

Evolving Landscape of the Treatment of Metastatic Clear Cell Renal Cell Carcinoma

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Abstract: The management of advanced clear cell renal cell carcinoma (RCC) has evolved over the past decade with the introduction of targeted therapies and immune checkpoint inhibitors. Recently, studies of dual checkpoint inhibition and of vascular endothelial growth factor (VEGF) inhibition combined with checkpoint inhibition have shown promising results, adding newer options to the treatment armamentarium for advanced RCC. Specifically, therapies combining checkpoint inhibitors of different classes and combining VEGF inhibitors with checkpoint inhibitors have gained much interest, and results from studies of several other combinations are awaited. These and previously approved treatments offer multiple options to patients with advanced RCC. In this review, we discuss the efficacy and safety results from the pivotal trials of these therapies, how the trial data can guide selection of the most appropriate therapy, and how to consider sequencing therapies in the care of patients with advanced RCC.

Introduction

Renal cell carcinoma (RCC) will be diagnosed in an estimated 65,340 persons and 14,970 will die of the disease in the United States in 2018.¹ Clear cell RCC (ccRCC) is the most common subtype of RCC, making up 80% of cases. RCCs with other, less common cell types include papillary RCC, chromophobe RCC, collecting duct carcinoma, and translocation carcinoma. Up to 30% of patients present with advanced disease at diagnosis, and 10% to 20% of patients treated for early-stage disease experience a recurrence.¹ The 5-year survival for advanced disease increased from 7.3% in 1992-1995 to 11.7% in 2006-2013, and 5-year survival rates as high as 23% have been reported in specialized centers.²

Substantial changes in the management of metastatic RCC (mRCC) have taken place over the past decade. Until the mid-2000s, treatment options were limited to interleukin 2 (IL-2) and interferon alfa (IFN- α), with use limited by high rates of adverse events and low response rates.³⁻⁶ Since then, 9 targeted therapies, immune

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checkpoint therapies, and combined immune checkpoint therapies have been approved for mRCC. Preliminary results of ongoing trials combining checkpoint blockade with targeted therapies are encouraging, and these combinations are likely to become the next wave of available treatment options for mRCC.

Targeted therapies, including inhibitors of vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathway, entered the landscape in the mid to late 2000s, expanding standard therapy options for mRCC. VEGF-targeting tyrosine kinase inhibitors (TKIs) and anti-VEGF antibodies—bevacizumab (Avastin, Genentech) plus IFN- α ; sunitinib (Sutent, Pfizer); axitinib (Inlyta, Pfizer); pazopanib (Votrient, Novartis); and cabozantinib (Cabometyx; Exelixis)—have an overall response rate (ORR) of 25% to 35% in treatment-naïve patients, with a disease control rate (DCR) of 65% to 80% and a median progression-free survival (PFS) ranging from 8.5 to 11 months.⁷⁻¹¹ Sorafenib (Nexavar, Bayer) has a lower ORR of approximately 15%, a DCR of 45%, and a PFS of 6.5 months.¹⁰ Lenvatinib (Lenvima, Eisai), another VEGF TKI, was studied in the second-line setting in combination with everolimus (Afinitor, Novartis) and found to have an ORR of 35%, a DCR of 80%, and a median PFS of 14.6 months.¹⁰ The mTOR inhibitors everolimus and temsirolimus (Torisel, Pfizer) have a lower ORR of approximately 2% and a PFS of approximately 5 to 6 months when used as single agents.^{12,13} Use of the immune checkpoint inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) as a single agent is approved by the US Food and Drug Administration (FDA) in the second-line setting in mRCC. The combination of ipilimumab (Yervoy, Bristol-Myers Squibb) and nivolumab is approved in the first-line setting for intermediate- and poor-risk mRCC per the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, or Heng score.

The most widely used prognostic models in mRCC are the Memorial Sloan Kettering Cancer Center (MSKCC) model, which was designed in patients treated with IFN- α , and the IMDC model, developed in patients treated with immunotherapy and VEGF-targeted therapies. The MSKCC model uses the following 5 prognostic factors: (1) interval from initial RCC diagnosis to treatment of less than 1 year, (2) Karnofsky performance status (KPS) of less than 80%, (3) serum lactate dehydrogenase (LDH) level more than 1.5 times the upper limit of normal (ULN), (4) corrected calcium level above the ULN, and (5) serum hemoglobin level below the lower limit of normal (LLN).¹⁴ The IMDC criteria identify 6 clinical parameters that are used to stratify patients into favorable-, intermediate-, and poor-risk groups. Of the 6 adverse prognostic factors, 4 are included in the MSKCC

model and predict short survival: (1) hemoglobin level below the LLN, (2) calcium level above the ULN, (3) KPS of less than 80%, and (4) time from initial diagnosis to initiation of therapy of less than 1 year. Additional adverse prognostic factors validated in this model are an absolute neutrophil count above the ULN and a platelet count above the ULN.¹⁵ In a recent assessment of common genomic alterations in mRCC, alterations in *BAP1* were associated with worse overall survival (OS), and alterations in *PBRM1* and *KDM5C* were associated with better survival.¹⁶ Assessment of alterations in these key genes can be used to further evaluate the prognosis of intermediate-risk patients by the IMDC criteria and may be incorporated into future prospective trials.

Most patients with mRCC require multiple therapies during the course of their disease, and understanding the clinical data can help determine the appropriate sequence of therapy. Here, we first provide a detailed discussion of key clinical data from each trial, then discuss how these therapies may be sequenced in the care of a given patient. We conducted a MEDLINE search for pivotal trial publications and a search of meetings of the American Society of Clinical Oncology, European Society for Medical Oncology (ESMO), and American Association for Cancer Research through June 2018.

Surgical Resection in Metastatic RCC

In 2 retrospective studies and a recently presented prospective study, the utility of cytoreductive nephrectomy (CN) in patients who have mRCC with synchronous metastases has been addressed. In the era of IFN- α (1992-2004), a combined analysis of 2 prospective randomized clinical trials from the European Organisation for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group (SWOG) demonstrated that OS was 13.6 months with CN followed by IFN- α vs 7.8 months with IFN- α alone, an increase of 5.8 months.¹⁷ Another large retrospective international study was performed to address the survival benefit of CN in patients who had mRCC treated with targeted therapy.¹⁸ The median OS was 20.6 months for patients receiving CN vs 9.6 months for patients not receiving CN ($P < .001$). Although the IMDC prognostic scores of the patients in the CN arm were more favorable than those of the patients in the non-CN arm, after adjustment for the difference between IMDC risk in the 2 populations, an OS benefit was still observed in the patients who underwent CN (hazard ratio [HR], 0.60; 95% CI, 0.52-0.69; $P < .001$). In this study, patients with a life expectancy of less than 12 months and 4 or more of the IMDC risk factors did not benefit from CN.¹⁸

CARMENA (Clinical Trial to Assess the Importance of Nephrectomy) is a phase 3 noninferiority trial

that randomly assigned 450 patients with synchronous mRCC to CN or CN followed by sunitinib. All patients had intermediate- or poor-risk IMDC features. OS in the sunitinib-alone arm was not inferior to that in the surgery plus sunitinib arm (OS, 18.4 months without surgery vs 13.9 months with surgery). Similar results were noted in subgroups consisting of intermediate-risk patients (OS, 23.4 vs 19 months) and poor-risk patients (OS, 13.3 vs 10.2 months). The results of this study indicate that patients with poor-risk, high-volume mRCC are less likely to benefit from CN and should proceed to systemic therapy. However, patients with low-volume metastases outside the primary tumor who have symptoms caused by their primary renal tumor may still benefit from palliative nephrectomy before systemic therapy. Several observational studies have demonstrated that carefully selected patients with mRCC may be rendered disease-free after resection or ablation of the primary tumor and metastatic sites. The benefit of local treatment of metastases in the management of mRCC has been quantified in 2 recent systematic reviews.^{19,20} In the first review, by Dabestani and colleagues, OS was significantly better in the patients who underwent complete metastasectomy than in those who underwent incomplete or no metastasectomy (40.8 vs 14.8 months).¹⁹ Zaid and colleagues also noted improved OS, ranging from 36.5 to 142 months in the patients undergoing complete metastasectomy and from 8.4 to 27 months in the patients undergoing incomplete metastasectomy.²⁰

VEGF Receptor-Targeted Therapies for Metastatic RCC

Bevacizumab is a recombinant humanized monoclonal antibody against circulating VEGF-A. A phase 3, double-blind trial called AVOREN (Phase III Trial of Bevacizumab Plus Interferon Alfa-2a in Patients With Metastatic Renal Cell Carcinoma) randomly assigned 641 patients to bevacizumab plus IFN- α or to placebo plus IFN- α . The addition of bevacizumab significantly increased PFS (10.2 vs 5.4 months) and ORR (30.6% vs 12.4%).²¹ A nonsignificant trend toward improved OS (23.3 vs 21.3 months) was noted. In the United States, a similar trial was performed by the Cancer and Leukemia Group B (CALGB), in which 732 patients were randomly assigned to receive IFN- α or a combination of bevacizumab plus IFN- α . The combination produced a superior PFS (8.5 vs 5.2 months) and a higher ORR (25.5% vs 13.1%). Once again, no significant difference was observed between median OS in the 2 groups.²²

Sunitinib was studied in a large multinational phase 3 trial in which 750 treatment-naïve patients with mRCC were randomly assigned to sunitinib or IFN- α . The

median PFS was 11 months for sunitinib and 5 months for IFN- α . The ORR was 31% for sunitinib vs 6% for IFN- α .⁸ A strong trend toward OS benefit was noted with sunitinib (26.4 vs 21.8 months; $P=.051$).²³ In these studies, sunitinib was administered at 50 mg once daily, 4 weeks on and 2 weeks off. Recently, an alternative dose of sunitinib (50 mg daily, 2 weeks on and 1 week off) was studied in a phase 2 trial. Although the primary endpoint of a rate of grade 3 or higher fatigue, diarrhea, or hand-foot syndrome below 15% was not met, the 2-weeks-on, 1-week-off schedule was associated with a lack of grade 4 toxicity, a low patient discontinuation rate, and greater efficacy, with an ORR of 57%, a median PFS of 13.7 months, and a median OS of not reached at 17 months of follow-up.²⁴

Pazopanib is a multikinase oral angiogenesis inhibitor targeting VEGF receptor 1 (VEGFR-1), VEGFR-2, VEGFR-3, platelet-derived growth factor receptor α (PDGFRA), platelet-derived growth factor receptor β (PDGFRB), and c-KIT. An international phase 3 study randomly assigned 435 treatment-naïve patients with ccRCC in a 2:1 ratio to pazopanib or placebo. The ORRs were 30% and 3% for pazopanib and placebo, respectively; the PFS was 11.1 for pazopanib and 2.8 months for placebo. OS was the same in the 2 groups, at 22.9 vs 20.5 months. This was likely due to extensive crossover and subsequent lines of therapy.⁹ Results of a large non-inferiority study of sunitinib vs pazopanib, COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma), showed similar efficacy in the 2 drugs, but pazopanib was associated with less fatigue, hand-foot syndrome, taste alterations, and thrombocytopenia compared with sunitinib; however, transaminase elevation was more common with pazopanib.⁷ The results of COMPARZ were supported by the results of another, smaller phase 3 study called PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer). In this trial, 169 patients were blinded and randomly assigned to pazopanib followed by sunitinib or to sunitinib followed by pazopanib, and patients and providers were asked which regimen they preferred. Approximately 70% of patients selected the pazopanib-first sequence owing to better quality of life, whereas only 22% selected the sunitinib-first sequence.²⁵ Importantly, the schedule of sunitinib in both trials was 4 weeks on, 2 weeks off, and the timing of quality-of-life assessments may have contributed to the preference of initial pazopanib over initial sunitinib.

Sorafenib is one of the earliest multikinase TKIs to have been studied and approved on the basis of a response rate advantage over IFN- α .⁶ Sunitinib, pazopanib, and axitinib are more selective inhibitors of VEGFR compared

with sorafenib.²⁶ Axitinib was first studied in the second-line setting in the AXIS study (Axitinib As Second Line Therapy For Metastatic Renal Cell Cancer), and its PFS was found to have been longer than that of sorafenib (6.7 vs 4.7 months).²⁷ Axitinib was then studied in the first-line setting in a phase 3 open-label trial in which patients were randomly assigned in a 2:1 ratio to receive axitinib or sorafenib. A nonsignificant difference was found between the axitinib and sorafenib arms in ORR (32% vs 15%), median PFS (10.1 vs 6.5 months), and OS (21.7 vs 23.2 months), respectively. No crossover between arms was allowed in this study, and the shorter OS may have been related to fewer subsequent lines of therapy in the patients.¹⁰ Another randomized phase 2 study evaluated the efficacy and safety of axitinib dose titration. In this study, patients with treatment-naïve mRCC received axitinib at 5 mg twice daily for 4 weeks and were then assigned to placebo titration or stepwise axitinib titration to a dose of 7 mg and then to a maximum dose of 10 mg daily. The ORR was 54% in the axitinib titration group vs 34% in the placebo titration group.²⁸

Cabozantinib inhibits VEGF receptors, MET, and AXL. It was first studied in heavily treated patients whose disease had progressed on prior anti-VEGFR therapies. A phase 3 trial called METEOR (A Study of Cabozantinib vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma) randomly assigned 658 patients to cabozantinib or everolimus. Median ORR and PFS were better in the cabozantinib arm than in the everolimus arm (21% vs 5% and 7.4 vs 3.8 months, respectively), a finding confirmed by an independent review committee.²⁹ Final analysis also showed an OS benefit with cabozantinib (21.4 vs 16.5 months).³⁰ In a subgroup analysis, ORR, PFS, and OS in patients who had bone metastases were much better with cabozantinib than with everolimus. Cabozantinib was then studied in the first-line setting in intermediate- or poor-risk patients in the CABOSUN trial (Cabozantinib-s-malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer), which compared cabozantinib with sunitinib. Cabozantinib achieved a significantly increased median PFS of 8.2 months vs 5.6 months with sunitinib.³¹ This trial has, however, been criticized for underperformance in cross-study comparison of the sunitinib control arm and assessment of PFS without independent review; in addition, 20% of patients were not evaluated for response or had missing data.³²

Lenvatinib is a multitargeted TKI that was studied in a phase 2 trial in which 153 patients who had mRCC previously treated with 1 TKI (ie, second-line only) were randomly assigned to receive lenvatinib plus everolimus, single-agent lenvatinib, or single-agent

everolimus. A significant improvement in median PFS (14.6 vs 5.5 months)³³ and in median OS (25.5 vs 15.4 months) was observed for lenvatinib plus everolimus vs everolimus monotherapy.³⁴ The combination of lenvatinib with everolimus was approved by the FDA on the basis of these data.

mTOR Inhibitors for Metastatic RCC

The mTOR inhibitors were evaluated and approved at approximately the same time as the first VEGF TKIs. Initially studied in patients with poor-risk disease, they have now found a niche for use following failure of VEGF inhibition and checkpoint inhibition, and in combination with lenvatinib. The earliest phase 3 study of mTOR inhibition in mRCC was ARCC (Study Evaluating Interferon And CCI-779 In Advanced Renal Cell Carcinoma), which randomly assigned 626 previously untreated patients with advanced RCC to temsirolimus, IFN- α , or a combination of the 2 drugs. Patients were required to have 3 or more unfavorable prognostic factors in the MSKCC model, along with metastases in multiple organs. The OS of the patients who received temsirolimus alone was significantly better than the OS of those receiving IFN- α alone or combination therapy. The median OS was 10.9 months for the patients on temsirolimus alone vs 7.3 months for those treated with IFN- α alone. OS and PFS were inferior and toxicity was increased in the combination arm.¹² Importantly, approximately 20% of the patients in this trial were non-ccRCC patients, and thus, on the basis of these data, temsirolimus was often used in this population.

Everolimus is an orally administered mTOR inhibitor that was subsequently studied in the post-TKI setting. RECORD-1 (RAD001 Plus Best Supportive Care Versus BSC Plus Placebo in Patients With Metastatic Carcinoma of the Kidney Which Has Progressed After Treatment With Sorafenib and/or Sunitinib), a multicenter, double-blind, randomized phase 3 trial, assigned 410 patients whose disease had progressed on treatment with sunitinib or sorafenib in a 2:1 ratio to everolimus or placebo. The median PFS was 4 vs 1.9 months, favoring everolimus.¹⁵ Temsirolimus has largely been supplanted by everolimus because mTOR inhibition is typically used beyond the first-line setting, and patients often prefer the ease of oral administration.

Programmed Death 1 Blockade

Programmed death 1 (PD-1) is a transmembrane protein expressed on activated effector T cells, but not on resting T cells. PD-1 has 2 known ligands, programmed death ligand 1 (PD-L1) and PD-L2, which can be expressed

on a variety of cells, including antigen-presenting cells, tumor cells, and T-cells themselves. When bound to its ligands, PD-1 inhibits signaling pathways that normally lead to an effective T-cell response.³⁵ Nivolumab is the only PD-1 inhibitor currently approved by the FDA for the treatment of patients with mRCC. The PD-L1 inhibitors atezolizumab (Tecentriq, Genentech), durvalumab (Imfinzi, AstraZeneca), pembrolizumab (Keytruda, Merck), and avelumab (Bavencio, EMD Serono) are being studied in patients with RCC but are not yet approved by the FDA for this indication.

Nivolumab

Nivolumab is approved as second-line or later therapy following the failure of antiangiogenic treatment in patients with advanced RCC. This approval was based on results from the phase 3 CheckMate 025 trial (Study of Nivolumab vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma), in which OS was significantly longer in the patients with mRCC who received nivolumab (n=406) than in those who received everolimus (n=397): 25 vs 19.6 months, respectively (HR, 0.73; $P=.002$).³⁶ The ORR was 5 times higher in the nivolumab arm than in the everolimus arm (25% vs 5%). The effect of continuing nivolumab treatment in patients with disease progression was retrospectively reviewed in CheckMate 025. The results showed that in approximately 50% patients with mRCC, nivolumab treatment beyond first progression was associated with subsequent reduction of the tumor burden. These patients had favorable disease characteristics compared with those who discontinued treatment after first progression, underscoring the patient selection bias in these data.³⁷ Nonetheless, treatment beyond progression is generally accepted practice for those patients felt to be deriving clinical benefit.

Nivolumab in combination with VEGF inhibitors.

Preclinical data suggest that VEGF inhibitors may reduce tumor-induced immunosuppression.³⁸ The cytokine VEGF-A can modulate immune response by promoting the development and regulation of myeloid-derived suppressor cells, which impair T-cell effector function directly, as well as indirectly, via the induction of regulatory T-cell formation.³⁹ On the basis of these hypotheses, nivolumab has been studied in combination with various VEGF inhibitors, including sunitinib, pazopanib, cabozantinib, and tivozanib.

A phase 1 trial investigated the combination of escalating doses of nivolumab with sunitinib (50 mg daily; 4 weeks on, 2 weeks off) or pazopanib (800 mg daily) in pre-treated patients with mRCC.⁴⁰ Although the pazopanib arm was closed because of several cases of high-grade liver

toxicity, in the sunitinib combination arm the dose of nivolumab was escalated, and this arm was also opened to treatment-naïve patients. Response rates as high as 52% in the sunitinib arm and 45% in the pazopanib arm were reported, although grade 3 or 4 adverse events occurred in 82% and 70% of the patients, respectively. Because of the poor tolerability, accrual to both arms was stopped.

The combination of cabozantinib plus nivolumab, alone or with the addition of ipilimumab, in patients having genitourinary tumors is being studied in a phase 1 trial (NCT02496208). Cabozantinib at 40 mg daily with nivolumab at 3 mg/kg every 2 weeks was recommended. Among 47 patients, 7 patients had RCC. Part 2 of the phase 1 study included 28 patients, 6 of whom had mRCC, treated with the triplet therapy (ipilimumab, nivolumab, and cabozantinib). Updated results from a phase 1 RCC expansion cohort reported an ORR of 53.9%, a 12-month PFS of 72.7%, and a 12-month OS rate of 50%.⁴¹ This combination is being further studied to define its activity in RCC.

A phase 1b/2 trial studied the combination of tivozanib (at 2 dose levels) with nivolumab. The combination was reported to be safe, and efficacy data are pending.⁴²

Nivolumab in combination with ipilimumab. Check-Mate 214 (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma) is a multicenter, phase 3, open-label study that randomly assigned 1096 patients in a 1:1 ratio to nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg given every 3 weeks for 4 doses, followed by nivolumab monotherapy at 3 mg/kg every 2 weeks or sunitinib monotherapy at 50 mg (4-weeks-on, 2-weeks-off schedule) in patients with advanced RCC.⁴³ Of the treated patients, 847 had intermediate- or poor-risk prognostic factors. In this group, the combination of nivolumab plus ipilimumab produced a higher ORR compared with sunitinib monotherapy (42% vs 27%). The 18-month OS rates also favored the combination arm, at 75% vs 60%, respectively. Grade 3 or 4 adverse events occurred in 43% and 63% of the patients, respectively. In the favorable-risk cohort, however, the efficacy of sunitinib was better than that of nivolumab plus ipilimumab in terms of 18-month OS rate (93% vs 88%), ORR (52% vs 29%), and median PFS (25.1 vs 14.3 months).⁴³

On the basis of these findings, the FDA approved ipilimumab with nivolumab for patients who have ccRCC with intermediate- or poor-risk factors and are treatment-naïve. The combination is now an option for these patients, along with VEGF TKIs, high-dose IL-2, and clinical trials, further expanding the treatment armamentarium in ccRCC.

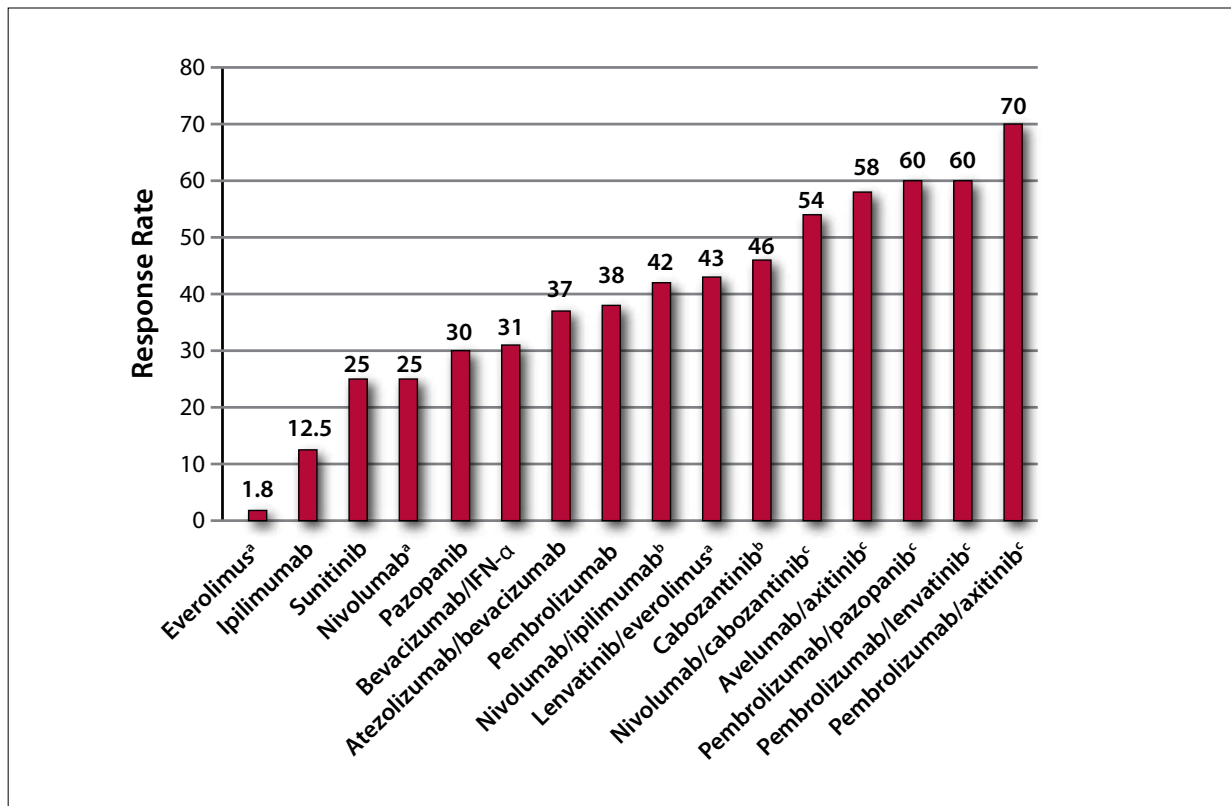


Figure. Response rates of various drug and drug combinations studied in advanced renal cell carcinoma for which final or preliminary clinical data are available.

IFN, interferon.

^a Second-line therapy.

^b Intermediate-/poor-risk patients.

^c Phase 1/1b data.

The ipilimumab/nivolumab combination also has been studied in previously treated patients. A phase 1 study called CheckMate 016 (Nivolumab in Combination With Sunitinib, Pazopanib, or Ipilimumab in Subjects With Metastatic Renal Cell Carcinoma) evaluated various doses of ipilimumab/nivolumab in treatment-naïve and previously treated patients with mRCC. Induction doses of ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg, along with ipilimumab at 3 mg/kg plus nivolumab at 1 mg/kg, were studied further. The ORR was 40% with both doses, and the 2-year OS rates were 67.3% and 69.6%, respectively. The confirmed ORRs in previously treated patients were 45.5% and 38.5%, respectively.⁴⁴ On the basis of these data, ipilimumab/nivolumab combination therapy is endorsed in the National Comprehensive Cancer Network guidelines for the treatment of patients with prior VEGF TKI therapy.

Pembrolizumab

Pembrolizumab is a humanized immunoglobulin G4

(IgG4) PD-1–blocking antibody that was investigated in a phase 1 trial enrolling patients with advanced solid tumors, including RCC.⁴⁵ Pembrolizumab is being studied as monotherapy in the frontline setting in KEY-NOTE-427 (Study of Pembrolizumab Monotherapy in Locally Advanced/Metastatic Renal Cell Carcinoma), which includes patients with both ccRCC and non-ccRCC. Early results from 110 patients in the ccRCC cohort were presented at the annual meeting of the American Society of Clinical Oncology in 2018. In these results, although they are immature, the ORR was 38% and the median PFS was 8.7 months.⁴⁶ Pembrolizumab is also being studied in combination with other therapies, such as the TKIs pazopanib (NCT02014636), axitinib (NCT02133742), and lenvatinib (NCT02501096).

Pembrolizumab in combination with VEGF inhibitors. The combination of pembrolizumab and axitinib was explored in an ongoing phase 1b study of patients with treatment-naïve advanced ccRCC. Pembrolizumab

at 2 mg/kg every 3 weeks and axitinib at 5 mg twice daily was considered safe and was used for expansion. The ORR in the combination arm was 73%, with approximately 8% of patients experiencing a complete response. The median PFS was 20.9 months at the data cutoff, and although elevation of liver enzymes occurred in approximately 17% of patients, the combination was otherwise well tolerated, with toxicities in line with what would be expected with either drug given as a single agent.⁴⁷ On the basis of these results, a phase 3 first-line trial comparing pembrolizumab plus axitinib with sunitinib monotherapy has completed accrual; results are expected in 2020 (NCT02853331).

Additionally, the combination of pembrolizumab and pazopanib was investigated in an ongoing phase 1/2 study. Preliminary data showed grade 3 or higher hepatotoxicity in 65% (13 of 20) of the patients.⁴⁸ The ORR was 40% for the total cohort, 60% for the group given pazopanib at 800 mg, and 20% for the group given pazopanib at 600 mg. An additional cohort was opened to determine whether the use of pazopanib alone for 9 weeks followed by a combination of pazopanib with pembrolizumab would mitigate the toxicity of the combination. Although the sequential schedule reduced hepatotoxicity, the combination was still considered toxic; grade 3/4 adverse events led to dose reduction in 80% of patients. The combination is therefore not being studied further.⁴⁹

Lenvatinib in combination with pembrolizumab was studied in a phase 1b/2 study that included patients with multiple previously treated solid tumors (NCT02501096). Results presented at the annual meeting of ESMO in 2017 indicated an ORR of 63.3% with this combination. The FDA granted the combination a breakthrough therapy designation in January 2018.

Updated results from ESMO 2017 indicated that 20 mg of lenvatinib per day plus 200 mg of intravenous pembrolizumab every 3 weeks is safe. At the time of the presentation, 8 patients with RCC were enrolled in the trial. A phase 3 trial comparing lenvatinib plus everolimus or pembrolizumab vs sunitinib alone in the first-line treatment of mRCC is ongoing (NCT02811861). Pembrolizumab is also being studied in combination with the VEGF inhibitors ziv-aflibercept (Zaltrap, Sanofi-Aventis/Regeneron; NCT02298959) and bevacizumab (NCT02348008).

Pembrolizumab in combination with other immunotherapies. Pembrolizumab with ipilimumab was evaluated in 1 of the 3 arms of a phase 1/2 study in patients with mRCC or melanoma (NCT02089685). The dose-escalation portion will investigate the safety of pembrolizumab in combination with ipilimumab or the cytokine pegylated IFN- α .

PD-L1 Inhibitors

Durvalumab

Durvalumab is a PD-L1 inhibitor that is currently being studied as monotherapy (NCT02669914) and in combination with the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-blocking antibody tremelimumab in a phase 1 study of selected patients with advanced solid tumors, including RCC (NCT01975831). Durvalumab is also being studied in combination with guadecitabine, a hypomethylating agent, in a phase 1b/2 study (NCT03308396).

Atezolizumab

Atezolizumab, a PD-L1 inhibitor, has been evaluated in combination with bevacizumab in the phase 3 IMmotion151 trial (A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma). In this trial, treatment-naïve patients were randomly assigned in a 1:1 ratio to intravenous atezolizumab at 1200 mg every 3 weeks plus intravenous bevacizumab at 15 mg/kg every 3 weeks or to sunitinib at 50 mg daily in a 4-weeks-on, 2-weeks-off schedule.⁵⁰ The coprimary endpoints of the study were PFS in patients with PD-L1 positivity (defined as expression $\geq 1\%$) by investigator review and OS in intention-to-treat (ITT) patients. The study showed a benefit in PFS in PD-L1-positive patients by investigator review (11.2 vs 7.7 months, favoring atezolizumab/bevacizumab), but in an independent review, the PFS benefit in PD-L1-positive patients was not significant. When all ITT patients were considered, the PFS benefit was seen in both investigator review and independent review. Interestingly, the ORRs did not differ between the 2 groups in the ITT population (33% vs 37%).⁵⁰ These are the first results of a large, prospective, randomized phase 3 trial of a VEGF TKI/immunotherapy combination to be reported, but the combination has yet to secure FDA approval. In addition, the clinical benefit of the combination is somewhat modest, particularly in relation to its projected cost. Its place in the mRCC landscape is likely uncertain given the results from CheckMate 214 and the pending results from the VEGF TKI/immunotherapy combination studies (Figure).

Atezolizumab is also being studied in combination with cabozantinib in a phase 1b study that will enroll patients with advanced urothelial cancer or RCC (NCT03170960).

Avelumab

An ongoing phase 1b study (NCT02493751) of avelumab at 10 mg/kg every weeks plus axitinib at 5 mg twice a day showed tolerable safety and encouraging antitumor activity

in treatment-naïve patients with mRCC.⁵¹ JAVELIN Renal 101 (A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer), a randomized, multicenter, phase 3 study (NCT02684006) comparing the combination vs sunitinib in treatment-naïve patients with mRCC, began enrollment in March 2016.

CTLA-4 Blockade

Another prominent immune checkpoint that is expressed on activated T cells and has been targeted successfully is CTLA-4. CTLA-4 binds with greater affinity and avidity than CD28 to B7 ligands and induces downstream inhibitory signaling, which ultimately leads to decreased T-cell proliferation.^{52,53} Ipilimumab and tremelimumab, 2 CTLA-4-directed monoclonal antibodies, have been studied as single agents and in combination with VEGFR TKIs in several trials. As previously mentioned, the combination of ipilimumab and nivolumab is now FDA-approved in the first-line setting for patients with mRCC who are at intermediate or poor risk.

In the phase 2 ipilimumab single-agent study, the response rate in the higher-dose cohort was 12.5%, with no complete or durable responses.⁵⁴ In a phase 1 trial, tremelimumab was studied in combination with sunitinib. The study enrolled 28 patients but was stopped because of excessive toxicity (1 death and 4 patients with renal failure), and this combination was aborted. Partial responses were achieved in 9 of 21 patients who were evaluable for response (ORR, 43%; 95% CI, 22%-66%).⁵⁵ To our knowledge, no trials evaluating single-agent tremelimumab are ongoing in RCC. As such, CTLA-4 antibody monotherapy in RCC has not been studied further.

The Role of PD-L1 in Metastatic RCC

The development of predictive biomarkers to determine which patients will derive clinical benefit from checkpoint inhibitors remains important clinically and is an area of active investigation. The use of PD-L1 immunohistochemistry has been confounded by multiple unresolved issues, including differing assays, different targets (expression on tumors cells, lymphocytes, or both), and different expression thresholds to define PD-L1 positivity.⁵⁶ The CheckMate 025 trial, which studied single-agent nivolumab in the second-line treatment of ccRCC, demonstrated that although PD-L1 expression was associated with a poor prognosis, lack of PD-L1 expression did not exclude the possibility of an objective response.^{36,57} As a result, investigators determined that PD-L1 status was not predictive in this setting. However, in the recent CheckMate 214 study, the ORR among patients with PD-L1 expression below 1% was 37% with nivolumab/ipilimumab and 28% with

sunitinib ($P=.03$). Among patients with PD-L1 expression of 1% or greater, the ORR was 58% with nivolumab/ipilimumab and 22% with sunitinib ($P<.001$).⁴³ A similar trend was observed in median PFS. Although the clinical use of PD-L1 to predict response to immunotherapy is premature, PD-L1 continues to be studied as a potential biomarker in various clinical trials, and a search for more promising biomarkers is needed. A recent analysis of pretreatment tumors in patients with mRCC who were receiving nivolumab showed that in those with biallelic *PBRM1* loss, OS and PFS were significantly longer than in patients without *PBRM1* loss of function.⁵⁸ Likewise, a clinical trial comparing atezolizumab/bevacizumab vs atezolizumab vs sunitinib in the frontline treatment of patients with mRCC showed a significantly higher ORR among patients in the sunitinib arm with a high angiogenesis signature than in patients in the sunitinib arm with a low angiogenesis signature.⁵⁹

Determining the Sequence of Therapy

In patients with oligometastatic disease, an indolent disease course, and good prognostic factors, treatment options include CN and metastasectomy (as previously discussed), as well as observation with serial imaging.⁶⁰ The results of the CARMENA trial indicate that patients with high-volume disease and intermediate or poor prognostic factors should proceed to systemic therapy and may not need CN. Cabozantinib and ipilimumab/nivolumab are now both FDA-approved first-line agents specifically for patients with intermediate- and poor-risk prognostic factors per the IMDC criteria. Pazopanib and sunitinib can also still be used in the first-line setting and are arguably the treatment of choice for low-risk patients. In a very selected subpopulation of healthy patients, high-dose IL-2 can be considered in the first-line setting. With other, better options available in this space, temsirolimus and sorafenib have been largely abandoned. Given the encouraging phase 1b data for pembrolizumab/axitinib and other VEGFR TKI/immunotherapy combination therapies, combination therapies may be approved in the first-line setting in the near future (Figure). Fewer grade 3/4 adverse effects were noted for atezolizumab/bevacizumab in comparison with pembrolizumab/axitinib (40% vs 54%), although this information was obtained by cross-trial comparison. On the basis of results previously noted, the lack of an ORR benefit in the ITT population, and the lack of PFS benefit by independent review in PD-L1-positive patients receiving atezolizumab/bevacizumab, the enthusiasm for this combination has been dampened to some extent. Enrollment in several open clinical trials of checkpoint inhibitor/VEGFR TKI combination therapy is strongly encouraged.

In the second-line setting, for patients who have previously received VEGFR TKI therapy, either a second VEGFR TKI or immune checkpoint inhibitor can be used. Although ipilimumab/nivolumab was studied in the frontline setting in CheckMate 214, phase 1 expansion data support this combination in patients whose disease has progressed on VEGFR TKI therapy. Naturally, this combination is associated with greater toxicity and should be administered only to appropriate patients. Nivolumab is currently FDA-approved in the second-line setting for patients with mRCC who have progressed on prior therapy. The VEGFR TKIs sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, and everolimus are all reasonable options for second-line and later treatment. Single-agent everolimus is usually not used in the first or second line of therapy and is reserved for later use if patients experience disease progression on other, more effective therapies. Other checkpoint inhibitor/VEGFR TKI combinations, as well as novel drugs such as HIF2a inhibitors, IDO1 inhibitors, and glutaminase inhibitors, are currently being studied in clinical trials.

Summary and Conclusions

The approval of multiple agents in the treatment of mRCC has offered promising options to patients with this disease. Given the abundance of clinical data, clinicians should make informed decisions with their patients, considering the level of evidence, adverse effects, available subgroup analysis, cost and insurance coverage concerns, and ease of treatment administration. With the recent approval of multiple agents in the first-line setting and beyond, the concept of “lines of therapy” in the treatment of mRCC as traditionally viewed by clinicians is collapsing. Rational combination approaches with TKIs, novel checkpoint inhibitors, and other immune modulators may become standard of care in the coming years.

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