analysis (median follow-up 30.6 mo)</td>
<td>OS, PFS</td>
<td>At extended follow-up analysis, PFS 13.4 vs 11.1 mo (HR, 0.71; 95% CI, 0.60–0.84; P&lt;.0001)</td>
<td>At extended follow-up analysis, OS NR vs 35.7 mo (HR, 0.68; 95% CI, 0.55–0.85; P=.0003)</td>
<td>HTN (22.1%), transaminits (13.3%), diarrhea (9.1%), HFS (5.1%)</td>
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<td>Pembrolizumab</td>
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<tr>
<td>Cabozantinib/</td>
<td>Cabozantinib, 40 mg PO daily, nivolumab, 240 mg IV q4w</td>
<td>Sunitinib, 50 mg PO daily, 4 wk on, 2 wk off</td>
<td>CheckMate 9ER</td>
<td>PFS</td>
<td>16.6 vs 8.3 mo (HR, 0.51; 95% CI, 0.41–0.64; P&lt;.001)</td>
<td>Median follow-up 18.1 mo</td>
<td>Median follow-up 18.1 mo</td>
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<td>Nivolumab</td>
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<tr>
<td>Lenvatinib/</td>
<td>Lenvatinib, 20 mg PO daily, pembrolizumab, 200 mg IV q3w</td>
<td>1. Lenvatinib, 18 mg PO daily, everolimus, 5 mg PO daily or 2. Sunitinib, 50 mg PO daily, 4 wk on, 2 wk off</td>
<td>CLEAR</td>
<td>PFS</td>
<td>Lenvatinib/ pembrolizumab, 23.9 mo vs sunitinib, 9.2 mo (HR, 0.39; 95% CI, 0.32–0.49; P&lt;.001)</td>
<td>Median follow-up 26.6 mo</td>
<td>Median follow-up 26.6 mo</td>
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<tr>
<td>Pembrolizumab</td>
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Only patients with clear cell carcinoma were included in each study. Benefit was shown in all risk groups for each study, except for the CLEAR trial, in which OS benefit was demonstrated in intermediate/poor risk patients only. Grades 3–4 trAEs are a representative list and not comprehensive for all grades 3–4 trAEs that occurred in the study.

Abbreviations: HFS, HFS, hand-foot syndrome; HR, hazard ratio; HTN, hypertension; NP, not powered to detect a difference; NR, not reached; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; trAE, treatment-related adverse effect.
Comorbidities and Performance Status
Although there are no absolute contraindications to immunotherapy, relative contraindications include active autoimmune disease or any condition requiring immunosuppressive therapy. irAEs occur frequently in patients receiving ipi/nivo (grades 3–4 irAEs occurred in 38%–46% of patients in CheckMate 214). Thus, this regimen should be avoided in patients who are unlikely to tolerate common irAEs, and should be used with caution in patients with underlying rheumatologic disease. Finally, in the event that irAEs occur, systemic steroids are frequently used to intervene; this possibility must be considered in patients with poorly controlled diabetes or in those who have a history of adverse reactions to systemic steroids. Conversely, relative contraindications to TKI therapy include active, uncontrolled vascular disease such as recent myocardial infarction, stable angina, cerebrovascular accident, or severe/uncontrolled hypertension.

Psychosocial and Economic Factors
Patient preference should be a factor in the decision-making process for a first-line systemic therapy. Individual patients may find the risk of certain adverse effects unacceptable, or they may prefer intravenous- or by mouth-only regimen. The ability to obtain a selected regimen without incurring significant financial toxicity should also be considered, taking into account factors such as ability to obtain insurance coverage, patient copays and out-of-pocket expenses, time and resources required to travel for infusions, and availability and feasibility of clinical trials, among others.

Discussion and Future Directions
As a result of the past decade of advancements in immunotherapy and VEGFR-targeted therapy, multiple treatment options exist for the first-line management of ccRCC and nccRCC. For ccRCC, preferred options include combination immune checkpoint blockade with ipi/nivo; TKI/immunotherapy combinations axi/pembro, cabo/nivo, and lenva/pembro; and cabozantinib monotherapy. For nccRCC, preferred regimen options include single-agent cabozantinib or sunitinib. In light of the multiple approved therapies with lack of direct comparisons among them, the initial management decision becomes highly personalized and depends on all of the

Figure 3. Schematic of molecular, cellular, clinical, and social considerations that factor into the first-line therapy decision for an individual patient.
Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; irAE, immune-related adverse effect; MSKCC, Memorial Sloan Kettering Cancer Center; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.
patient-specific factors discussed herein. The optimal second-line regimens to follow the first-line options discussed herein are unknown; thus, it remains unclear whether available second-line therapies should be considered a factor in first-line decision-making.

A comprehensive and rational method for personalizing first-line treatment decisions will continue to be essential as the field of RCC moves forward. Novel thera-

tpeutic targets are emerging and are currently under inves-

tigation in clinical trials; these include HIF-2α, histone deacetylase, mTOR (via third-generation inhibitors), and novel immune checkpoints (eg, LAG3, CD40), among others. Novel HIF-2α belzutifan is of particular interest, given its recent approval for use in VHL disease–driven RCC; it is currently being investigated for use in the first-line setting for ccRCC in combination with cabozantinib (ClinicalTrials.gov identifier: NCT03634540) and lenvatinib (NCT04736706). Adoptive cell therapies (eg, CAR T cells targeting CD-70 and others) are also under exploration.12 As novel therapies emerge, a meth-

odologic and personalized approach to management decisions will allow optimal patient-centered navigation of the expanding treatment landscape for metastatic RCC.

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References


19. Rassy E, Flippot R, Algibes L. Tyrosine kinase inhibitors and immunother-

apy combinations in renal cell carcinoma. Ther Adv Med Oncol 2020;12:


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Supplemental online content for:

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<td>Cabozantinib for ccRCC</td>
<td>Cabozantinib, 60 mg PO daily</td>
<td>Sunitinib, 50 mg PO daily, 4 wk on, 2 wk off</td>
<td>Alliance A031203 CABOSUN trial1</td>
<td>PFS</td>
<td>8.6 vs 5.3 mo (HR, 0.48; 95% CI, 0.31–0.74; P=.12)</td>
<td>NP; 30.3 vs 21.8 mo (adjusted HR, 0.8; 95% CI, 0.5–1.26)</td>
<td>Median follow-up 34.5 mo</td>
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<td>Cabozantinib for nccRCC</td>
<td>Cabozantinib, 60 mg PO daily</td>
<td>N/A</td>
<td>Retrospective multileft analysis2</td>
<td>N/A</td>
<td>NP; 7.0 mo</td>
<td>NP; 12.8 mo</td>
<td>HTN (4%), skin toxicity (4%), diarrhea (3%)</td>
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<td>Sunitinib for ccRCC</td>
<td>Sunitinib, 50 mg PO daily</td>
<td>Interferon alpha</td>
<td>Motzer et al3</td>
<td>PFS</td>
<td>11 vs 5 mo (HR, 0.42; 95% CI, 0.32–0.54; P&lt;.001)</td>
<td>NP; median NR</td>
<td>At interim analysis, death rate 15% vs 17% (HR, 0.65; 95% CI, 0.45–0.94; P=.02)</td>
</tr>
<tr>
<td>Sunitinib for nccRCC</td>
<td>Sunitinib, 50 mg PO daily</td>
<td>Everolimus, 10 mg PO daily</td>
<td>ASPEN trial4</td>
<td>PFS</td>
<td>8.3 vs 5.6 mo (HR, 1.41; 80% CI, 1.03–1.92; P&lt;.16)</td>
<td>NP; 31.5 vs 13.2 mo (HR, 1.12; 95% CI, 0.7–2.1; P=.6)</td>
<td>Median follow-up 15 vs 12 mo</td>
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Grades 3–4 trAEs are a representative list and not comprehensive for all grades 3–4 trAEs that occurred in the study.

Abbreviations: ccRCC, clear cell renal cell carcinoma; HFS, hand-foot syndrome; HR, hazard ratio; HTN, hypertension; N/A, not applicable; nccRCC, non-clear cell renal cell carcinoma; NP, not powered to detect a difference; NR, not reached; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; trAE, treatment-related adverse effect.

### References