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ABOUT COVER

Editorial board member of *World Journal of Clinical Oncology*, Dr. Takura is a Project Professor in the Department of Healthcare Economics and Health Policy, Graduate School of Medicine, University of Tokyo, Japan. He is part-time Research Fellow of the Cabinet Office and Chairman of the Specialized Agency of Cost-effectiveness Evaluation, Ministry of Health, Labour and Welfare. Dr. Takura also serves as a Guest Professor at Osaka University Graduate School of Medicine. Dr. Takura's research has focused on socioeconomic evaluation of cancer treatments and renal transplantation, and cost effectiveness analysis of revascularization for ischemic heart disease. His current approach to this work involves integrating big data from various sources. (L-Editor: Filipodia)

AIMS AND SCOPE

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RESPONSIBLE EDITORS FOR THIS ISSUE

Combination drug regimens for metastatic clear cell renal cell carcinoma

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Abstract

Renal cell carcinomas (RCC) make up about 90% of kidney cancers, of which 80% are of the clear cell subtype. About 20% of patients are already metastatic at the time of diagnosis. Initial treatment is often cytoreductive nephrectomy, but systemic therapy is required for advanced RCC. Single agent targeted therapies are moderately toxic and only somewhat effective, leading to development of immunotherapies and combination therapies. This review identifies limitations of monotherapies for metastatic renal cell carcinoma, discusses recent advances in combination therapies, and highlights therapeutic options under development. The goal behind combining various modalities of systemic therapy is to potentiate a synergistic antitumor effect. However, combining targeted therapies may cause increased toxicity. The initial attempts to create therapeutic combinations based on inhibition of the vascular endothelial growth factor or mammalian target of rapamycin pathways were largely unsuccessful in achieving a profile of increased synergy without increased toxicity. To date, five combination therapies have been approved by the U.S. Food and Drug Administration, with the most recently approved therapies being a combination of checkpoint inhibition plus targeted therapy. Several other combination therapies are under development, including some in the phase 3 stage. The new wave of combination therapies for metastatic RCC has the potential to increase response rates and improve survival outcomes while maintaining tolerable side effect profiles.

Key words: Renal cell carcinoma; Immunotherapy; Targeted therapy; Vascular endothelial growth factor; Programmed-death receptor 1; Programmed-death receptor ligand-1; Tyrosine kinase inhibitors

Core tip: The treatment of metastatic clear cell renal cell carcinoma (ccRCC) remains a challenge given the broad spectrum of disease presentations and outcomes, variety of treatment options without clear optimal sequencing, and the low rate of complete response to systemic monotherapy. The core of this work reviews the current status of systemic combination drug options in the treatment of metastatic ccRCC, encompassing the novel combinations of tyrosine kinase inhibitors and immune checkpoint inhibitors, with a focus on rationale for use, efficacy, and side effect profiles. We also discuss the role of biomarkers in the development of future therapeutic options.

INTRODUCTION

Kidney cancer is one of the top 10 most common cancers in men and women. In the United States, there are expected to be about 65340 new cases of kidney cancer in 2019 with about 14970 deaths. Renal cell carcinomas (RCC) account for approximately 3.8% of all new cancers and make up about 90% of renal cancers[1]. According to the American Cancer Society, the risk for developing kidney cancer in men is 1 in 47 and in women is 1 in 82[2].

Most renal masses are incidentally found and small (≤ 4 cm). Even patients with advanced disease are often asymptomatic at the time of diagnosis with about 20% of patients having metastatic disease at the time of presentation. The 5-year survival rate for metastatic RCC is 12.0%[3]. Approximately 80% of renal cell carcinomas are clear cell renal cell carcinomas (ccRCC). The other 15%-20% are non-clear cell renal cell carcinomas (nccRCC) which comprise a diverse group of histologic subtypes, each with varying molecular profiles. Histologies include clear cell-papillary, papillary type I or II, chromophobe, collecting duct, and other rare forms[4]. The focus of this paper will be management of clear cell histology.

Patients with metastatic RCC (mRCC) are categorized into risk groups by combining independent prognostic factors for survival. In addition to the Tumor, Nodes, Metastasis (TNM) staging system[5], the two most widely used RCC prognostic models are the Memorial Sloan Kettering Cancer Center (MSKCC)[6] and the International Metastatic RCC Database Consortium (IMDC)[7]. Table 1 summarizes the three prognostic models. The heterogeneous clinical behavior and variable response to therapy seen in RCC pose a challenge in developing therapeutic drug trials.

Surgery is considered the first line of treatment for Stage I to III disease while cytoreductive nephrectomy (CN) followed by systemic therapy is often used to treat metastatic disease[8]. However, the role of CN in advanced RCC is has been challenged in recent years given the efficacy of newer systemic therapies[9]. RCC is not highly responsive to cytotoxic chemotherapy or radiotherapy[10], making systemic targeted therapies and immune checkpoint inhibitors (ICI) critically important, which will be the focus of this review.

MECHANISMS OF ACTION

The state-of-the-art therapy for RCC has undergone rapid transformation over the past fifteen years. Prior to 2005, cytokine therapy with interferon alpha (IFN-α) and then high dose interleukin 2 (HDIL-2) were considered the standard of care for the treatment of metastatic renal cell carcinoma[11,12]. The antitumor mechanism of HDIL-2 and IFN-α are mediated *via* activation of cytotoxic T lymphocytes and other cytokines. Since response rates were modest with these agents, high doses were administered, which resulted in substantial toxicity[13,14]. HDIL-2 side effects often need to be managed in an intensive care unit and were associated with a mortality rate of 1% to 5%[15]. The overall response rates (ORR) of IL-2 and IFN-α range between 5% to 20% with a median overall survival (OS) of about 10 to 15 mo[13]. Though the use of HDIL-2 has mostly fallen out of favor, some centers continue its use, often in clinical trials in

Table 1 Renal cell carcinoma prognostic models

Model	Prognostic factors	Prognostic risk groups
Memorial Sloan Kettering Cancer Center[6]	(1) Interval from diagnosis to treatment of less than 1 year; (2) Karnofsky performance status less than 80%; (3) Serum lactate dehydrogenase greater than 1.5 times the upper limit of normal (ULN); (3) Corrected serum calcium greater than the ULN; and (4) Serum hemoglobin less than the lower limit of normal	(1) Low-risk group: No prognostic factors; (2) Intermediate-risk group: One or two prognostic factors; and (3) Poor-risk group: Three or more prognostic factors
International Metastatic RCC Database Consortium[7]	(1) Less than one year from time of diagnosis to systemic therapy; (2) Performance status < 80% (Karnofsky); (3) Hemoglobin < lower limit of normal; (4) Calcium > upper limit of normal; (5) Neutrophil > upper limit of normal; and (6) Platelets > upper limit of normal	(1) Favorable-risk group: No prognostic factors; (2) Intermediate-risk group: One or two prognostic factors; and (3) Poor-risk group: Three to six prognostic factors
Tumor, Nodes, Metastasis Staging System for Kidney Cancer[5]	(A) Primary tumor (T): (1) Primary tumor cannot be assessed (TX); (2) No evidence of primary tumor (T0); (3) Tumor ≤ 7 cm in greatest dimension, limited to the kidney (T1); (4) Tumor > 7 cm in greatest dimension, limited to the kidney (T2); (5) Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's Fascia (T3); and (6) Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland) (T4); (B) Regional Lymph Nodes (N): (1) Regional lymph nodes cannot be assessed (NX); (2) No regional lymph node metastasis (N0); and (3) Metastasis in regional lymph node(s) (N1); and (C) Distant Metastasis (M): (1) No distant metastasis (M0); and (2) Distant metastasis (M1)	Stage I: T: T1; N: N0; M: M0; Stage II: T: T2; N: N0; M: M0; Stage III: T: T1-T2; N: N1; M: M0; and T: T3; N: NX,N0-N1; M: M0; Stage IV: T: T4; N: Any N; M: M0; and T: Any T; N: Any N; M: M1

RCC: Renal cell carcinoma.

combination with immune checkpoint inhibitors[16].

Targeted therapies

Advances in genomics and molecular biology have led to the development of targeted therapies for RCC[17,18]. The turning point has been the identification of mutation or loss of von-Hippel Landau (VHL) tumor suppressor gene in 60% to 90% of sporadic cases of RCC either through somatic mutation or promoter methylation[19]. Inactivation of VHL leads to overexpression of hypoxia-inducible factors (HIF) and transcription of genes such as vascular endothelial growth factor (VEGF)[20,21]. HIF-1α is an important stimulus to angiogenesis. VEGF binds to VEGF receptor (VEGFR) on endothelial cells and is a potent mediator of angiogenesis. It leads to increased vascular permeability, endothelial cell proliferation, migration, and cancer progression[22]. This has led to the development of various strategies to inhibit VEGF signal transduction such as humanized neutralizing anti-VEGF monoclonal antibodies and VEGFR inhibitors.

Bevacizumab is the only monoclonal antibody targeting VEGF that has been approved for RCC by the U.S. Food and Drug Administration (FDA). Currently, six small molecule oral tyrosine kinase inhibitors (TKIs) with potent activity against VEGF receptors have been approved for use in RCC (axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, and sunitinib).

Another critical regulating factor in RCC is mammalian target of rapamycin (mTOR), a serine/threonine kinase, an important component of the phosphoinositide 3-kinase/AKT signaling pathway, which is often dysregulated in RCC. Hyperactivity of mTOR signaling promotes cell growth and proliferation leading to growth and invasiveness of tumor cells. The mTOR component 1 (mTORC1) increases cellular levels of HIF-α and TNF-α, which in turn can cause overproduction of VEGF, PDGF-α and TNF-α in tumor cells resulting in further increase in mTOR signaling. Inhibition of mTOR would result in decreased cell growth, proliferation, cellular metabolism and angiogenesis[23-25]. FDA approved mTOR inhibitors for treatment of RCC are everolimus and temsirolimus.

Immune checkpoint inhibitors

While targeted therapies have changed the course of RCC by improving outcomes, the duration of response is limited by the development of drug resistance and complete responses are rare[26]. This spurred a search for novel therapeutic strategies—specifically in the realm of immuno-oncology. The ICIs are the latest class of immunotherapy (IO) under development. These include programmed death receptor 1/programmed death receptor ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocytes antigen 4 (CTLA-4) inhibitors. PD-1 is a transmembrane protein present on activated effector T cells and has two known ligands (PD-L1 and PD-L2) found on other cells including tumor cells. When bound to its ligand, PD-1 normally acts as an

"off switch" preventing an effective T-cell response. Most RCC tumor cells express PD-L1 on the cell membrane which helps them evade an immune attack. The immune checkpoint inhibitors, by providing PD-1 inhibition or PD-L1 inhibition block this pathway, releasing the "off switch" on the immune system, increasing the ability of T-cells to kill tumor cells[27,28]. CTLA-4 inhibition stops autoreactive T cells during the immune priming phase, thereby supporting the activation and proliferation of effector T cells[29]. FDA has approved two PD-1 inhibitors (nivolumab and pembrolizumab), and one CTLA-4 inhibitor (ipilimumab) for use in RCC. PD-L1 inhibitors under development for use in RCC include atezolizumab, and durvalumab. A CTLA-4 inhibitor under development for RCC is tremelimumab. The precise and detailed mechanism of action of different drugs, their molecular pathways, and the pathophysiologic effects on tumor cells and their microenvironments are beyond the scope of this article. Table 2 summarizes the FDA approved monotherapies for the treatment of clear cell RCC.

COMBINATION THERAPY

Rationale for combination therapy

The goal of combining various modalities of systemic therapy is to potentiate a synergistic antitumor effect. However, combining various targeted therapies may cause increased toxicity. As of now there are five FDA approved combination treatments for metastatic ccRCC: Bevacizumab plus IFN-α, lenvatinib plus everolimus, ipilimumab plus nivolumab, and most recently, pembrolizumab plus axitinib, and axitinib plus avelumab. The more recently approved combinations of immunotherapy and TKIs also allow for combinations of very different therapeutic mechanisms of actions with the aim of improved and potentially rapid response rates as well as potential durable responses.

Unsuccessful combination therapies

Table 3 summarizes initial attempts of combination therapies with unexpectedly high toxicity or lack of anticipated antitumor synergy. Patients with mRCC treated on a phase I study of the combination of bevacizumab and sunitinib were found to have a high degree of hypertension, vascular, and hematologic toxicities at the maximum tolerated dose level (sunitinib 50 mg plus bevacizumab 10 mg/kg). Discontinuation of treatment was observed in 48% of patients due to adverse events[30].

In a phase II combination study of bevacizumab and everolimus, the median progression-free survival (PFS) and OS in previously untreated mRCC patients was longer than inpatients previously treated with sunitinib and sorafenib (PFS: 9.1 mo *vs* 7.1 mo; OS: 21.3 mo *vs* 14.5 mo, *P* = 0.11). Median PFS for all patients was 8.1 mo (95%CI: 6.3 to 10.8 mo). However, 14% of patients discontinued treatment due to serious adverse events (SAEs) such as proteinuria, pulmonary embolism, stomatitis, and anorexia[31].

Similarly, in a phase I combination study of everolimus and sorafenib in mRCC patients, a partial response (PR) rate of 25% was observed. However, due to gastrointestinal toxicities and dose reductions, study discontinuation was necessary. Moreover, there was a higher than expected incidence of rash typically seen with either drug as a single agent[32].

In a phase III trial, the combination of temsirolimus plus interferon-α was compared with temsirolimus or interferon-α alone with the primary end point of OS. OS in the combination-therapy group did not differ significantly compared with the interferon group [Hazard ratio (HR), 0.96; 95%CI: 0.76 to 1.20; *P* = 0.70]. Median OS in the interferon group, the temsirolimus group, and the combination-therapy group was 7.3, 10.9, and 8.4 mo, respectively. Ultimately, the addition of temsirolimus to interferon did not improve survival[33].

In a phase I dose escalation combination trial of tremelimumab plus sunitinib in mRCC patients, 9 of 21 (43%) evaluable patients achieved partial response. All patients developed treatment - related AEs, ten patients (36%) had serious AEs, and seventeen patients (61%) had grade 3 or 4 AEs. DLTs were reported in 2/5 patients receiving sunitinib 50 mg/d plus tremelimumab 6 mg/kg resulting in further exploration done with lowered sunitinib dose at 37.5 mg/d. Of these 4/14 (29%) and 3/6 (50%) developed DLTs with tremelimumab at 10 mg/kg and 15 mg/kg, respectively. Acute renal failure was the most common DLT reported in 4 patients (14%)[34] though it is not a common toxicity with either drug used alone. Acute renal failure did not appear to be related to tremelimumab concentration as deduced from the limited

Table 2 Food and Drug Administration approval monotherapies for the treatment of renal cell carcinoma

Drug	Mechanism of action	Line of therapy	Study	PFS	OS	ORR	Associated toxicities	Ref.
Pazopanib	TKI	First	Pazopanib *vs* placebo	9.2 mo *vs* 4.2 mo HR 0.46; 95%CI: 0.34 to 0.62; *P* < 0.0001	22.9 mo (95%CI: 19.9 to 25.4) *vs* 20.5 (95%CI: 15.6 to 27.6) mo; HR 0.91; 95%CI: 0.71-1.16; one sided stratified log rank *P* = 0.224	30% (95%CI: 25.1 to 35.6) *vs* 3% (95%CI: 0.5 to 6.4), median duration of response 58.7 wk by independent review[1]	Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting. Grade 3 toxicities included elevated ALT (30%) and AST (28%)	[99,100]; Comment: Lack of correlation between OS and PFS was attributed to extensive crossover of placebo-treated patients to pazopanib group
Pazopanib	TKI	Second	Pazopanib *vs* placebo after prior progression on sunitinib or bevacizumab	7.5 mo (95%CI: 5.4 to 9.4) *vs* 7.5 (95%CI: 5.5 to 14.1) *vs* 6.7 mo (95%CI: 3.6 to 9.3)	14.8 mo (95%CI: 12 to 28.8) *vs* 24.2 mo (95%CI: 14.7 to not reached) *vs* 10.9 (95%CI: 8.2 to 12)	27% (95%CI: 17% to 40%) *vs* 26% (95%CI: 15% to 41) *vs* 31% (95%CI: 14 to 55%)	Grade 1 and 2 toxicities were common. Grade 3 and 4 occurring in ≥ 10% included fatigue (185), proteinuria (13%), hypertension (13%), and diarrhea (11%)	[101]
Sunitinib	TKI	First	Sunitinib *vs* interferon	11 mo (95%CI: 11 to 13 mo *vs* 5 mo (95%CI: 4 to 6); HR 0.42 (95%CI: 0.451 to 0.643); *P* < 0.001	26.4 mo (95%CI: 23 to 32.9) *vs* 21.8 mo (95%CI: 17.9 to 26.9); HR, 0.821; 95%CI: 0.673 to 1.001; *P* = 0.051	31% (95%CI: 26 to 36) *vs* 6% (95%CI: 4 to 9; *P* < 0.001)	Grade 3 events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%)	[102,103]
Axitinib	TKI	First	Axitinib *vs* sorafenib	10.1 mo (95%CI: 7.2 to 12.1) *vs* 6.5 mo (95%CI: 4.7 to 8.3); Stratified HR; 0.77 (95%CI: 0.56 to 1.05)[1]	Median OS (95%CI: 21.7 mo (18.0-31.7) with axitinib *vs* 23.3 mo (18.1-33.2) with sorafenib (stratified HR, 0.995; 95%CI: 0.731-1.356; 1-sided *P* = 0.4883)	32% *vs* 15%; risk ratio 2.21; (95%CI: 1.31 to 3.75; stratified one-sided *P* = 0.0006)	Diarrhea (50%), hypertension (49%), weight decrease (40%), decreased appetite (29%), dysphonia (23%). Any grade events were more common n axitinib *vs* sorafenib ≥ 10%	[104,105]
Axitinib	TKI	Second	AXIS: Axitinib *vs* sorafenib after 1 prior systemic therapy	8.3 mo (95%CI: 6.7 to 9.2) *vs* 4.7 mo (95%CI: 4.7 to 6.5); HR 0.656, 95%CI: 0.552 to 0.779; one sided *P* < 0.001	20.1 mo (95%CI: 16.7 to 23.4) *vs* 19.2 (95%CI: 17.5 to 22.3)	19% (95%CI: 15.4 to 23.9) *vs* 34% (95%CI: 6.6 to 12.9), *P* = 0.0001	Adverse events of all grades were more frequent with axitinib were hypertension, fatigue, dysphonia, and hypothyroidism. Adverse events more frequent with sorafenib with hand-foot syndrome, rash, alopecia, and anemia	[57,106]
Sorafenib	TKI	Second line	TARGET: Sorafenib *vs* placebo for patients who progressed on prior therapy	5.5 mo *vs* 2.8 mo	17.8 mo *vs* 14.3 mo, HR= 0.88; *P* = 0.146		Skin rash/ desquamation, hand foot skin reaction, fatigue. Hypertension and cardiac ischemia were rare but SAEs.	[107]
Cabozantinib	Inhibitor of multiple TKReceptors including MET, VEGFRs, and AXL	First	The Alliance A031203 CABOSUN Trial: Cabozantinib *vs* sunitinib	8.2 mo (95%CI: 6.2 to 8.8 mo) *vs* 5.6 mo (95%CI: 3.4 to 8.1 mo); Adjusted HR, 0.66; 95%CI: 0.46 to 0.95; one-sided *P* = 0.012	30.3 mo (95%CI: 14.6 to 35.0 mo) *vs* 21.8 mo (95%CI: 16.3 to 27.0 mo); Adjusted HR, 0.80; 95%CI: 0.50 to 1.26	33% (95%CI: 23% to 44%) *vs* 12% (95%CI: 5.4% to 21%)	Fatigue, hypertension, diarrhea, AST/ALT elevation	[62]
Cabozantinib		Second	METEOR: Cabozatinib *vs* everolimus for those that progressed on anti VEGF therapy	7.4 mo (95%CI: 5.6 to 9.1) *vs* 3.8 mo (95%CI: 3.7 to 5.4); HR 0.51 (95%CI: 0.41 to 0.62); *P* < 0.001	21.4 mo (95%CI: 18.7-not estimable) *vs* 16.5 mo (95%CI: 14.7 to 18.8); HR 0.66 (95%CI: 0.53 to 0.83; *P* = 0.00026)	17% (95%CI: 13 to 22) *vs* 3% (95%CI: 2 to 6), *P* < 0.0001	Grade 3 or 4 events were hypertension (15%), diarrhea (13%), fatigue (11%), palmar-plantar erythrodysaesthesia syndrome (8%)	[63,108]

Everolimus	mTOR Inhibitor	Third	RECORD-1: Patients who progressed on sunitinib, sorafenib, or both were given everolimus *vs* placebo	4.9 mo (95%CI: 3.7 to 5.5) *vs* 1.9 (95%CI: 1.8 to 1.9); HR 0.33, 95%CI: 0.25 to 0.43; *P* < 0.001	14.8 mo *vs* 14.4 mo; HR 0.87, 95%CI: 0.65 to 1.15; *P* = 0.162	1% *vs* 0%	Stomatitis (40% *vs* 8%), rash (25% *vs* 4%), fatigue (20% *vs* 16%), pneumonitis (8%)	[109,110]
Temsirolimus	mTOR Inhibitor	First	IFN-α-alone *vs* temsirolimus alone *vs* IFN-α+ temosirolimus[1], poor risk patients with ≥ 3 of 6 unfavorable prognostic factors.	3.1 mo (95%CI: 2.2 to 3.8) *vs* 5.5 (95%CI: 3.9 to 7) *vs* 4.7 (95%CI: 3.9 to 5.8); (*P* < 0.001)	7.3 mo (95%CI: 6.1 to 8.8) *vs* 10.9 mo (95%CI: 8.6 to 12.7) *vs* 8.4 mo (6.6 to 10.3); HR for death, 0.73; 95%CI: 0.58 to 0.92; *P* = 0.008	4.8% (95%CI: 1.9 to 7.8) *vs* 8.6% (95%CI: 4.8 to 12.4) *vs* 8.1% (95%CI: 4.4 to 11.8); HR, 0.96; 95%CI: 0.76 to 1.20; *P* = 0.70)	Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimusgroup, asthenia was more common in the interferon group (26% *vs* 11%)	[33]
Temsirolimus	mTOR Inhibitor	Second	INTORSECT: Temsirolimus *vs* sorafenib as second line after treatment with sunitinib[1] with response duration < 180 d	4.3 mo (95%CI: 4 to 5.4) *vs* 3.9 mo (95%CI: 2.8 to 4.2); Stratified HR = 0.87; 95%CI: 0.71 to 1.07; two-sided *P* = 0.19	12.3 mo (95%CI: 10.1 to 14.8) *vs* 16.6 mo (95%CI: 13.6 to 18.7); Stratified HR, 1.31; 95%CI: 1.05 to 1.63, *P* = 0.01 (two sided log-rank)	8% *vs* 8%	Rash and fatigue more commonly associated with temsirolimus and PPE + diarrhea higher in sorafenib group	[111]
Nivolumab	ICI- Anti PD-1 Inhibitor	Second	Checkmate 025: Nivolumab *vs* everolimus	4.6 mo (95%CI: 3.7 to 5.4) *vs* 4.4 mo (95%CI: 3.7 to 5.5); HR, 0.88; 95%CI: 0.75 to 1.03; *P* = 0.11	25.0 mo (95%CI: 21.8– NR for nivolumab) *vs* 19.6 mo (95%CI: 17.6–23.1)	25% *vs* 5%; odds ratio, 5.98 (95%CI: 3.68 to 9.72); *P* < 0.001	Fatigue	[66,67]

[1]Not statistically significant. HR: Hazards Ratio; NR: Not reached; mAb: Monoclonal antibody; DFS: Disease-free survival; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

pharmacokinetic data available. The relationship with sunitinib could not be determined. Fever was noted to accompany all acute renal failure events postulating the possibility of an immune-related mechanism when the two drugs are used in combination. Given the high incidence of renal failure, further evaluation of doses more than 6 mg/kg tremelimumab plus sunitinib 37.5 mg daily was not recommended.

Approved combination therapies

Currently, there are five FDA approved combination therapies for mRCC (Table 4).

Bevacizumab plus IFN-α: A multicenter, randomized, double-blind phase III trial compared OS, PFS, and safety in 649 patients who either received bevacizumab plus IFN-α or placebo plus IFN-α. A total of 641 patients were treated with 325 in the combination group and 316 in the placebo plus IFN-α group. The combination group of bevacizumab plus IFN-α had a significantly longer PFS (10.2 mo *vs* 5.4 mo) and ORR (30.6% *vs* 12.4%). There were significantly more grade 3 or higher adverse events for the bevacizumab group than the control group in terms of fatigue (12% *vs* 8%) and asthenia (10% *vs* 7%)[35], but toxicity was felt to be acceptable.

In a similar trial, patients with previously untreated mRCC (*n* = 732) were randomized to receive either IFN-α monotherapy or the combination of bevacizumab

Table 3 Unsuccessful combination therapy trials

Combination therapy	TrialPhase	Comparator	Side-effect profile	Comments	Ref.
Bevacizumab + sunitinib	I	3 cohorts of escalating doses of Sunitinib	High degree of hypertension, vascular and hematologic toxicities, leading to discontinuation in 48%		[30]
Bevacizumab + everolimus	II		Increased proteinuria, pulmonary embolism, stomatitis and anorexia leading to discontinuation in 14%		[31]
Everolimus + sorafenib	I		Discontinuation due to high gastrointestinal toxicity and grade 3 rash		[32]
Temsirolimus + IFN-α	III	IFN-α		Failed to improve overall survival	[33]
Tremelimumb + sunitinib	I		Rapid onset renal failure		[34]

plus IFN-α. The PFS of the combination group was higher than the control group (8.5 mo *vs* 5.2 mo) but the OS was not significant (18.3 mo *vs* 17.4 mo). The combination group had a higher objective response rate (25.5% *vs* 13.1%). There was significantly greater toxicity in the bevacizumab plus IFN-α group than the control group in the form on grade 3 to 4 hypertension, fatigue, anorexia, and proteinuria[36]. In July 2009, the FDA granted approval for the use of bevacizumab in combination with IFN-αfor the treatment of patients with metastatic RCC. Despite bevacizumab being approved as combination therapy with IFN, many practitioners have used bevacizumab as monotherapy rather than combination as the added benefit of IFN was unclear[37].

Everolimus plus lenvatinib: Resistance to targeted monotherapy in RCC is believed to be due to feedback mechanisms that are mediated *via* biological changes permitting tumor growth and perfusion independent of VEGF or mTOR pathways. This can offset targeted inhibition and permit tumor growth[38,39]. Hence, sequential treatments with a single anti-VEGF agent followed by a mTOR inhibitor often results in the development of resistance. Consequently, combination therapy with both VEGF and mTOR inhibitors was thought to potentially surmount monotherapy resistance[40]. Lenvatinib is a tyrosine kinase inhibitor ofVEGFR1, VEGFR2, VEGFR3 and everolimus is an mTOR inhibitor.

Motzer *et al*[41] conducted a phase II, randomized, open-label efficacy and safety study with lenvatinib or everolimus alone, or lenvatinib plus everolimus in patients with metastatic or unresectable, locally advanced, clear cell RCC who had received prior treatment with a VEGF-targeted therapy and progressed within 9 mo of drug discontinuation. The primary objective was PFS using investigator-assessed objective responses. Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone (14.6 mo *vs* 5.5 mo, $P = 0.0005$), but not compared with lenvatinib alone (7.4 mo, $P = 0.12$). Single agent lenvatinib significantly prolonged PFS compared with everolimus alone ($P = 0.048$). But retrospective independent radiological review of the study did not show any significant difference in PFS between lenvatinib alone *vs* everolimus alone groups ($P = 0.12$). This was attributed to small sample size.

Lenvatinib plus everolimus showed significantly increased median OS of 25.5 mo (95%CI: 20.8-25.5), compared with 18.4 mo (13.3–NE) for single-agent lenvatinib, and 17.5 mo (11.8–NE) for single-agent everolimus. In the post-hoc updated analysis, median OS between patients assigned lenvatinib plus everolimus was significantly improved at 25.5 mo (95%CI: 16.4–NE) compared with single-agent everolimus 15.4 mo (11.8-19.6); HR 0.51, 95%CI: 0.30-0.88; $P = 0.024$. However, OS did not differ between patients who received lenvatinib plus everolimus (HR 0.75, 0.43-1.30; $P = 0.32$), and single-agent lenvatinib [median OS 19.1 mo (95%CI: 13.6-26.2)] or single-agent everolimus (HR 0.68, 95%CI: 0.41-1.14; $P = 0.12$)[41].

The safety profile for lenvatinib plus everolimus was similar to the known toxic effects of each individual agent. Grade 3-4 treatment-emergent adverse event (TEAE), occurred in fewer patients allocated single-agent everolimus (50%) compared with those assigned lenvatinib alone (79%) or lenvatinib plus everolimus (71%). The most common grade 3 or 4 TEAE in patients allocated lenvatinib plus everolimus was diarrhea (20%),in those assigned single-agent lenvatinib it was proteinuria (19%), and in those assigned single-agent everolimus it was anemia (12%). One case of fatal drug-related AE (cerebral hemorrhage) was reported in the lenvatinib plus everolimus group.

Table 4 Approved combination therapies

Combination therapy	FDA approval date	Line of therapy	Trial	Comparator	Efficacy outcomes						Side-effect profile	Comments	Ref.
					OS (exp) (Mo)	OS (contr) (Mo)	PFS (exp) (Mo)	PFS (contr) (Mo)	RR (exp) (%)	RR (contr) (%)			
Bevacizumab + IFN-α	2009	1st	AVOREN	IFN-α	23.3	21.3	10.2	5.4	30.6	12.4		No significant increase in SEs in combination *vs* IFN; OS difference not significant	[35]
Bevacizumab + IFN-α	2009	1st	CALGB	IFN-α	18.3	17.4	8.5	5.2	25.5	13.1		Increased toxicity in combination; No significant increase in OS	[36]
Lenvatinib + Everlimus	2016	2nd		Everolimus	25.5	15.4	14.6	5.5			Fatigue, mucosal inflammation, proteinuria, diarrhea (20%), vomiting, hypertension, and nausea, Grade 3-4 SEs occurred in 71% compared with 50% in everlimus group	Median OS for lenvatinib alone was 18.4 mo	[41]
Nivolumab + Ipilimumab	2018		CheckMate 214	Sunitinib	Not reached	26			42	27	Similar SE profile but discontinuation in 22% *vs* 12% in comparison group		[44]
Pembrolizumab + axitinib	2019	1st	KEYNOTE-426	Sunitinib			15.1	11.1	59.3	35.7	Gr3 or higher adverse event of any cause occurred in 75.8% of patients in the pembrolizumab-axitinib group and in 70.6% in sunitinib group		[45]
Avelumab + axitinib	2019	1st	JAVELIN Renal 101	Sunitinib	ongoing	ongoing	13.8	8.4	51.4	25.7	Grade 3 or higher treatment-elated AEs in the overall population groups, were reported in 71.2% of patients in combination arm *vs* 71.5% in sunitinb arm with discontinuation in 7.6% and 13.4% respectively	Similar responses were observed for PFS and ORR in the PD-L1positive patients	[46]

DFS: Disease-free survival; ORR: Objective response rate; OS: Overall survival; PD-L1: Programmed cell death-ligand 1; PFS: Progression-free survival.

These efficacy results were promising and in May 2016 led to the FDA approval for the treatment of advanced RCC after failure of prior antiangiogenic (TKI) therapy at the lenvatinib dose of 18 mg/daily in combination with everolimus 5 mg/daily.

Nivolumab plus ipilimumab: In April 2018, the FDA approved the combination therapy of ipilimumab and nivolumab for the treatment of intermediate or poor risk advanced RCC. Both of these drugs work to prevent the inactivation of T-cells but *via* different mechanisms, which is why they are effective in combination.

The CheckMate 016 study was an open-label, parallel-cohort, phase 1 study that evaluated the safety and efficacy of nivolumab plus ipilimumab. The study included patients with poor (*n* = 6), intermediate (*n* = 47), and favorable risk (*n* = 47) disease according to the MSKCC risk categorization. Patients in the expansion cohort (intermediate and favorable risk patients) were treatment naïve with the exception of

either prior adjuvant or neoadjuvant therapy or cytokine treatment. Patients were separated into three treatment arms: 3 mg/kg nivolumab plus 1 mg/kg ipilimumab (N3l1), 1 mg/kg nivolumab plus 3 mg/kg ipilimumab (N1l3), 3 mg/kg nivolumab plus 3 mg/kg ipilimumab (N3l3). All the patients in the N3l3 group were censored out of the study because of dose-related toxicities. The N3l1 and N1l3 combination groups had similarly efficacious results (2-year OS was 67.3% and 69.6% respectively) but the N3l1 group had significantly less treatment related adverse events (38.3% *vs* 61.7%)[42].

The CheckMate 214 trial was an open-label phase III study evaluating OS and PFS for the combination of nivolumab plus ipilimumab *vs* sunitinib monotherapy, in previously untreated patients with advanced ccRCC. Patients (*n* = 1096) were assigned to either the combination group of 3 mg/kg nivolumab with 1 mg/kg ipilimumab or the control group of 50 mg sunitinib. The co-primary end points were OS, PFS, and ORR in the intermediate or poor-risk patients (*n* = 425/550 patients in combination arm and *n* = 422/546 patients in sunitinib arm). The median OSwas not reached for the combination group *vs* 26 mo (HR for death, 0.63; *P* < 0.001) for the sunitinib group. The ORRs were significantly higher with combination therapy than with sunitinib monotherapy (42% *vs* 27%, *P* < 0.001), and the complete response rate (CRR) was 9% *vs* 1% (*P* < 0.001). This is the best CR rate any RCC treatment has shown to date, and an updated 30 mo follow-up analysis reported slightly higher CR rate 11%[43].

The 18-mo OS rate in the intermediate or poor-risk patients was 75% (95%CI: 70-78) with combination therapy and 60% with sunitinib (95%CI: 55-65). The median PFS (11.6 mo *vs* 8.4 mo, HR, 0.82, *P* = 0.03) was not statistically significant. Similar numbers of treatment-related AEs occurred in both the combination and sunitinib groups (93% *vs* 97%) however these AEs led to discontinuation of 22% of the nivolumab plus ipilimumab group *vs* 12% of the sunitinib group. Grade 3 or 4 events occurred in 46% and 63% patients, respectively. The most common types of AEs were fatigue, rash, diarrhea, pyrexia, and arthralgia[44].

The intent-to-treat population in the CheckMate 214 study also included favorable-risk patients (*n* = 125 in combination arm and *n* = 124 in sunitinib group). The 18-mo OS in the overall intent-to-treat population favored nivolumab plus iplimumab *vs* sunitinb (78% *vs* 68%), but exploratory analyses of just favorable-risk patients favored sunitinib (88% *vs* 93). The ORR (29% and 52%; *P* < 0.001) and median PFS (14.3 and 25.1 mo; HR, 2.18; 99.1%CI: 1.29-3.68; *P* < 0.001) were also lower in the favorable group patients taking nivolimumab plus ipilimumab *vs* sunitinib.

Pembrolizumab plus axitinib: In April 2019, the FDA approved the combination therapy of pembrolizumab plus axitinib for first-line treatment of patients with advanced RCC irrespective of risk category. In the phase 3 KEYNOTE-426 trial, 861 patients with previously untreated ccRCC were randomly assigned to receive axitinib plus pembrolizumab (*n* = 432) or sunitinib (*n* = 429) in the first line setting. The IMDC risk factors were favorable for 31.2%, intermediate for 56.2%, and poor for 12.5% patients.. The dual primary end points were PFS and OS and the secondary end point was ORR, both as decided by blinded independent central review. Median PFS was 15.1 (95%CI: 12.6 to 17.7) mo in the axitinib plus pembrolizumab group and 11.1 mo (95%CI: 8.7 to 12.5) (HR = 0.69; 95%CI: 0.57 to 0.84, *P* < 0.0001) in the sunitinib group. ORR in the axitinib plus pembrolizumab group was 59.3% (95%CI: 54.5 to 63.9) and 35.7% (95%CI: 31.1 to 40.4) in the sunitinib group (*P* < 0.001). In the axitinib plus pembrolizumab group, the complete response rate was 5.8% (*n* = 25) *vs* 1.9% (*n* = 8) in the sunitinib group. After 1 year, 90% of patients were alive in the combination group *vs* 78% in the sunitinib group (HR for death, 0.53; 95%CI: 0.38 to 0.74; *P* < 0.0001). Grade 3 or higher adverse event of any cause occurred in 75.8% of patients in the pembrolizumab plus axitinib group and in 70.6% in sunitinib group with the most common adverse event of any cause being diarrhea and hypertension[45]. Medication discontinuation due to AEs of any cause and deaths attributed to treatment-related AEs occurred in 30.5% and 4/11 patients, respectively in pembrolizumab plus axitinib group. The corresponding data was 13.9% and 7/15 patients in sunitinib group.

Avelumab plus axitinib: In May 2019, the FDA approved avelumab in combination with axitinib for first-line treatment of patients with advanced RCC irrespective of risk category. In the phase III JAVELIN Renal 101 trial, patients with advanced untreated ccRCC (*n* = 886) were randomized in a one to one fashion to receive either avelumab plus axitinib (*n* = 442) or sunitinib (*n* = 444) as first line therapy. Patients across all MSKCC and IMDC prognostic risk groups were included. The dual primary end points were PFS and OS among patients with PD-L1 positive (> 1%) tumors. Secondary end points were PFS and OS among all patients regardless of PD-L1 expression. These determinations were made by blinded independent central review.

Among patients with PD-L1-positive tumors, median PFS (13.8 mo *vs* 7.2 mo), confirmed ORR (55.2% *vs* 25.5%) and CRR (4.4% *vs* 2.1%) were approximately twice as robust with the avelumab plus axitinib *vs* sunitinib groups, respectively.

Similar responses were observed in the overall population, with PFS (13.8 mo *vs* 8.4 mo), confirmed ORR (51.4% *vs* 25.7%) and CRR (3.4% *vs* 1.8%) in the avelumab plus axitinib *vs* sunitinib groups, respectively.

Grade 3 or higher treatment-related AEs in the overall population were reported in comparable percentage of patients (71.2% *vs* 71.5%) inavelumab plus axitinib *vs* sunitinib groups, respectively. However, discontinuation was higher in the sunitinib group compared to the avelumab plus axitinib group (13.4% *vs* 7.6%, respectively). The most common adverse reactions were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain and headache. Of patients treated with combination arm, 38.2% experienced immune-related AEs of which 9% had severity grade 3 or higher, and the most common immune-related AE was hypothyroidism. Serious adverse reactions occurred in 35% of patients receiving combination regimen and the incidence of major adverse cardiovascular events was also higher compared with sunitinib[46].

ONGOING TRIALS AND FUTURE DIRECTIONS

Table 5 summarizes ongoing phase 3 trials of combination therapy in RCC, studies designed in part to further optimize optimal first line regimens. New agents under investigation in the treatment of RCC include NKTR-214 and abexinostat. NKTR-214 is a novel IL2 pathway agonist, designed to provide sustained signaling through heterodimeric IL2 receptor $\beta\gamma$ to drive increased proliferation and activation of CD8+T and natural killer cells without unwanted expansion of T regulatory cells in the tumor microenvironment[47]. Abexinostat is a novel histone deacetylase (HDAC) inhibitor. HDAC inhibitors target HDAC enzymes leading to highly acetylated histones and chromatin reshaping. In addition to altering histone acetylation, HDAC inhibitors can also influence the degree of acetylation on non-histone proteins, increasing or repressing their activity. HDAC inhibition thus inhibits the proliferation of cancer cells and induce cancer cell death, or apoptosis. Through the epigenetic modulation of vascular endothelial growth factor expression, it is thought that abexinostat can prolong the therapeutic effect of pazopanib and prevent resistance[48]. In a recently completed Phase Ib/II trial of pembrolizumab with bevacizumab, the combination regimen was found to be safe and effective in the treatment of mRCC[49]. It may be potentially helpful in patients who cannot tolerate TKIs.

Atezolizumab plus bevacizumab

In the phase III IMmotion151 trial, patients (*n* = 915) were stratified by PD-L1 status (*n* = 362 PD-L1+), MSKCC risk score[6] and presence of liver metastases. In PD-L1+ patients, PFS was 11.2 mo (95%CI: 8.9 to 15.0) in atezolizumab plus bevacizumab *vs* 7.7 mo (95%CI: 6.8 to 9.7) in sunitinib (*P* = 0.0217); ORR was 43% (95%CI: 35 to 50) in atezolizumab plus bevacizumab *vs* 35% (95%CI: 28 to 42) in sunitinib. Duration of response was not reached for atezolizumab plus bevacizumab *vs* 12.9 mo for sunitinib treated patients. The combination arm was well tolerated. Treatment-related grade 3-4 AEs were noted in 40% of atezolizumab plus bevacizumab and 54% of sunitinib treated patients; 12% and 8% of treatment-related all-Grade AEs led to discontinuation, respectively[50]. Five treatment–related deaths were recorded in combination group *vs* 1 with sunitinib. Although the PFS benefit was met in the PD-L1+patients as well as in other subgroups and in the intent to treat (ITT) population, the Independent Radiological Review-assessed PFS in PD-L1 patients did not show a statistically significant benefit. Because of this variance, the fate of this combination is uncertain.

TREATMENT SELECTION

Treatment dilemma

There is no single established sequence of systemic therapies in metastatic ccRCC. Treatment choices are based on evidence-based efficacy data, individual patient

Table 5 Ongoing phase 3 trials of combination therapy in renal cell carcinoma

Treatment	Trial name	ClinicalTrials.gov No.	Enrollment	Primary endpoint	Status
Nivolumab-cabozantinib *vs* sunitinib	CheckMate 9ER	NCT03141177	630	PFS	Estimated primary completion date: January 2020
Lenvatinib-everolimus or lenvatinib-pembrolizumab *vs* sunitinib	CLEAR	NCT02811861	1050	PFS	Estimated primary completion date: April 2020
Nivolumab-ipilimumab followed by nivolumab *vs* nivolumab-cabozantinib	NCI-2018-03694	NCT03793166	1046	OS	Estimated primary completion date: September 2021
NKTR-214-nivolumab *vs* sunitinib or cabozantinib	CA045002	NCT03729245	600	ORR	Estimated primary completion date: December 2021
Pazopanib-abexinostat *vs* pazopanib	XYN-602	NCT03592472	413	PFS	Estimated primary completion date: January 2022
Nivolumab-ipilimumab *vs* placebo	CheckMate 914	NCT03138512	800	DFS	Estimated primary completion date: September 2022
Nivolumab-ipilimumab *vs* nivolumab	CA209-8Y8	NCT03873402	418	PFS	Estimated primary completion date: December 2022

DFS: Disease-free survival; ORR: Objective response rate; OS: Overall survival; PD-L1: Programmed cell death-ligand 1; PFS: Progression-free survival.

factors, co-morbidities, and the toxicity profiles of the potential agents.

The National Comprehensive Cancer Network (NCCN) Kidney Cancer Panel has categorized all systemic kidney cancer regimens as "preferred", "other recommended", or "useful under certain circumstances"[51].

The first line therapies are further categorized according to the IMDC[7,52] prognostic model which provides the primary selection criteria. Patients are largely stratified into low- or favorable-risk and intermediate-or poor-risk groups, based on clinical and laboratory risk factors.

First-line therapies: (1) Low-or favorable-risk patients: The NCCN preferred category 1option for low-risk patients is the combination of pembrolizumab plus axitinib, which was recently approved (April 2019) across all risk groups. KEYNOTE 426[45] demonstrated a 47% lower risk of death and a 31% lower risk of disease progression or death on treatment with pembrolizumab plus axitinib compared with sunitinib. The ORR was 23% higher in the combination group than in sunitinib group. The benefits of improved PFS and OS were observed in all subgroups of patients, including across all IMDC risk groups and regardless of PD-L1 expression. The significant improvement in OS is of utmost importance because this has not been achieved before with any single or combination therapy. A head to head trial is needed to compare the combination of pembrolizumab plus axitinib with a newer TKI monotherapy, such as cabozantinib, *vs* other combinations to make further progress in selecting preferred category 1 option in low-risk patients.

The alternative category 1 options for low-risk patients are pazopanib and sunitinib. A phase III non-inferiority direct comparison of pazopanib *vs* sunitinib (COMPARZ study)[53,54] in treatment naïve mRCC patients showed a comparable efficacy profile. The PFS with pazopanib was non-inferior (median 8.4 mo) to sunitinib (median 9.5 mo). The median OS was 28.4 and 29.3 mo respectively. Certain adverse events were more frequent with sunitinib, namely fatigue 63% *vs* 55%, hand-foot syndrome 50% *vs* 29%, and thrombocytopenia 78% *vs* 41%. Although liver function abnormalities (60% with pazopanib *vs* 43% with sunitinib), weight loss and alopecia were noted more with pazopanib, several quality-of-life indicators favored pazopanib[51,53]. This is further supported by phase III crossover study (Pisces study) where significantly more patients preferred pazopanib (70%) over sunitinib (22%) while only 8% had no preference[55]. In a subgroup analysis of COMPARZ trial, safety profile of the two drugs was studied in Asian *vs* non-Asian populations[56]. In general, Asian patients experienced higher incidences of hypertension, hematologic toxicity, hand-foot syndrome, liver chemistry abnormalities with either drug compared to non-Asian patients. On the other hand, non-Asian patients experienced higher incidences of gastrointestinal AEs, mucosal inflammation, and headache. This may reflect ethnic differences in absorption, metabolism, and tolerance of the drugs. Effects of other translational factors related to genetic and non-genetic factors may also be into play

and will require further research.

The other options approved for low-risk group are cabozantinib, nivolumab plus ipilimumab, and axitinb plus avelumab. Cabozantinib use as category 2B is extrapolated from its response in intermediate to poor risk patients. The nivolumab plus ipilumumab combination was FDA approved (CheckMate 214 trial)[44] for intermediate to poor-risk patients. However, it may be used in low-risk patients who cannot receive a TKI, as in severe hepatic impairment, uncontrolled hypertension, or significant cardiovascular disease or in patients with high PD-L1 expression in the tumor cells.

In May 2019 the FDA approved avelumab plus axitinib as part of a combination regimen, regardless of tumor PD-L1 expression. In the JAVELIN Renal 101 study, patients with advanced RCC across IMDC prognostic risk groups (21% favorable, 62% intermediate and 16% poor) demonstrated significantly improved median PFS (13.8 mo *vs* 8.4 mo) and ORR (51.4% *vs* 25.7%) with the combination of avelumab plus axitinib compared with sunitinib. The study is continuing for OS and further data are expected. The grade 3 or higher AEs were similar in the two groups. Hypertension, diarrhea, fatigue, nausea, and palmar-plantar erythrodysesthesia were the most frequent AEs and not significantly different in safety profiles of these drugs used individually or in combination. Axitinib was selected as VEGFR inhibitor in preference to sunitinib, because it has demonstrated longer PFS than sorafenib among patients treated previously with sunitinib, though the benefit was relatively small[57]. Secondly, it reduces the risk of potential hepato-toxicity observed with sunitinib and pazopanib combined with nivolumab, an immune checkpoint inhibitor[58].

Active surveillance may be considered an initial option in patients with slowly progressive, asymptomatic disease given the toxicity and non-curative nature of systemic therapy. In a prospective phase 2 trial, 52 patients with treatment-naive, asymptomatic, mRCC were enrolled and observed until start of systemic therapy, with specific radiologic assessments timed per protocol. Therapy was initiated at the discretion of the treating physician. Median time on surveillance until initiation of systemic therapy was 14.9 mo in the 48 patients analyzed. Higher numbers of IMDC adverse risk factors and metastatic disease sites were associated with a shorter surveillance period, as per multivariate analysis. Twenty-two (46%) patients died during the study period, all from mRCC. However, selection criteria, risk/benefit, and end-point criteria have not been validated[59].

And (2) Intermediate-or poor-risk patients: Nivolumab plus ipilimumab is a preferred category 1 option for patients with intermediate or poor-risk disease, particularly given its significant complete response rate[60]. At 30 mo of follow up of intermediate and poor-risk previously untreated ccRCC patients from the CheckMate 214 trial, OS was 60% *vs* 47%, ORR were 42% *vs* 29%, CRR was 11% *vs* 1%, respectively, between immunotherapy combination and sunitinib groups. The number of deaths were least in younger age group (< 65 year) compared with elderly (75 years), but this was also noted in sunitinib group. The overall safety profile was similar to prior trials of nivolumab plus ipilimumab. The relatively higher discontinuation rate of treatment due to AEs (22% in nivolumab plus ipilimumab *vs* 12% in the sunitinib groups) may be due to inability for dose reduction of the combination *vs* sunitinib. The most common grade 3/4 AEs in the combination group were fatigue (4%) and diarrhea (4%). In the sunitinib arm, the most common grade 3/4 AEs were hypertension (16%), fatigue (9%), and palmar-plantar erythrodysesthesia syndrome (9%). The combination is however, contraindicated in patients with autoimmune or neuromuscular disorders, or receiving immunosuppressive therapies.

The combination of pembrolizumab plus axitinib was recently approved (April 2019) as a preferred category 1 option as well, though indicated across all risk groups.

Cabozantinib is a recommended category 2A preferred first-line treatment for intermediate to poor risk patients based on the CABOSUN study. This study demonstrated a significantly improved investigator assessed median PFS (8.2 mo *vs* 5.6 mo), which was consistent with an independent post-hoc retrospective radiology review committee (IRC) assessment. The ORR per IRC was 20% for cabozantinib *vs* 9% for sunitinib. All responses were partial. The disease control rate (complete responses + partial responses +stable disease) was 75% with cabozantinib and 47% with sunitinib. These results are further significant given the disease burden and poor prognostic features in addition to 81% classified as intermediate risk and 19% as poor risk as per the IMDC criteria. Notably, 25% had no prior nephrectomy and 36% had bone metastases[61].

Further, subgroup analysis of PFS per IRC assessment based on stratification factors and MET expression level were consistent with overall results. The observed improvement in PFS with cabozatinib compared with sunitinib may be due, in part, to

inhibition of MET and AXL by cabozantinib in addition to VEGF receptors. Subgroup analyses of PFS based on MET expression level favored cabozantinib over sunitinib (HR < 1) regardless of MET status. Although the HR more strongly favored cabozantinib for MET-positive *vs* MET-negative tumors, subgroup sizes were small. Grade 3 or 4AEs occurred for 68% cabozantinib-treated patients and 65% sunitinib-treated patients. The most common grade 3 or 4 adverse events in the cabozantinib and sunitinib treatment groups were hypertension (28% *vs* 21%), diarrhea (10% *vs* 11%), fatigue (6% *vs* 17%), palmar-plantar erythrodysesthesia (8% *vs* 4%), and thrombocytopenia (1% *vs* 11%)[62].

Additionally, pazopanib, sunitinib, and avelumab plus axitinib are listed as other recommended option for the first-line treatment of patients with intermediate –poor-risk features.

High dose IL-2 (category 2A), given its significant toxicity profile, is approved as first-line treatment only in a highly selected subgroup of patients for all risk groups. The selection is based largely on assessment of safety *vs* risk factors. Axitinib (category 2B) is used as single agent generally only as a highly advanced line of therapy across all risk groups. Temsirolimus is still included as category 1 first line treatment option in poor-risk patients but must be used only if TKIs and immunotherapy are contraindicated. Sorafenib is excluded given better treatment options.

Subsequent-line therapies: The need for subsequent therapy is currently based on intolerable AEs or progression of disease on first-line therapy. There is uncertainty yet, regarding the optimal duration of first-line therapy for patients who respond to treatment, particularly IOs, and do not experience significant adverse events. Induction of resistance remains a concern and indices for optimizing therapy duration will need to be ascertained as more prospective data becomes available.

In patients with progression after previous TKI or immunotherapy, cabozanitinb is the current preferred NCCN category 1 choice[51,63,64]. As demonstrated in the METEOR trial, cabozanitib was found superior to everolimus in patients who progressed on anti VEGFR therapy, with a significantly improved median OS (21.4 mo *vs* 16.5 mo) and ORR (17% *vs* 3%). The most common treatment-related grade 3 or 4 AEs with cabozantinib were hypertension, diarrhea, and fatigue and those with everolimus were anemia, fatigue, and hyperglycemia. The rate of treatment discontinuation due to AEs was similar in both arms. Cabozantinib is particularly recommended in patients with bone metastasis. In a subgroup of patients with bone metastases in the METEOR trial, median PFS (7.4 mo *vs* 2.7 mo), OS (20.1 mo *vs* 12.1 mo), and ORR (17% *vs* 0%) were all improved for patients treated with cabozantinib *vs* everolimus[61]. In a meta-analysis comparing cabozanitinb with everolimus, nivolumab, axitinib, sorafenib, or best supportive care, cabozanitinb appeared to show a longer PFS as a second line treatment choice[65].

Nivolumab is another preferred category 1 option. It was found to be superior to everolimus in patients who progressed on prior antiangiogenic therapy (excluding mTOR) in a phase III trial (CheckMate 025) with a median OS 5.4 mo longer in comparison.The ORR was also 5 times greater with nivolumab compared to everolimus. Treatment related AEs of any grade were reported in 79% with nivolumab, in 88% with everolimus and grade 3-4 AEs were noted in 19% and 37% respectively. Treatment discontinuation from toxicities was seen in 8% with no treatment-related deaths in nivolumab patients. Corrresponding numbers were 13% and 2 deaths respectively in everolimus patients[66,67]. The effect of nivolumab continuation was evaluated after first Response Evaluation Criteria in Solid Tumors (RECIST) disease progression in CheckMate 025 trial patientswho showed clinical benefit and tolerated the therapy. A reduction in tumor burden was seen in approximately50% patients of which 13% of patients had a ≥ 30% tumor burden reduction[51]. AEs of any grade were reported less frequently after progression (59%) than before progression (71%)[68].

Lenvatinib, a multi-targeted TKI plus everolimus, an mTOR inhibitor, is another category 1 combination approved for subsequent therapy. In a phase II trial, patients with advanced RCC, previously treated with antiangiogenic therapy were randomized to receive the combination of lenvatinib plus everolimus *vs* everolimus alone *vs* lenvatinib alone. The median PFS (14.6 mo *vs* 5.5 mo; HR 0.40; 95%CI: 0.24-0.68) and OS (25.5 mo *vs* 15.4 mo; HR 0.67; 95%CI: 0.42-1.08) were significantly improved for the combination compared to everolimus alone[41,69].

Nivolumab plus ipilimumab is preferred as category 2A in patients who have progressed on one prior systemic therapy. Several other regimes may be recommended in appropriate settings as indicated in NCCN guidelines[51]. Although, single agent everolimus is not used as first or second line therapy, it may be worth

considering it in patients with mutation in mTOR pathway but future studies directed at this strategy are required[70,71]. However, determining the ideal combination of therapies and the sequence in which they can be used remains an area for exploration.

Biomarkers

Development of a sensitive biomarker would help to formulate an efficacious therapeutic course, and to prognosticate outcomes[72]. While prognostic biomarkers play a role in forecasting patient outcomes, predictive biomarkers identify the best treatment options with the fewest adverse effects and toxicities. Given that many ccRCC cases are diagnosed in the advanced or metastatic stage, development of validated and reliable biomarkers is a crucial goal. To date, perhaps, the IMDC model remains the single most validated clinical prognostic model in mRCC. It is used for patient counseling, risk stratification in clinical trials, and treatment selection. Although several biomarkers have been the focus of recent research, no single other biomarker has been validated for use in ccRCC[73]. Therefore, several biomarkers are used in combination to generate a patient tailored approach.

PD-L1 expression continues to be a potential biomarker of clinical interest[74]. However, in the CheckMate 025, a phase II trial, a positive response was observed with nivolumab irrespective of PD-L1 expression. This was postulated to be related to variation in histologic subclasses. In CheckMate 214, phase II study of nivolumab plus ipilimumab *vs* sunitinib, a longer median PFS was observed in nivolumab plus ipilimumab treated subjects with 1% or greater PD-L1 expression (22.8 mo *vs* 5.9 mo) but not in those with less than 1% PD-L1 expression (11 mo *vs* 10.4 mo). Similar result was observed among patients with ≥ 5% or < 5% PD-L1 expression. A higher ORR was observed with nivolumab plus ipilimumab across all patient groups *vs* sunitinib but the response was more robust in patients with 1% or greater PD-L1 expression (58% with nivolumab plus ipilimumab *vs* 22% with sunitinib) compared with those with less than 1% PD-L1 expression (37% *vs* 28%)[66,74]. In IMmotion 151, phase III study, with atezolizumab (PD-L1 inhibitor) plus bevacizumab (VEGF inhibitor) *vs* sunitinib, patients were stratified by their PD-L1 expression (< than 1% *vs* ≥ 1% expression). Patients with clear cell as well as sarcomatoid histology were included. The two treatment arms were PD-L1 ≥ 1% and the entire ITT population. A higher PFS was noted in both groups compared with sunitinib. The response was higher in PD-L1 positive patients (but the difference was small). Higher PFS was observed in patients with sarcomatoid histology. The role of PD-L1 expression, although limited as a prognostic biomarker, continues to be explored as a predictive biomarker[75,76].

In addition to the varying levels of PD-L1 expression in tumor cells, recent advances in genetic and genomic studies have shown significant inter-tumor and intra-tumor genomic heterogeneity of ccRCC. Of these, mutation in the *VHL* gene, located on 3p25, is the fundamental event and most researched but it is not the single driver gene. Several other tumor suppressor genes are now identified, importantly *PBRM1* (40%), *SETD2* (15%), and *BAP1* (10%) *KDM5C* (7%), and *TP53* (5%) and the oncogene *MTOR* (5%-6%)[77]. *PBRM1*, *SETD2*, and *BAP1* are all located on 3p21 and encode for tumor suppressor chromatin-and histone-modifying proteins and their mutations are associated with more aggressive clinical features for all stages of ccRCC[78,79].

SETD2 mutations are associated with advanced stage, grade and worse cancer specific survival. An overall metastatic rate of 36% is reported in *SETD2* mutated ccRCC tumors, suggesting a link between *SETD2* and cancer metastasis[80,81]. However, *SETD2* loss is not yet correlated with poor targeted treatment outcomes[82,83]. This needs further validation and additional studies evaluating response of targeted therapies.

BAP1 mutations are prevalent in about 10% of human ccRCC cases, and loss of *BAP1* function is associated with tumors of high grade, worse cancer specific survival[80] as well as overall poor clinical response despite targeted therapy[83,84]. As such, *BAP1* regulated pathways are an appropriate future therapeutic target. The relatively inferior OS noted with *BAP1* mutations in comparisons with *SETD2* and *KDM5C* mutations by Tennenbaum *et al*[83] needs further research and confirmation. *BAP1* and *PBRM1* mutations are usually mutually exclusive. Their simultaneous occurrence, which is observed rarely are associated with more aggressive disease.

Two distinct subtypes and prognostic features (ccA/ccB) are defined by molecular stratification of ccRCC using consensus clustering[85]. The ccB classified tumors demonstrated increased tumor size, grade and rate of metastasis as well as decreased recurrence free survival and OS[86]. ClearCode 34 is a genetic signature developed from this classification to predict recurrence[87]. This tool is validated despite limitation from tumor heterogeneity, making it a potentially valuable prognostic biomarker.

Another prognostic multigene signature has been proposed using a 16-gene assay to predict recurrence after nephrectomy in localized RCC[88]. The recurrence score was

validated as a predictor of outcome in patients with stage I-III ccRCC. A signature of four specific genomic aberrations using FISH) was developed which can identify tumors with a high metastatic potential, and may be a better predictor of OS, CSS CSM and PFS, compared with clinico-pathologic variables[89].

Although c-Met overexpression has been observed and correlated with significantly worse pathological features in RCC, its clinicopathological impacts remain uncertain[90]. OS, PFS, and ORR were improved with cabozantinib *vs* sunitinib in patients with advanced RCC[62], but the benefit was noted regardless of tumor expression levels of MET in the METEOR study[63]. Thus its role as a biomarker appears to have limitations.

The role of pathogenic variants in genes associated with DNA damage repair (DDR), frequently encountered in mRCC patients, was evaluated. Presence of a deleterious DDR gene alteration was associated with improved survival in patients treated with IO (HR 0.29, *P* = 0.04) but not in those treated with TKI. However, DDR alterations were not associated with improved PFS in either group. Despite limitations of the study, it requires validation and can provide another path forward in treatment selection[91].

Given the relation between hypercalcemia and poor prognosis in ccRCC patients (IMDC), investigators have recently studied the prognostic role of calcium-sensing genes on plasma membrane. In one study, higher levels of DYSF (Dysferlin) were found in ccRCC cells compared with normal kidney cells and this, within ccRCC patients, was a predictor of improved prognosis[92]. It is postulated that DYSF may act as a metastasis suppressive gene and perhaps be a promising prognostic tool in ccRCC patients, but replication of data is required by future studies.

Recently, use of plasma and urine nucleic acids as biomarkers in ccRCC also have been a focus of investigations and need reproduction and validation[93].

DISCUSSION

The landscape of first-line therapy for advanced RCC is evolving very rapidly with recent FDA approvals of ICI in combination with another ICI or with an anti-VEGFR TKI. Combination therapies, as outlined below, are the current standard of care in the management of RCC.

For patients with favorable risk disease, the preferred current choice of treatment is combination of pembrolizumab (ICI) plus axitinib (TKI). KEYNOTE-426 trial[45] showed improved OS, ORR and PFS with combination of pembrolizumab plus axitinib compared to sunitinib (TKI). Although this benefit was noted across all risk groups and independent of PD-L1 expression, the choice of therapy is less clear in the intermediate to poor risk patients, where another effective option is available.

For patients with intermediate to poor risk disease, the preferred current choice is nivolumab plus ipilimumab (ICI + ICI). In the CheckMate 214 trial[44], CRR was 9% with nivolumab plus ipilimumab, the best so far, compared to that of 1% in control arm with sunitinib. The updated 30 mo follow-up analysis reported an even higher CR rate of 11%. The OS and ORR were also significantly better in the combination arm. Comparing the combinations of pembrolizumab plus axitinib with that of nivolumab plus ipilimumab, both tested against sunitinib, although the ORR was higher (59% *vs* 42%) in the former combination, it was the CRR of 9% (and 11% on 30 mo follow-up) in the nivolumab plus ipilimumab combination compared to 5.8% in pembrolizumab plus axitinib, that makes it one of the preferred choice in patients with intermediate to poor risk RCC. In terms of AEs also, nivolumab plus ipilimumab combination appeared to be tolerated better with Grade 3 or 4 AEs encountered in 46% of patients compared to grade 3 or higher AEs in 76% patients who received pembrolizumab plus axitinib. In contrast, combination of nivolumab plus ipilimumab did not hold up in favorable risk patients, in whom ORR and PFS favored sunitinib over combination of nivolumab plus ipilimumab. However, OS data from long term follow up are still awaited.

Two VEGFR agents (pazopanib and sunitinib) are also recommended options as first-line therapy in favorable-risk patients with advanced RCC who cannot receive ICIs (pembrolizumab plus axitinib). Pazopanib was non-inferior to sunitinib in the COMPARZ study[53] with several quality of life indicators and AEs profile favoring pazopanib. The VEGFR alternative to ICI therapy in patients with intermediate to poor risk is cabozantinib. Cabozantinb (CABOSUN study)[62] had significantly improved ORR and PFS in comparison with sunitinib but all responses were partial. Grade 3 or 4 AEs occurred in a comparable percentage of patients in the two groups. Cabozantinib

is particularly recommended in patients with bone metastasis. Of new interest is the combination of avelumab (ICI) plus axitinib (TKI), approved by the FDA in May 2019 (JAVELIN Renal 101 trial) for first-line treatment of patients in advanced RCC across all risk groups. PFS and OR benefit were observed irrespective of PD-L1 expression but results of OS are awaited.

The consensus on second-line treatment is still controversial. The general understanding to date is that for patients who progress on immunotherapy, VEGFR targeted therapy is recommended. For patients who progress on initial VEGFR targeted therapy, either single agent nivolumab or the combination ICI regimen nivolumab plus ipilimumab is recommended. If ICI therapy is unavailable or not advisable, other VEGFR agents can be tried. For patients who progress on VEGFR-agent plus ICI, the choices are combination of nivolumab plus ipilimumab or a different VEGFR-agent. Large retrospective and prospective studies are mandated to further analyze the differential benefit/risk ratios of the different available options. Although the choice of a specific therapeutic agent remains controversial, the current trend is discussed below.

For patients treated previously with IO, cabozantinib may be the preferred agent for subsequent therapy. Cabozantinib showed significantly improved PFS and OS compared to everolimus in the METEOR trial. It is particularly beneficial in patients with bone metastasis. In a retrospective analysis of 69 patients with progression on IO alone, or in combination with VEGFR agent or others, the one-year OS was 53% with cabozantinib as a subsequent agent[94]. The appropriate drug holiday before starting a TKI after progression on ICI is undecided. Although an overlap may potentially improve efficacy, it must be remembered that ICIs have long half-lives and can contribute to both, continued response as well as AEs long after discontinuation[68,95]. There is also very limited data evaluating the safety and efficacy of VEGFR agents following progression on IOs[96,97] and larger future studies are awaited. It is imperative to note here that AEs from IO agents can be severe, can affect any organ system, and can be life-threatening. Grade 2 toxicities can be managed by treatment interruption and supportive care but grade 3 or higher toxicities may require high-dose glucocorticosteroids over a prolonged time period. Close monitoring is therefore required for all patients on IO agents.

For patients who progressed on prior VEGFR-agent (but not mTOR inhibitor), nivolumab was found superior to everolimus (CheckMate 025 trial) in ORR and OS benefit. Additionally, nivolumab treatment continuation beyond first progression was noted to have benefit in a subset of patients[68]. Based on the initial success of nivolumab plus ipilimumab (CheckMate 016 trial)[98] which was later confirmed in further study (CheckMate 214 trial), this is a leading alternative.

Other recommended regimens and potential drug choices under specific conditions are as listed in the NCCN guidelines[51]. Ultimately the choice of therapy is a multifactorial decision, depending not only on patient clinical factors but also on other external variables such as cost and availability, practice setting and treatment experience of health care provider. Many questions still remain challenging and unanswered. Several promising drug trials are underway and we expect slow but steady evolutions to treatment regimes. Ultimately, the discovery of sensitive predictive and prognostic biomarkers, or more likely a combination of biomarkers, will define the therapeutic success in treating patients with RCC.

CONCLUSION

The emergence of ICIs and combination therapies has revolutionized the treatment of ccRCC. Significant improvement in efficacy profiles have been appreciated. The best preferred combination regimen and sequencing of treatments will continue to evolve as newer therapeutic agents get FDA approved. These will have to be tried and judged in the balance of AE profiles. Would there be place for a triple drug combination instead of dual drug combination treatment without further adding to the burden of adverse events? In the face of this changing horizon, need for a reliable and validated biomarker(s) is both an increasingly pressing need and a challenge.

Biomarkers can guide in initial treatment selection as well as in sequencing treatments and follow-ups. The IMDC risk model is currently the only validated biomarker based on clinical data and laboratory tests, which classifies metastatic ccRCC patients as having favorable, intermediate/poor prognostic status and accordingly defines their treatment options as first-, second-, or third- line therapies. However, risk stratification based initially on the TNM staging system[5] and later

modified by IMDC classification[7] does not address the critical factor of genetic heterogeneity, differential metastatic potentials, or aggressive subtypes. In view of the high intertumoral and intratumoral heterogeneity, multiple genetic and molecular biomarkers may be required to identify specific responsible genes and the genetic/molecular pathways that are activated in aggressive tumors. The future generation of preferred therapeutic options for ccRCC should molecularly target the most common and aggressive pathways affected by different mutations. Further, prospective clinical trials are required to evaluate the clinical utility of suggested genetic and molecular signatures. Ultimately, the biomarkers may allow treatment to be personally tailored to the needs of each patient, enabling patients to get maximal potential benefit while minimizing unnecessary risks by avoiding regimens with limited efficacy.

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