Sequencing Therapies for Metastatic Renal Cell Carcinoma

Nazli Dizman, MD[a], Zeynep E. Arslan, MD[b], Matthew Feng[a], Sumanta K. Pal, MD[a,*]

KEYWORDS

• Targeted therapy • Immunotherapy • Sequencing • RCC • Kidney cancer

KEY POINTS

- In an era of several available therapeutic options, optimal treatment sequencing is crucial to providing patients with the most effective therapy and promoting quality of life.
- In clear cell renal cell carcinoma, a combination approach with an immunotherapy backbone, such as nivolumab/ipilimumab or axitinib/pembrolizumab, has established a key role in the first-line setting. Safety and activity data support the transition to single-agent targeted therapies (cabozantinib or axitinib) in the second-line setting. Nivolumab monotherapy possesses clinical and mechanistic rationale as a second-line therapeutic option for patients treated with targeted therapies in the first-line setting.
- Programmed cell death protein 1 and programmed death-ligand 1 expression levels currently are not used to guide treatment selection in clinical practice, due to lack of supporting evidence. At present, gene expression models are being generated from large prospective clinical trial data sets.

INTRODUCTION

United States–based epidemiologic studies indicate that more than 70,000 individuals are diagnosed with renal cell carcinoma (RCC) annually, and 17% of these present with metastatic disease.[1–3] RCC encompasses several histologic subtypes that bear distinct biologic and clinical features. Clear cell RCC (ccRCC) accounts for approximately 80% of all cases whereas papillary RCC represents the second major subtype and is seen in approximately 10% to 15% of cases. Rare subtypes comprise the remaining RCC population and include chromophobe RCC, collecting duct RCC, renal medullary carcinoma, and others.[4–6] In addition, sarcomatoid histology represents up to 15% of all the RCC cases and can be seen either as an isolated entity or as sarcomatoid differentiation accompanying other histologic subtypes. Tremendous efforts have been made to individualize treatment strategies in this diverse patient population with the intent of lengthening survival while maintaining the quality of life of patients with metastatic RCC (mRCC).[7,8] Accordingly, the treatment algorithm for mRCC has changed drastically within the past 2 decades.[8,9] **Fig. 1** represents the mRCC therapeutics with regulatory approval to date and their indications.

Currently available mRCC therapies can be categorized broadly as targeted therapies and immunotherapies. Mechanistically, targeted therapies blockade tumor angiogenesis via vascular endothelial growth factor (VEGF) tyrosine kinase

[a] Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010, USA; [b] Istanbul Medipol University Medical School, Kavacık Mah. Ekinciler Cad. No: 19, Kavacık Kavşağı, 34810 Beykoz, Istanbul, Turkey
* Corresponding author.
E-mail address: spal@coh.org

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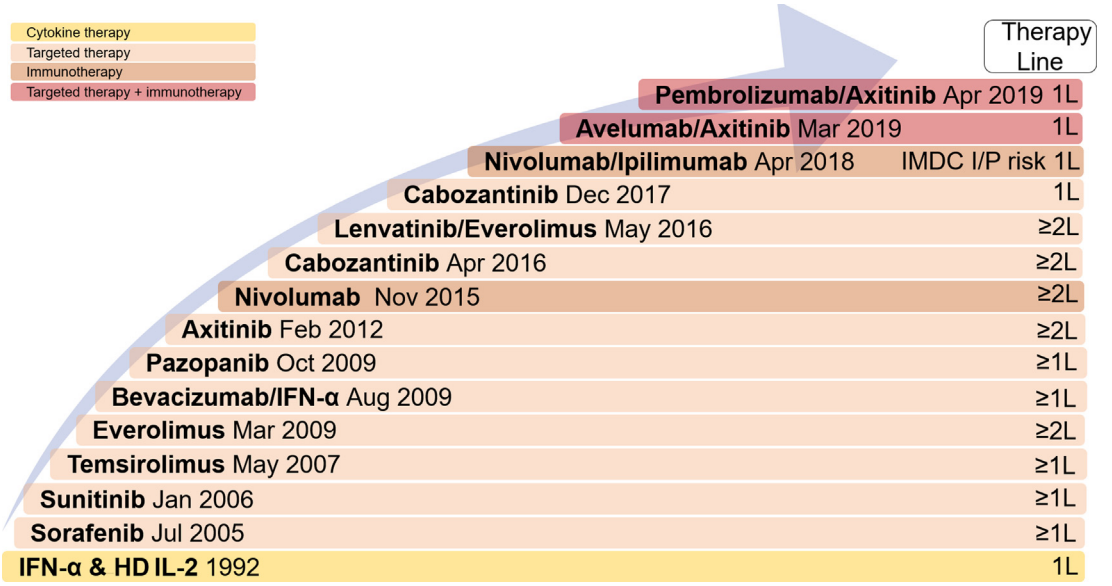

Fig. 1. Agents approved by FDA in first-line and further-line treatment of mRCC. HD, high-dose; I/P, Intermediate/Poor.

inhibitors (sunitinib, cabozantinib, axitinib, sorafenib, and pazopanib), anti-VEGF monoclonal antibodies (bevacizumab), or mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus). Traditional immunotherapies, such as interferon (IFN)-α and interleukin 2, have been the mainstay of mRCC treatment in the era prior to targeted therapies. Despite moderate clinical benefit among mRCC patients, the excessive toxicities associated with traditional immunotherapies led to limitations in their utilization.[10,11] Modern immunotherapies include agents that disable tumor cells' ability to evade the immune system via inhibition of programmed cell death protein 1 (PD-1) (eg, nivolumab and pembrolizumab), programmed death-ligand 1 (PD-L1) (eg, atezolizumab and avelumab), or cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) (eg, ipilimumab).[12–14] For each of these aforementioned treatment modalities, only a certain proportion of the patients have demonstrated benefit across various measurable outcomes, including progression-free survival (PFS), overall survival (OS), objective response rate (ORR), toxicity, and patient-reported outcomes. As such, all forms of treatment currently serve crucial roles in the current paradigm for the treatment of mRCC, as evidenced by the approval of 15 different therapeutic approaches, 10 agents in first-line treatment and 11 agents in further-line treatment.[7]

As the list of therapeutic options has grown, the selection of treatment among individual patients has become more challenging. Existing clinical decision making in daily practice currently relies on assumptions based on cross-trial comparisons; however, there is a growing body of evidence regarding clinical and genomic features that potentially might guide treatment selection. For example, the CheckMate 214 study has offered insights into decision making by demonstrating benefit for International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favorable-risk patients with sunitinib and for intermediate-risk and poor-risk patients with nivolumab and ipilimumab combination as first-line treatment.[12] In addition, investigators have analyzed data from phase III trials of immunotherapy and targeted therapy combinations to develop models involving molecular characteristics and gene expression patterns of tumors to predict patients' response to therapies.[15] This article presents the current state of knowledge concerning treatment options for mRCC patients and proposes an algorithm for sequencing therapies, based on existing scientific evidence, in the hopes of prolonging survival and promoting quality of life.

CLEAR CELL RENAL CELL CARCINOMA FIRST-LINE TREATMENT OPTIONS

Targeted Therapies

The most common oncogenic event in ccRCC pathogenesis is the loss of chromosome 3p and subsequent *VHL* tumor suppressor gene alterations with either absence or malfunction of the VHL protein; hypoxia-inducible factors accumulate and prompt overexpression of growth factors, including VEGF and platelet-derived growth factor

B, culminating in tumor cell growth, proliferation, and aberrant angiogenesis. Targeted therapies that block the VEGF pathway were the first breakthrough treatment of patients with mRCC.

In 2006, Motzer and colleagues[16] reported the survival and response outcomes of first-line sunitinib versus IFN-α, with results favoring sunitinib in all major measures, including ORR, PFS, OS, and quality of life. Soon after, sunitinib was granted US Food and Drug Administration (FDA) approval, initiating a shift in the RCC treatment landscape from traditional immunotherapies (ie, high-dose interleukin and IFN-α) to the more tolerable and effective targeted therapies. Concurrently, temsirolimus, an mTOR inhibitor, showed improved PFS and OS compared with IFN-α and the combination of IFN-α and temsirolimus in patients with poor prognostic features.[17] Single-agent temsirolimus was better tolerated and provided the greatest benefit.[17] This study remains important by both demonstrating efficacy of temsirolimus in this vulnerable patient population and highlighting the value of offering a balance between efficacy and toxicity profiles during treatment planning. Pazopanib also has been utilized and evaluated widely, with initial studies among patient populations who were either treatment-naïve or pretreated with cytokine therapies.[18] Studies suggested that there was significant PFS improvement compared with placebo, results that led to a clinical trial comparing pazopanib with sunitinib in the first-line setting.[19] In this noninferiority trial, clinical outcomes were comparable between arms with PFS of 8.4 months (95% CI, 8.3–10.9) versus 9.5 months (95% CI, 8.3–11.1), respectively, and OS of 28.4 months (95% CI, 26.2–35.6) versus 29.3 months (95% CI, 25.3–32.5), respectively, for pazopanib and sunitinib.[19] The toxicity profile of pazopanib was more favorable, particularly in terms of fatigue, hand-foot syndrome, and thrombocytopenia.

The more recent next-generation targeted therapies tested in the first-line setting include axitinib, which demonstrates highly selective activity on target VEGF receptors, and cabozantinib, which inhibits multiple tyrosine kinases. Axitinib, a selective inhibitor of VEGF receptors 1, 2, and 3, failed to show a PFS improvement over sorafenib in first-line treatment.[20,21] Despite that the higher ORR with axitinib than with sorafenib might suggest activity signals, the study did not meet its primary endpoint.[21]

Evidence suggests that cabozantinib, a multikinase inhibitor of VEGF receptor, AXL, and MET, has MET and AXL receptor tyrosine kinases that are up-regulated by the accumulated hypoxia-inducible factors under pseudohypoxia conditions commonly present in RCC cells.[22,23] The combined inhibition of multikinases by cabozantinib was tested against sunitinib in the phase II CABOSUN study in first-line treatment of mRCC patients with IMDC intermediate-risk and poor-risk disease.[24,25] In a cohort of 157 mRCC patients, median PFS was 8.6 months with cabozantinib versus 5.3 months with sunitinib, per independent review committee assessment (**Table 1**). The difference in PFS was statistically significant, with a hazard ratio (HR) of 0.48, with 20% of patients in the cabozantinib arm achieving objective responses compared with only 9% of patients with sunitinib.[24,25] Whereas one-fifth of patients achieved an objective response in the cabozantinib arm, only 9% achieved a similar response with sunitinib. Toxicity profiles of the 2 regimens were comparable. Updated OS data after a median follow-up of 34.5 months revealed a numerical difference between the cabozantinib and sunitinib arms; however, statistical significance was not achieved.[25]

Perhaps more importantly, the results of the CABOSUN study in the patient population with bone metastases raised significant interest. Bone is the second most common metastatic site, with approximately one-third of patients developing bone metastases during the course of their mRCC progression.[14] Several studies, including a meta-analysis, have shown that bone metastasis is a poor prognostic feature for patients treated with targeted therapies.[26–28] The CABOSUN trial involved stratification and randomization based on the presence of bone metastasis, thus allowing in-depth analysis of outcomes in this vulnerable patient population. Subsequently, a significant PFS benefit was observed with cabozantinib over sunitinib in patients with bone metastasis. This elevated cabozantinib to the preferred first-line treatment option for IMDC intermediate-risk and poor-risk patients with bone involvement, per National Comprehensive Cancer Network (NCCN) guidelines.[7]

Sunitinib has remained the standard-of-care targeted therapy and main comparator arm to clinical trials in first-line mRCC treatment for more than a decade.[10,29] Development of first-line combination therapies, however, discussed later, subordinated sunitinib. In addition, the observed PFS and ORR benefits with cabozantinib over sunitinib also have encouraged the utilization of cabozantinib in first-line treatment, as opposed to sunitinib.[24] Currently, among the many available first-line targeted therapy agents, cabozantinib represents a suitable targeted therapy option, especially among immunotherapy-ineligible patients, such as those with active autoimmune disease or systemic steroid use (**Fig. 2**).

Table 1
Efficacy and safety outcomes in first-line clinical trials in metastatic renal cell carcinoma

	CABOSUN[24,25]	IMmotion151 (Intention-to-Treat Population)[41,42]	IMmotion 151 (Programmed Death-Ligand 1+)[41,42]	CheckMate 214 (Intention-to-Treat Population)[12]	CheckMate 214 (IMDC Favorable)[12]	CheckMate 214 (IMDC Interm-ediate/ Poor)[12]	KEYNOTE-426[13]	JAVELIN Renal 101 (Intention-to-Treat Population)[14]	JAVELIN Renal 101 (Programmed Death-Ligand 1+)[14]
Arms	Cabozantinib vs sunitinib	Atezolizumab + bevacizumab vs sunitinib		Nivolumab + ipilimumab vs sunitinib			Pembro-lizumab + axitinib vs sunitinib	Avelumab + axitinib vs sunitinib	
Accrual (N)	157	915	362	1096	249	847	861	886	560
Phase	II	III		III			III	III	
Stratification factors	IMDC risk group Bone metastasis	MSKCC risk group Liver metastasis PD-L1 expression (<1% vs ≥1%)		IMDC risk group Geographic region			IMDC risk group Geographic region	ECOG performance status Geographic region	
PFS (mo) HR (95% CI) *P* value	8.6 vs 5.3 0.48 (0.31–0.74) *P* = .0008	11.2 vs 8.4 0.83 (0.70–0.97) *P* = .0219	11.2 vs 7.7 0.74 (0.57–0.96) *P* = .0217	9.7 vs 9.7 0.85 (0.73–0.98) *P* = .027	NR vs NR 1.23 (0.90–1.69) *P* = .19	8.2 vs 8.3 0.77 (0.65–0.90) *P* = .0014	15.1 vs 11.1 0.69 (0.57–0.84) *P*<.001	13.8 vs 8.4 0.69 (0.56–0.84) *P*<.001	13.8 vs 7.2 0.61 (0.47–0.79) *P*<.001
OS (mo) HR (95% CI) *P* value	26.6 vs 21.2 0.80 (0.53–1.21)	33.6 vs 34.9 0.93 (0.76–1.14) *P* = .4751	34.0 vs 32.7 0.84 (0.62–1.15) *P* = .2857	NR vs 37.9 0.71 (0.59–0.86) *P* = .0003	NR vs NR 1.22 (0.73–2.04) *P* = .44	NR vs 26.6 0.66 (0.54–.080) *P*<.0001	89.9% vs 78.3% at 12 mo 0.53 (0.38–0.74) *P*<.0001	NE	NE
ORR (%)	20 vs 9	37 vs 33	43 vs 35	41 vs 34	39 vs 50	42 vs 29	59.3 vs 35.7	51.4 vs 25.7	55.2 vs 5.5
Complete response (%)	0 vs 0	5 vs 2	9 vs 4	11 vs 2	8 vs 4	11 vs 1	5.8 vs 1.9	3.4 vs 1.8	4.4 vs 2.1

Partial response (%)	20 vs 9	31 vs 31	34 vs 30	31 vs 32	31 vs 46	31 vs 28	53.5 vs 33.8	48 vs 23.9	50.7 vs 3.4
Stable disease (%)	54 vs 38	39 vs 39	32 vs 35	30 vs 41	44 vs 39	26 vs 41	24.5 vs 39.4	29.6 vs 45.5	26.7 vs 3.1
Progressive disease (%)	18 vs 29	18 vs 19	19 vs 21	22 vs 16	12 vs 5	25 vs 19	10.9 vs 17	11.5 vs 18.7	11.1 vs 1.7
NE (%)	8 vs 23	7 vs 9	7 vs 10	7 vs 10	5 vs 6	7 vs 10	1.9 vs 1.4	5.7 vs 7.9	4.4 vs 7.2
Adverse events									
All grade (%)	92 vs 89	91 vs 96		81 vs 83			98.4 vs 99.5	99.5 vs 99.3	
Grade 3–4 (%)	68 vs 65	40 vs 54		47 vs 64			62.9 vs 58.1	71.2 vs 71.5	
Treatment discontinuation (%)	21 vs 22	5 (both), 2 (atezolizumab), 5 (bevacizumab) vs 8		22 vs 12[a]			10.7 (both), 30.5 (either) vs 13.9	7.6 (both) vs 13.4	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NE, not evaluable; NR, not reached.

[a] 29% received ≥40-mg prednisone.

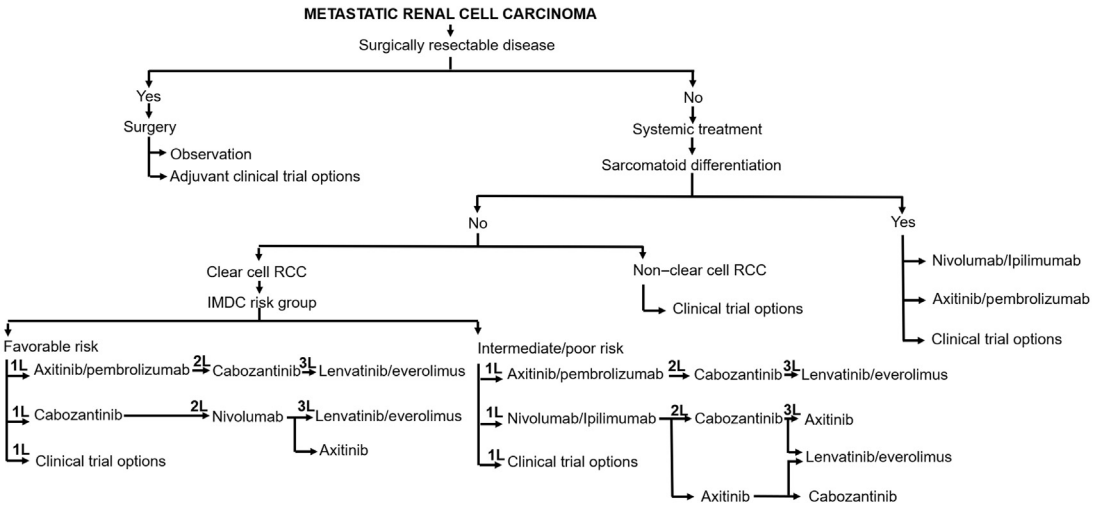

Fig. 2. Authors' proposed management algorithm for patients with mRCC.

Immunotherapies

In addition to possessing angiogenic characteristics, RCC bears high immunogenicity.[15,30] Traditional immunotherapies, cytokines, had been the mainstay of mRCC treatment in the era prior to targeted therapies. By the early 2000s, identification of immune checkpoint molecules, such as CTLA-4 and PD-1 on the surface of T cells and PD-L1 on dendritic cells and tumor cells, restored scientific interest in immuno-oncology agents.[31] In the realm of RCC therapeutics, the PD-1 inhibitor, nivolumab, was the first immunotherapy to establish activity, with better OS outcomes and tolerability over everolimus in patients who failed on treatment with a targeted therapy.[32]

The immuno-oncology approach later was adopted in the first-line setting as part of a more aggressive strategy, including a combination nivolumab and ipilimumab in the phase III CheckMate 214 clinical trial.[12] The results of this study brought essential insights on the efficacy of immunotherapeutics in mRCC.[12] In total, 1096 treatment-naïve mRCC patients were enrolled and received either a combination of nivolumab and ipilimumab or single-agent sunitinib (see **Table 1**).[12] Randomization was stratified based on IMDC risk categories (favorable risk vs intermediate–high risk) and geographic region.[12] The treatment regimen in the combination arm employed administration of nivolumab, 3 mg/kg, and ipilimumab, 1 mg/kg, every 3 weeks for 4 courses, and then maintenance nivolumab, 3 mg/kg, every 2 weeks, whereas a traditional treatment schedule was used in the sunitinib arm, with 50 mg/d orally, with 4 weeks on 2 weeks off.[12]

The initial results of 25 months follow-up revealed notable activity of the combination over sunitinib in a patient population with IMDC intermediate-risk or high-risk disease. OS was not reached in the combination arm versus 26 months in the sunitinib arm. Moreover, HR for death was 0.63, reflecting a 37% reduction of risk of death with the combination agent, and the 18-month OS rates were 75% and 60% in the combination arm and the sunitinib arm, respectively.[12] PFS accordingly was longer in the combination arm, but the difference was not statistically significant (11.6 months vs 8.4 months; HR 0.82; 99.1% CI, 0.64–1.05). Response rates favored the combination treatment, with ORRs of 42% and 27%, respectively, with 9% of the patients experiencing a complete response in the immunotherapy arm versus 1% in the sunitinib arm.[12] Direction of benefit, however, was the inverse in the favorable-risk patient population; the 18-month OS rate was 88% with combination therapy and 93% with sunitinib and demonstrated an HR of 1.45 (99.8% CI, 0.51–4.12).[12] Median PFS was 15.3 months in the combination arm versus 25.1 months in the sunitinib arm (HR 2.18; 99.1% CI, 1.29–3.68), and ORR was 29% with the combination versus 52% with sunitinib.[12] Importantly, the combination of nivolumab and ipilimumab provided a complete response in 11% of the patients in the favorable-risk population, whereas only 6% achieved a similar response with sunitinib.

Updated outcomes of the CheckMate 214 trial, after a minimum follow-up of 42 months, have confirmed the sustained OS and ORR benefits associated with this combination therapy in

intermediate-risk and poor-risk populations.[33] In addition, over this extended follow-up period, the difference in PFS between the combination arm and the sunitinib arm increased and reached statistical significance (12.0 months vs 8.3 months, respectively; HR 0.76 [0.63–0.91]). In the overall population, the 42-month OS rate was 56% in the combination arm versus 47% with sunitinib, recording a *P* value of 0.0002. Similar to the results of the initial analyses, a median OS was not reached and the difference between arms was not significant in the favorable-risk patient group. The combination of nivolumab and ipilimumab demonstrated higher complete response rates over sunitinib in the overall cohort, intermediate–poor-risk disease cohort, and favorable-risk cohort, with rates of 11% versus 2%, respectively; 10% versus 1%, respectively; and 13% versus 6%, respectively. Notably, 86% of complete responses were ongoing at the time of data cutoff, and 28 of the 59 complete responders did not require a subsequent treatment after discontinuation of nivolumab and ipilimumab after a median duration of 34.6 months.

Concerning safety outcomes, both all-grade and grade 3–4 adverse events were seen more frequently in the sunitinib arm. Despite this, treatment discontinuation due to adverse events was more common with immunotherapy (22%) than sunitinib (12%), patient-reported outcomes reported by Cella and colleagues[34] suggested better tolerability of the immunotherapy combination over sunitinib.[12]

The substantial survival benefit and the longevity of the responses observed with nivolumab and ipilimumab combination led to approval of the combination agents for metastatic ccRCC patients with IMDC intermediate-risk and poor-risk patients. The NCCN and Society for Immunotherapy of Cancer (SITC) guidelines now recommend nivolumab and ipilimumab combination as preferred treatment in metastatic ccRCC patients with IMDC intermediate-risk or poor-risk disease.[7,35]

Importantly, the contrasting benefit patterns in different IMDC risk classes with 2 mechanistically distinct approaches brought about a new perspective to the field. IMDC risk classification originally was developed as a prognostic tool among a large cohort of mRCC patients receiving targeted therapy.[36] Benefit from immunotherapy in this patient population, which was previously identified as bearing poor prognosis, extended this domain of investigation to identifying molecular correlates of response to immunotherapies. The CheckMate 214 study included exploratory analyses of clinical outcomes based on PD-L1 expression; however, among the intermediate-risk and high-risk cohorts, OS benefit with the immunotherapy combination over sunitinib was independent of PD-L1 expression levels.[12] When a positive PD-L1 expression level was defined by greater than or equal to 1%, ORR favored immunotherapy in both PD-L1–positive and PD-L1–negative patients.[12] Therefore, the predictive capability of PD-L1 expression was considered inconclusive and possibly not clinically significant with the nivolumab and ipilimumab combination.

Pembrolizumab also was studied in the first-line treatment of mRCC in the phase II Keynote-427 study.[37] An analysis of the 107 enrolled patients demonstrated efficacy with ORR of 33.6% and the treatment had favorably safety.[13] Single-agent pembrolizumab has not been investigated further, however, given the profound efficacy of combination therapy involving pembrolizumab in first-line treatment of mRCC, data that are discussed later. Single-agent immunotherapy currently is not considered appropriate first-line therapy.

Instead, combination nivolumab and ipilimumab is a standard-of-care option for immunotherapy-eligible patients with IMDC intermediate-risk and poor-risk disease (see **Fig. 2**).

Combination Therapies

Following the success of targeted therapies and immunotherapies in mRCC treatment, further efforts were directed to evaluating combination therapies that could inhibit angiogenesis and foster immune surveillance simultaneously.[13,14] Investigators sought to attain immediate decreases in tumor burden with PFS benefit, combined with durable responses and OS benefit, with a favorable toxicity profile. In addition, basic science research showed that targeted therapies bear immunomodulatory effects within the tumor microenvironment by prompting regulatory T cells, myeloid-derived suppressor cells, and cytokines to suppress ongoing immune escape.[38–40] Thus, a combination of the two active compounds could possess a potential synergistic activity beyond their additive effects.

The randomized phase III IMmotion151 trial was the first to report outcomes of the combination approach in first-line treatment of mRCC patients with clear cell or sarcomatoid histology (see **Table 1**).[41] The study enrolled 915 patients randomized to sunitinib or a combination of bevacizumab and atezolizumab. Stratification factors included PD-L1 expression (<1% vs ≥1%) on tumor-infiltrating lymphocytes, presence of liver metastasis, and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic group.[41] Median PFS in the

PD-L1–positive population and in the intention-to-treat population both favored the bevacizumab/atezolizumab combination over sunitinib (11.2 months vs 7.7 months, respectively, HR 0.74; and 11.2 months vs 8.4 months, respectively, HR 0.83). OS was comparable, however, across both arms in both PD-L1–positive and the intention-to-treat analyses.[41] In this study, important results emerged among those with sarcomatoid histology[42]; 61% of patients with sarcomatoid histology were PD-L1–positive and there was substantial improvement observed in ORR and PFS when those patients were treated with bevacizumab/atezolizumab.[42] In the PD-L1–positive sarcomatoid RCC patients, PFS results favored bevacizumab/atezolizumab, with an HR of 0.46. More importantly, the superior efficacy of bevacizumab/atezolizumab in terms of ORR and PFS was independent from PD-L1 status among sarcomatoid RCC patients.[42] Despite that, the IMmotion151 trial met its first coprimary endpoint, the PFS benefit in a PD-L1–positive patient population, the second co-primary endpoint of OS benefit in the overall population was not met, and thus the combination has not received regulatory approval.

Two other breakthrough studies in the realm of mRCC treatment were reported in 2019; the KEYNOTE-426 and JAVELIN Renal 101 trials (see **Table 1**). KEYNOTE-426 compared the combination of pembrolizumab and axitinib with sunitinib, whereas JAVELIN Renal 101 compared the combination of avelumab and axitinib with sunitinib.[13,14] Both combinations obtained immediate FDA approval within months. In the KEYNOTE-426 study, pembrolizumab and axitinib met primary endpoints of OS and PFS along with the key secondary endpoint of ORR.[13] At the 12-month cutoff of OS analysis, 89.9% versus 78.3% of the patients were alive in the combination and sunitinib arms, respectively.[13] The statistical difference favored pembrolizumab/axitinib with an HR of 0.53. Median PFS was 15.1 months in the pembrolizumab/axitinib arm versus 11.1 months in the sunitinib arm. In the combination arm, 59.3% of the patients achieved an objective response, with 5.8% having complete response; in contrast, ORR was 35.7% and only 1.9% of the patients achieved complete response in the sunitinib arm.[13] The randomization of the study was stratified based on IMDC risk status of patients, and the results showed that OS and PFS benefits with the combination were independent of IMDC risk status or PD-L1 expression status.

In the JAVELIN Renal 101 study, the combination of avelumab and axitinib demonstrated improved PFS over sunitinib in both the PD-L1 positive ($\geq$1% on immune cells) and overall population (13.8 months vs 7.2 months, respectively [HR 0.61; 95% CI, 0.47–0.79], and 13.8 months vs 8.4 months, respectively [HR 0.69; 95% CI, 0.56–0.84].[14] In the overall population, ORR was 51.4% with the combination treatment versus 25.7% with sunitinib, with complete response rates of 3.4% and 1.8%, respectively. At the time of the first publication, OS data of the study were not mature and only a small number of patients were deceased in each group.[14]

When evaluating the results of the 2 FDA-approved combination therapies involving a targeted therapy and immunotherapy, toxicity profile becomes an important area of consideration. The proportions of the patients who developed any grade adverse event appeared comparable in KEYNOTE-426 and JAVELIN Renal 101, 98.4% and 95.4%, respectively, with 10.7% and 7.6%, respectively, of patients requiring discontinuation of the combination due to side effects.[13,14] Rates of fatigue, hypertension, and rash were similar in both combination therapies. The combination of pembrolizumab/axitinib was associated with a higher rate of hypothyroidism (35.4% vs 24.9%) and gastrointestinal toxicities, such as diarrhea (62.2% vs 54.3%) and nausea (34.1% vs 27.7%) compared with avelumab/axitinib. Overall, the toxicity profiles of the pembrolizumab/axitinib and avelumab/axitinib were similar.

Whereas both combinations obtained almost immediate FDA approval, most current guidelines of NCCN and SITC both recommend pembrolizumab/axitinib as the preferred immunotherapy-targeted therapy combination in the first-line setting, regardless of IMDC risk category, due primarily to the lack of OS data in the JAVELIN 101 clinical trial.[7,35] The authors' preferences are in line with these guideline recommendations (see **Fig. 2**).

FURTHER-LINE TREATMENT

Decisions regarding second-line treatment strategies are based broadly on the type of first-line therapeutic a patient has received. According to a large 2014 study, VEGF–tyrosine kinase inhibitors were the agents utilized most commonly by US-based medical oncologists for patients with RCC.[43] Although the results of this report might now be outdated with addition of the novel immunotherapeutics and combination therapies, there remains a considerable number of patients who received or have been receiving first-line targeted therapies. Second-line options for this patient population include single-agent nivolumab or 1 of the other targeted therapies, including mTOR

inhibitors or VEGF-directed therapies. Details of clinically relevant second-line and further-line studies are presented in **Table 2**.

For patients who had been treated with first-line targeted therapies, nivolumab represents a sensible option based on the results of the CheckMate 025 study, wherein nivolumab was compared with everolimus in targeted therapy–exposed mRCC patients.[32,44] In this study, approximately two-thirds of patients had received sunitinib, whereas the remaining received pazopanib or axitinib prior to the study therapy. Median OS was reached at 25 months (95% CI, 21.8-NE) with nivolumab compared with 19.6 months (95% CI, 17.6–23.1) with everolimus, with HR of death of 0.73 (98.5% CI, 0.57–0.93). OS benefit with nivolumab remained significant within different subgroups of patients with regard to IMDC risk stratification, age, metastatic sites, and type of prior targeted therapeutic.[32,44] Importantly, forest plots showed more prominent benefit with nivolumab in patients with IMDC poor-risk disease. Whereas PFS was similar between the 2 cohorts, a notable 25% of the patients had objective response in the nivolumab arm versus 5% in the everolimus arm.[32,44] In light of the results of CheckMate 025, the most

Table 2
Outcomes in clinical trials examining second-line and further-line therapies in metastatic renal cell carcinoma

	Axitinib vs Sorafenib[20]	Lenvatinib + Everolimus vs Lenvatinib vs Everolimus[54]	Nivolumab vs Everolimus[32]	Cabozantinib vs Everolimus[51]
Accrual (N)	723	153	821	658
Phase	III	II	III	III
PFS (mo) HR (95% CI) *P* value	8.3 vs 5.7 0.66 (0.55–0.78) *P*<.0001	14.6 vs 7.4 vs 5.5 0.40 (0.24–0.68) *P* = .005[a] 0.66 (0.39–1.10) *P* = .12[b] 0.61 (0.38–0.98) *P* = .048[c]	4.6 vs 4.4 0.88 (0.75–1.03) *P* = .11	7.4 vs 3.8 0.58 (0.45–0.75) *P*<.001
OS (mo) HR (95% CI) *P* value	20.1 vs 19.2 0.97 (0.80–1.17) *P* = .374	25.5 vs 19.1 vs 15.4 0.51 (0.30–0.88) *P* = .024[a] 0.75 (0.43–1.30) *P* = .32[b] 0.68 (0.41–1.14) *P* = .12[c]	25 vs 19.6 0.73 (0.57–0.93) *P* = .002	21.4 vs 16.5 0.66 (0.53–0.83) *P* = .00026
ORR (%) *P* value	19 vs 11 *P* = .0007	43 vs 27 vs 6[a] *P*<.0001[a] *P* = .10[b] *P* = .0067[c]	25 vs 5 *P*<.001	17 vs 3 *P*<.0001
Complete response (%)	0 vs <1	2 vs 0 vs 0	1 vs <1	0 vs 0
Partial response (%)	19 vs 11	41 vs 27 vs 6	24 vs 5	17 vs 3
Stable disease (%)	58 vs 59	41 vs 52 vs 62	34 vs 55	65 vs 62
Progressive disease (%)	17 vs 18	4 vs 6 vs 21	35 vs 28	12 vs 27
Not evaluable (%)	7 vs 11	12 vs 15 vs 8	6 vs 12	5 vs 8
Adverse events				
All grade (%)	NA vs NA	99 vs 94 vs 96	79 vs 88	100 vs 100
Grade 3–4 (%)	NA vs NA	71 vs 79 vs 50	19 vs 37	71 vs 60
Treatment discontinuation (%)	4 vs 8	24 vs 25 vs 12	8 vs 13	12 vs 11

Abbreviation: NA, not available.
[a] Lenvatinib and everolimus versus everolimus.
[b] Lenvatinib and everolimus versus lenvatinib.
[c] Lenvatinib versus everolimus.

current guidelines of NCCN and SITC recommend nivolumab as a preferred subsequent-line treatment, for those who progressed on first-line targeted therapies.[7,35]

Due to the increasing number of patients receiving first-line combination therapy involving 2 immunotherapeutics or an immunotherapeutic and a VEGF-directed therapy, second-line treatment selection after progression on first-line combinations is an emerging and increasingly critical issue. At present, there have been no published studies prospectively evaluating the efficacy of individual subsequent therapies, and thus the current state of knowledge is based on the retrospective reports in the literature.[45–49] Overall, studies examining this question have revealed efficacy and safety of VEGF-directed therapies after both immunotherapy doublet and immunotherapy and VEGF-directed therapy combinations.[45–49] For example, Dudani and colleagues[49] examined the IMDC cohort and reported outcomes with second-line targeted therapies after immunotherapy combinations. A total of 188 patients were included in the analysis, of which 113 patients were treated with first-line immunotherapy and targeted therapy combination and the remainder with nivolumab and ipilimumab. Response rates, OS rates, and times to treatment failure were similar between the 2 cohorts. Dudani and colleagues[49] carefully analyzed the clinical outcomes associated with subsequent therapies after combination therapy and revealed several hypothesis-generating results. Response to subsequent-line targeted therapies was higher in patients who received first-line nivolumab and ipilimumab than in those who received an immunotherapy and VEGF-directed therapy combination (45% versus 15%, respectively; $P = .040$), whereas times to treatment failure were 5.4 months and 3.7 months, respectively, although this latter difference was not statistically significant.[49]

As demonstrated in **Fig. 1**, in addition to nivolumab, several targeted therapy options exist in the treatment of mRCC patients after failure of first-line therapy. The NCCN kidney cancer guidelines recommend cabozantinib, axitinib, or lenvatinib/everolimus combination as preferred and category 1 targeted therapy in second-line and further-line settings.[7] Unfortunately, due to the unparalleled development and utilization of novel first-line combinations, no prospective evidence exists concerning the comparative efficacy of individual targeted therapies after novel first-line combinations. Recommendations on treatment sequencing in this state are based largely on studies testing the aforementioned agents in targeted therapy–treated patients. **Table 2** represents the results of the clinical trials testing mentioned therapies.

Cabozantinib represents a widely used and studied option in second-line setting of mRCC. Preclinical studies have revealed that previous sunitinib treatment enhances invasive ability of RCC cells and accelerates tumor growth. Blockade of MET and AXL via cabozantinib was shown to decrease tumor size and overcome the sunitinib-induced aggressive characteristics in xenograft models.[50] In parallel with this strong biologic rationale, cabozantinib has demonstrated improvement in 3 endpoints, PFS, OS, and ORR, compared with everolimus, in a population of patients treated previously with targeted therapies.[51] Subgroup analyses in this trial showed sustained efficacy for both OS and PFS outcomes regardless of IMDC groups, MET status of tumors, number of the prior therapies, and metastatic sites.[51] Importantly, for patients with bone metastases, cabozantinib represented an appropriate option with subgroup analyses favoring cabozantinib in patients with bone metastases. Regarding the post-immunotherapy efficacy of cabozantinib, a retrospective analysis showed disease control rates of 82% in patients exposed to prior-line immunotherapy and 75% in patients with previous treatment of immunotherapy and targeted therapy combination.[52] Thus, either after a combination therapy involving either 2 immunotherapies or an immunotherapy and targeted therapy, cabozantinib is a better option due to its mechanistic rationale and clinical evidence (see **Fig. 2**).

The next generation of clinical trials in the realm of mRCC will need to prioritize addressing issues in sequencing therapies under standardized conditions. The phase III PDIGREE trial (NCT03793166) has taken an important step to elucidate the sequencing strategies with immunotherapies and cabozantinib. In this ongoing clinical trial, patients with IMDC intermediate-risk or high-risk metastatic ccRCC are enrolled and initiated on nivolumab and ipilimumab combination. Following a preplanned management strategy based on treatment response, patients with progressive disease are switched to cabozantinib, whereas patients with complete response continue with single-agent nivolumab maintenance therapy. Patients who do not progress but do not achieve a complete response are randomized into either nivolumab maintenance therapy alone or in combination with cabozantinib. The PDIGREE trial aims to maximize treatment benefit by upscaling treatment strategies for those without an objective response and sparing responders from side effects of unnecessarily aggressive treatment combinations and

offers the potential to address various questions regarding treatment sequencing.

Axitinib has been introduced to the arena with a promising safety profile due to its highly selective inhibition of VEGF receptors. The profound antitumor activity of axitinib was demonstrated by significant PFS and ORR benefit over sorafenib in the second-line setting.[21] The number of adverse events seen with axitinib appeared similar to agents of the same therapeutic class, and side effects generally were more manageable. In addition, in this trial, the investigators included and periodically obtained the objective measures of symptom burden (Functional Assessment of Cancer Therapy–Kidney Symptom Index [FKSI] questionnaire and FKSI–Disease-related Symptoms subscale) as endpoints, with results revealing that symptom deterioration was significantly delayed in the axitinib arm compared with the sorafenib arm.[21] More recently, Ornstein and colleagues[53] published the phase II clinical data of axitinib in a novel dosing schedule that allowed dose adjustments based on side effects in a patient population previously treated with immune checkpoint inhibitors. This novel dosing scheme demonstrated the manageability of side effects associated with axitinib, with individualized dose adjustments or interruptions, without compromising efficacy. In detail, the novel schedule provided ORR of 20%, with an additional 50% of the patients possessing stable disease and a median PFS of 8.8 months. Importantly, none of the patients in this study required permanent treatment discontinuation due to adverse events.[53] Accordingly, for all patients after first-line nivolumab and ipilimumab treatment, or for fragile patients in further lines of therapy, axitinib would be a logical next step given the evident efficacy and tolerability (see **Fig. 2**).

The combination of lenvatinib and everolimus gained approval based on the results of a phase II clinical trial comparing the combination with single-agent everolimus, an mTOR inhibitor, and single-agent lenvatinib.[54] The combination exhibited better OS and PFS compared with single-agent everolimus but failed to show a statistically significant difference over single-agent lenvatinib with regard to OS and PFS (see **Table 2**).[54] Importantly, the combination of lenvatinib and everolimus provided ORR of 43%, with an additional 41% of patients experiencing disease stabilization. In light of the findings of this phase II study, the FDA approved the lenvatinib/everolimus combination in the treatment of targeted therapy–treated mRCC patients. Efforts currently are under way to explore the efficacy of this combination with a lower dose of lenvatinib in a phase II clinical trial (NCT03173560) in postimmunotherapy or post-targeted therapy setting and to compare the combination with sunitinib or a combination of pembrolizumab and lenvatinib (NCT02811861) in first-line setting.

Given that the evidence about the efficacy of this combination currently relies on phase II clinical trial data and the lack of benefit supporting superiority of the combination over lenvatinib in terms of PFS and OS, the authors consider the lenvatinib/everolimus combination as a further treatment option after failure on second-line cabozantinib or axitinib.

For patients who progressed on more than 2 therapies, the reliability of comparative evidence gradually decreases. In current clinical practice, utilization of next-generation sequencing emerges as a preferred approach to identify targetable genomic alterations.[55] Next-generation sequencing can be implemented in clinical practice through various commercial platforms that sequence tumor tissue specimens obtained by surgical interventions or biopsies or on circulating tumor DNA (ctDNA) extracted from a blood sample (ie, liquid biopsy).[55,56] Despite the fact that such alterations are not as highly predictive as in other solid cancer types, such as *EGFR* in non–small cell lung cancer or *BRAF* in melanoma, a growing body of evidence in mRCC points to certain associations with prognosis and prediction of benefit from therapies. For example, *PBRM1* mutations were found to be good prognostic indicators overall and to possess sensitivity to immunotherapies.[57,58] *BAP1* mutations have been associated with worse prognostic features, whereas alterations in genes contributing to mTORC1 signaling (ie, *MTOR*, *TSC1*, *TSC2*, and *PIK3CA*) were associated with enhanced benefit from mTOR inhibitors.[59–61] Evolution of tumor genomic characteristics with exposure to therapeutics also deserves attention. Sequential ctDNA assessment of 220 mRCC patients during their disease course yielded changes in rates of genomic alterations by time, suggesting a rationale for repeat screening for formation of new genomic alterations.[62] Ongoing investigations analyzing genomic findings of patients participating in large clinical trials are promising to provide better predictive markers to help personalize therapeutic approaches in both first line and subsequent lines of mRCC treatment.

SUMMARY

Within the past 2 decades, the mRCC treatment landscape has been rapidly revolutionized with the development of novel therapeutics, such as targeted therapies, immunotherapies, and

combination approaches. As a result, mRCC patients now have the potential to achieve longer survival durations without experiencing detrimental treatment side effects. Sequencing available therapies in a way that would enable a balance of survival benefit and toxicity profile is crucial. For ccRCC patients or for those with sarcomatoid histology, a combination therapy with an immunotherapy backbone, such as nivolumab and ipilimumab or pembrolizumab and axitinib, has established a role in front-line treatment, with evidence of improved PFS, OS, and ORR compared with single-agent targeted therapy. For those with contraindications for immunotherapies, cabozantinib provides a beneficial option with observed PFS and ORR benefit over sunitinib. The selection of subsequent lines of treatment largely relies on the mechanistic category of prior line of therapy. Second-line nivolumab is the recommended approach for immunotherapy-naïve patients. Following failure of nivolumab and ipilimumab, further options include a sequence of cabozantinib and axitinib, which is guided by available retrospective activity and tolerability data. Cabozantinib represents an appropriate option after progression on pembrolizumab and axitinib.

DISCLOSURE

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