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Review – Kidney Cancer

Systemic Treatment of Metastatic Clear Cell Renal Cell Carcinoma in 2018: Current Paradigms, Use of Immunotherapy, and Future Directions

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Abstract

Context: Systemic therapy for metastatic clear cell renal cell carcinoma (mccRCC) has greatly evolved over the last 15 yr. More recently, combination strategies involving contemporary immunotherapy have emerged as key opportunities to further shift the treatment landscape.
Objective: To review the evidence regarding the efficacy and safety of standard therapeutic options in mccRCC as well as combination immunotherapy options on the horizon.
Evidence acquisition: PubMed/Medline, Embase, Web of Knowledge, and Cochrane Library databases were searched up to February 2018 and according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. A narrative review of studies was performed.
Evidence synthesis: Twenty-six studies were included regarding therapies for metastatic RCC including vascular endothelial growth factor (VEGF)-directed therapy ($n = 9$), mTOR inhibitors ($n = 2$), cytokines ($n = 3$), vaccines ($n = 3$), and immune checkpoint inhibitors (ICIs, $n = 9$). VEGF tyrosine kinase inhibitor monotherapy had been the standard therapy, and its use is evolving in the front-line setting with ICIs; cabozantinib provides superior progression-free survival versus sunitinib in intermediate- and poor-risk patients, by International Metastatic RCC Database Consortium criteria. The mTOR therapy is largely inferior to VEGF-directed therapy, although it has a role in combination strategies. Cytokines have largely been replaced in current practice throughout most regions, and vaccines have failed to show improved survival in phase III studies to date. ICIs have now become standard care in untreated patients with intermediate and poor risks, given overall survival benefit seen with CheckMate-214 study; survival data from IMmotion 151 are not yet mature. Several ongoing phase III combination trials, with promising early-phase data, are due to be read out.
Conclusions: The treatment landscape for mccRCC has evolved since the introduction of VEGF inhibitors. Combination therapies involving checkpoint inhibitors could be the next standard of care.
Patient summary: With the expanding role of immune checkpoint inhibitors in metastatic renal cell carcinoma, the treatment paradigm has shifted to include combination therapy in the untreated setting. As the field advances, the bar has been raised in evaluating ongoing combination strategies.

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1. Introduction

Renal cell carcinoma (RCC), the seventh most common cancer in Europe, accounts for nearly 4% of all new cancer cases and 2.5% of cancer deaths worldwide [1]. While the majority of these patients will present with localized disease, 25–40% of those treated with curative intent will develop distant disease and 20–25% of patients will present with metastatic disease at diagnosis [2]. Over the past decade, there have been considerable advances in the treatment of advanced RCC where the majority of data are based on trials of patients with clear cell RCC (ccRCC), which accounts for 70% of RCCs.

On the basis of these relatively recent therapeutic advances, the prognosis of metastatic clear cell RCC (mccRCC) has improved. The initial prognostic model known as the Memorial Sloan Kettering Cancer Center (MSKCC) criteria looked at five different risk factors (performance status, lactate dehydrogenase levels, serum calcium, hemoglobin, and time from initial diagnosis to systemic treatment) in the cytokine era. Median survival was 26 mo for those with zero to one risk factor (good) versus 14 mo for one to two risk factors (intermediate) and 7 mo for more than two risk factors (poor) [3]. With the introduction of vascular endothelial growth factor (VEGF)-targeted therapy, the International Metastatic RCC Database Consortium (IMDC) criteria evolved to include performance status, hemoglobin, calcium, and time from initial diagnosis to systemic therapy in addition to neutrophil and platelet counts [4]. In a subsequent validation study, the median overall survival (OS) for good-, intermediate-, and poor-risk disease was markedly better than those seen in the cytokine era at 43.2, 22.5, and 7.8 mo, respectively [5].

Immune checkpoint inhibitors (ICIs) and multitarget tyrosine kinase inhibitors (TKIs) such as cabozantinib have already been shown to improve survival in the second-line setting [6,7]. With further study of ICIs and combination strategies in the front line showing impressive response rates (including complete response [CR]) and in some instances improved survival [8], the treatment paradigm for metastatic RCC (mRCC) is currently shifting worldwide.

The aim of this review is to summarize the available data on the efficacy and safety of established systemic treatments for advanced ccRCC with a focus on immunotherapy strategies and future directions in this evolving therapeutic landscape.

2. Evidence acquisition

2.1. *Search strategy*

A systematic search of PubMed/Medline, Embase, Web of Knowledge, and Cochrane Library was conducted in February 2018 by an expert librarian. The complete free-text search terms and the search strategy are given in the Supplementary material. Our procedure for evaluating records identified during the literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Fig. 1). Cited references from selected studies were also retrieved.

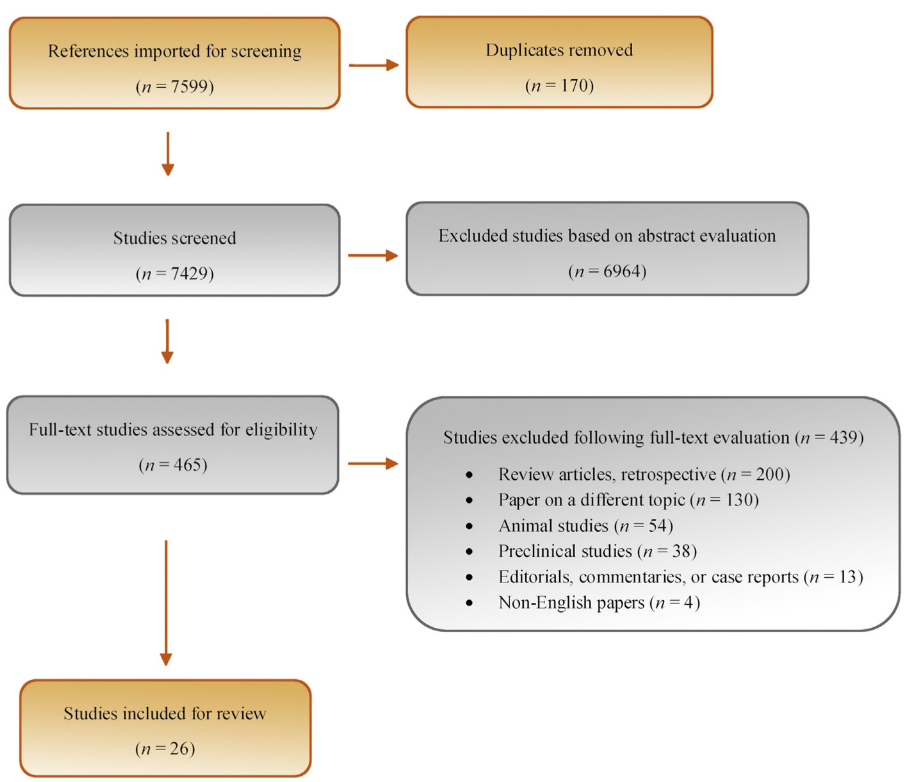

Fig. 1 – Flow diagram of evidence acquisition in a systematic review on systemic therapy for treatment of metastatic renal cell carcinoma.

2.2. Inclusion criteria

All authors participated in the design of the search strategy and inclusion criteria. The study population included patients >18 yr of age diagnosed with mRCC, focusing predominantly on clear cell disease (search terms in the Supplementary material). Outcome measures included, but were not restricted to, objective response rates (ORRs), OS, progression-free survival (PFS), adverse events (AEs), and quality of life (QoL) measures. We limited these criteria to studies published in the English language, original studies, and meta-analyses. Review articles, case reports, editorials, and commentaries were excluded. In addition, studies with ≤10 participants were not accepted for inclusion. If multiple studies reporting on the same or overlapping series met our inclusion criteria, the latest study was selected, unless different endpoints were investigated or different subgroup analyses were performed.

2.3. Data extraction

Two independent reviewers (A.A.L. and B.A.M.) assessed relevant articles for study eligibility, and any disagreement was resolved by requiring majority vote via discussion with the senior author. Using a standardized data form, the following details were extracted: study design, number of patients, patient characteristics, experimental and control interventions, efficacy outcomes, AEs, and QoL measures.

3. Evidence synthesis

Our search, conducted in February 2018, identified 7599 studies. After removing duplicates, two reviewers (A.A.L. and B.A.M.) screened titles and abstracts. Of these, 465 full-text articles were reviewed and 26 original articles were selected for inclusion (Fig. 1, and Tables 1 and 2).

3.1. Targeted therapy

3.1.1. First-line oral VEGF treatment

TKIs have been a mainstay of the treatment of mccRCC since 2007. Most studies include predominantly good- or intermediate-risk disease, with poor-risk disease often representing <10% of patients enrolled. In an international multicenter trial, 750 patients with treatment-naïve mccRCC were randomized to interferon-alpha (IFN-α) or sunitinib, administered orally at a dose of 50 mg once daily in 6-wk cycles consisting of 4 wk of treatment followed by 2 wk without treatment (4/2 schedule). The primary endpoint of PFS was 11 versus 5 mo ($p < 0.001$) favoring sunitinib [9]. With extended follow-up, median OS was also improved (26.4 vs 21.8 mo; hazard ratio [HR] 0.82, $p = 0.051$) [10]. Pazopanib was subsequently evaluated in a randomized phase 3 trial where 435 treatment-naïve ($n = 233$) or cytokine-pretreated ($n = 201$) mccRCC patients were treated with pazopanib 800 mg daily or placebo. The primary endpoint of PFS was 9.2 versus 4.2 mo (HR 0.46, 0.34–0.62, $p < 0.001$) favoring pazopanib, with a more pronounced benefit noted in the treatment-naïve group (PFS 11.1 vs 2.8 mo; HR 0.40, 0.27–0.60, $p < 0.001$) [11].

Sunitinib and pazopanib were compared in the international multicenter noninferiority COMPARZ trial; 1110 patients were randomized to pazopanib 800 mg daily or sunitinib 50 mg daily on a 4/2 schedule. With primary endpoint of PFS, pazopanib was noninferior to sunitinib (target upper boundary for HR <1.25), with median PFS 8.3 versus 9.5 mo (HR 1.05, 0.90–1.22). Regarding grade 3 or 4 toxicities, those on sunitinib had a higher incidence of fatigue (17% vs 10%), hand-foot syndrome (11% vs 6%), and hematological toxicities (14–22% vs <1%), while those on pazopanib had increased levels of alanine aminotransferase (ALT; 17% vs 4%) or aspartate aminotransferase (AST; 12% vs 3%) [12]. An improved toxicity profile of pazopanib was supported by the PISCES trial; 169 patents randomized to pazopanib 800 mg daily for 10 wk followed by sunitinib 50 mg daily in a 4/2 schedule or the reverse were assessed for a patient preference. Seventy percent of patients preferred pazopanib ($p < 0.01$), with patients reporting less fatigue and better QoL with pazopanib [13].

Other TKIs continue to be evaluated in the treatment of RCC. Tivozanib was evaluated in a phase 3 trial where 517 patients with mccRCC (postnephrectomy) were randomized to tivozanib 1.5 mg once per day for 3 wk followed by a week off versus sorafenib 400 mg twice daily. Median PFS, the primary endpoint, was 11.9 versus 9.1 mo (HR 0.797, 0.639–0.993, $p = 0.042$) favoring tivozanib. ORRs were also improved with tivozanib versus sorafenib (33.1% vs 23.3%, $p = 0.04$), with a comparable toxicity profile. However, final OS showed a trend toward longer survival on the sorafenib arm (29.3 vs 28.8 mo; HR 1.245, 0.954–1.624, $p = 0.105$). Sixty-three percent of patients who received sorafenib received additional therapy, while only 13% did so in the tivozanib arm, perhaps explaining the dichotomous results [14]. Tivozanib is approved in the European Union for advanced RCC patients who are naïve to VEGFR and mTOR inhibitors following disease progression after one prior treatment with cytokine therapy.

Cabozantinib was compared with sunitinib in the randomized phase 2 CABOSUN trial. Patients with exclusively intermediate- or poor-risk disease per IMDC criteria ($n = 157$) were randomized to cabozantinib 60 mg daily or sunitinib 50 mg daily on a 4/2 schedule. Thirteen percent of patients had Eastern Cooperative Oncology Group performance status 2, and 37% had bone metastases. While no CRs were reported, ORR was 33% versus 9% favoring cabozantinib. The primary endpoint of PFS by an independent review was 8.6 versus 5.3 mo (HR 0.48, 0.31–0.74, $p = 0.0008$) and median OS was 26.6 versus 21.2 mo (HR 0.8, 0.53–1.21), both favoring cabozantinib. Grade 3 or 4 AEs approached 70% for all patients with diarrhea comparable on both arms; patients on cabozantinib experienced more hypertension (28% vs 21%), while fatigue (17% vs 6%) and thrombocytopenia (11 vs 1%) were more common in those on sunitinib [8].

3.1.2. mTOR inhibitors

Given the role of mTOR as a downstream inhibitor of the PI3-K/Akt/mTOR pathway, mTOR inhibitors have been explored in RCC in both treatment-naïve and refractory

Table 1 – Pivotal trials of established systemic agents in metastatic clear cell renal cell carcinoma

Study	Experimental arms	Control arm(s)	Median overall survival (HR, 95% CI)	Median progression-free survival (HR, 95% CI)
First-line setting				
Motzer et al (2007) [9]	Sunitinib (*n* = 375)	IFN (*n* = 375)	26.4 vs 21.8 mo (0.82, 0.67–1.00)	11 vs 5 mo (0.42, 0.32–0.54)
Escudier et al (2007, 2010) [25,26]	Bevacizumab + IFN (*n* = 327)	Placebo + IFN (*n* = 322)	23.3 vs 21.3 mo (0.86, 0.72–1.04)	10.2 vs 5.4 mo (0.63, 0.52–0.75)
Hudes et al (2007) [15]	IFN + temsirolimus (*n* = 210) Temsirolimus (*n* = 209)	IFN (*n* = 207)	8.4 vs 10.9 vs 7.3 mo (0.96, 0.76–1.20 [a] and 0.73, 0.58–0.92 [b])	4.7 vs 5.5 vs 3.1 mo (0.66, 0.53–0.81 [b])
Rini et al (2008, 2010) [27,28]	Bevacizumab + IFN (*n* = 369)	IFN (*n* = 363)	18.3 vs 17.4 mo (0.86, 0.73–1.01)	8.5 vs 5.2 mo (0.71, 0.61–0.83)
Sternberg et al (2010) [11]	Pazopanib (*n* = 290)	Placebo (*n* = 145)	22.9 vs 20.5 mo (0.91, 0.71–1.16)	9.2 vs 4.2 mo (0.46, 0.34–0.62)
Motzer et al (2013) [12]	Pazopanib (*n* = 557)	Sunitinib (*n* = 553)	28.3 vs 29.1 mo (0.92, 0.79–1.06)	8.4 vs 9.5 mo (1.05, 0.90–1.22)
Motzer et al (2013) [14] [c]	Tivozanib (*n* = 260)	Sorafenib (*n* = 257)	28.8 vs 29.3 mo (1.245, 0.95–1.62)	11.9 vs 9.1 mo (0.79, 0.64–0.99) 12.7 vs 9.1 mo (0.75, 0.58–0.98) [d]
Choueiri et al (2018) [40] [e]	Cabozantinib (*n* = 79)	Sunitinib (*n* = 78)	26.6 vs 21.2 mo (0.80, 0.53–1.21)	8.6 vs 5.3 mo (0.48 0.31–0.74)
Escudier et al (2017) [39]	Nivolumab + ipilimumab (*n* = 550)	Sunitinib (*n* = 546)	NR vs 26.0 mo (0.63, 0.44–0.89 [f])	11.6 vs 8.4 mo (0.82, 0.64–1.0 [g])
Motzer et al (2018) [33]	Atezolizumab + Bevacizumab (*n* = 454)	Sunitinib (*n* = 461)	NR vs NR (0.81, 0.63–1.0 [h])	11.2 vs 7.7 mo (0.74, 0.57–0.96 [i])
Subsequent-line setting				
Motzer et al (2010) [18]	Everolimus (*n* = 272)	Placebo (*n* = 138)	14.8 vs 14.4 mo (0.87, 0.65–1.15)	4.9 vs 1.9 mo (0.33, 0.25–0.43)
Escudier et al (2007, 2009) [19]	Sorafenib (*n* = 451)	Placebo (*n* = 452)	17.8 vs 15.2 mo (0.88, 0.74–1.04)	5.5 vs 2.8 mo (0.44, 0.35–0.55)
Rini et al (2011, 2013) [20]	Axitinib (*n* = 361)	Sorafenib (*n* = 362)	20.1 vs 19.2 mo (0.97, 0.80–1.17)	6.7 vs 4.7 mo (0.66, 0.55–0.81)
Motzer et al (2015) [23]	Lenvatinib + everolimus (*n* = 51) Lenvatinib (*n* = 52)	Everolimus (*n* = 50)	25.5 vs 19.1 vs 15.4 mo (0.59, 0.36–0.97 [j] and 0.75, 0.47–1.2 [k])	14.6 vs 7.4 vs 5.5 mo (0.40, 0.24–0.68 [j] and 0.61, 0.38–0.98 [k])
Motzer et al (2015) [7]	Nivolumab (*n* = 406)	Everolimus (*n* = 397)	25 vs 19.6 mo (0.73, 0.57–0.93 [l])	4.6 vs 4.4 mo (0.88, 0.75–1.03)
Choueiri et al (2016, 2018) [6,40]	Cabozantinib (*n* = 330)	Everolimus (*n* = 328)	21.4 vs 16.5 mo (0.66, 0.53–0.83)	7.4 vs 3.9 mo (0.51, 0.41–0.62)

CI = confidence interval; HR = hazard ratio; IFN = interferon-α; IL-2 = interleukin-2; ITT = intention-to-treat; NR = not reached; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; OS = overall survival.
[a] HR for the comparison of IFN + temsirolimus with IFN.
[b] HR for the comparison of temsirolimus with IFN.
[c] Trial included patients with zero or one prior treatment; data presented are for the entire cohort.
[d] PFS for treatment-naïve patients.
[e] Trial included only intermediate- and poor-risk group patients.
[f] Results for the intermediate- and poor-risk group patients; 99.8% confidence interval was used for the HR.
[g] Results for the intermediate- and poor-risk group patients; 99.1% confidence interval was used for the HR.
[h] Results for OS in the ITT population (coprimary endpoint).
[i] Results for PFS in the PD-L1+ population by investigator review (coprimary endpoint).
[j] HR for the comparison of lenvatinib + everolimus with everolimus.
[k] HR for the comparison of lenvatinib with everolimus.
[l] 98.5% confidence interval was used for the HR.

settings. The intravenous mTOR inhibitor temsirolimus was studied in the front-line setting for patients with MSKCC poor-risk disease in a phase 3 trial randomizing 626 treatment-naïve patients to temsirolimus 25 mg IV weekly, temsirolimus in combination with IFN-α, or IFN-α alone. ORRs were comparable among the three groups at 8.1%, 8.6%, and 4.8%, respectively. As compared with IFN alone, temsirolimus monotherapy improved OS (HR 0.73, 0.58–0.92, p = 0.008), with median OS of 7.3 mo with IFN, 10.9 mo with temsirolimus, and 8.4 mo with combination therapy [15]. However, while this was a small trial with results not being statistically significant, the role of temsirolimus in the front-line setting is called into question by the randomized phase 2 data of 69 patients with poor-risk disease randomized to pazopanib 800 mg daily or temsirolimus 25 mg IV weekly, where 43% of patients had prior treatment. ORRs (26% vs 6%, p = 0.046) and median PFS (5.2 vs 2.6 mo; p = 0.16) both favored pazopanib. This translated into an improvement of median OS from 7.3 to 12 mo (p = 0.56) [16].

The oral mTOR inhibitor everolimus does not have a role in the front-line setting; a randomized phase 2 study

Table 2 – Phase I/II results of ongoing systemic combination studies in metastatic renal cell carcinoma

Study	Population included	Mechanisms of drugs studied	Experimental arm(s), dose	Endpoint(s)	Ongoing phase III study
Choueiri et al (2018) [34] NCT02493751	Untreated mRCC with clear cell component	PD-L1 + TKI	Avelumab 10 mg/kg q 2 wk + axitinib 5 mg BID (*n* = 55)	ORR 58.2% – PD-L1+ = 65.9%	JAVELIN 101 (NCT02684006) [a] Experimental arm: avelumab + axitinib Estimated enrolment: *n* = 830 Primary endpoints: PFS, OS in PD-L1+
Atkins et al (2018) [35] NCT02133742	Untreated clear cell mRCC	PD-1 + TKI	Pembrolizumab 2 mg/kg q 3 wk + axitinib 5 mg BID (*n* = 52)	ORR 73% – PD-L1+ = 89%	KEYNOTE 426 (NCT02853331) + Experimental arm: pembrolizumab + axitinib Estimated enrolment: *n* = 840 Primary endpoints: PFS, OS
Lee et al (2017) [36] NCT02501096	Untreated and treated clear cell mRCC	PD-1 + TKI	Pembrolizumab 200 mg q 3 wk + lenvatinib 20 mg daily (*n* = 30)	ORR 63% – PD-L1+ = 58%	CLEAR (NCT02811861) [a] Experimental arms: pembrolizumab + lenvatinib, or everolimus + lenvatinib Estimated enrolment: *n* = 735 Primary endpoint: PFS
Nadal et al (2018) [38] NCT02496208	Treated genitourinary malignancies	PD-1 + TKI ± CTLA-4	Nivolumab 3 mg/kg q 2 wk + cabozantinib 40 mg daily (*n* = 49) ± ipilimumab 1 mg/kg q 3 wk × 4 doses (*n* = 29)	ORR 36% mRCC (*n* = 13) = 53.9%	CHECKMATE 9ER (NCT03141177) [a] Experimental arm: nivolumab + cabozantinib Estimated enrolment: *n* = 630 Primary endpoint: PFS
Amin et al (2015) NCT00678119	Untreated clear cell mRCC	Autologous dendritic cell vaccine + TKI	AGS-003 induction q 3 wk × 5 doses then q 12 wk + sunitinib 50 mg daily in 4 wk on/2 wk off schedule (*n* = 21)	ORR 43% – PFS 11.2 mo – OS 30.2 mo	ADAPT (NCT01582672) [a] Experimental arm: AGS-003 + sunitinib Estimated enrolment: *n* = 462 Primary endpoint: OS

BID = twice daily; CI = confidence interval; CTLA-4 = cytotoxic T-lymphocyte associated protein 4 antibody; mRCC = metastatic/advanced renal cell carcinoma; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; q = every; TKI = tyrosine kinase inhibitor'
[a] Phase III studies with control arm of sunitinib (50 mg, 4 wk on and 2 wk off schedule).

showed that everolimus was not noninferior to sunitinib [17]. In the second-line setting, everolimus was studied in a phase 3 trial randomizing 410 patients with mccRCC in 2:1 fashion to everolimus 10 mg daily or placebo. Everolimus significantly prolonged PFS (primary endpoint) at 4.9 versus 1.9 mo (HR 0.33, 0.25–0.43; $p < 0.0001$), although the ORR was only 1.8%. Grade 3 or higher AEs occurring in >5% included dyspnea (7%) and fatigue (5%). OS was not improved at 14.8 versus 14.4 mo (HR 0.87, 0.65–1.15, $p = 0.162$), although this was confounded by 80% of patients crossing over to receive open-label everolimus [18].

3.1.2. Subsequent-line oral VEGF treatment

With a poor response to mTOR in the second line, the role of VEGF inhibition in the treatment-refractory setting continues to evolve. In an international phase 3 study, 903 patients, of whom >80% received prior cytokines, were randomized to sorafenib 400 mg twice daily or placebo. With an ORR of 10% including one CR, sorafenib improved PFS (primary endpoint) to 5.5 from 2.8 mo ($p < 0.001$) with a similar toxicity profile to other TKIs [19]. Sorafenib was the first VEGF TKI to be approved in the USA for treating mRCC. Sorafenib was later compared with axitinib in a randomized phase 3 trial of 723 patients with treatment-refractory mccRCC, of whom 54% received sunitinib. Patients were randomized to axitinib 5 mg twice daily titrating up to 10 mg BID as tolerated or sorafenib 400 mg BID, with 37% of patients achieving the escalated the dose of axitinib. Median PFS (primary endpoint) was 6.7 versus 4.7 mo favoring axitinib (HR 0.665, 0.544–0.812, $p < 0.0001$). Benefit was most pronounced in those receiving cytokine therapy (median PFS 12.1 vs 6.5 mo; HR 0.464, 0.318–0.676, $p < 0.0001$). In those treated with sunitinib, median PFS was worse in both arms (4.8 vs 3.4 mo; HR 0.741, 0.573–0.958, $p = 0.0107$). The most common AEs of grade 3 or higher were hypertension (11%), diarrhea (16%), and fatigue (11%) with axitinib, and hand foot syndrome (16%) and hypertension (11%) with sorafenib [20]. With extended follow-up, median OS was not found to differ (20.1 vs 19.2 mo; HR 0.969, 0.800–1.174. $p = 0{\cdot}3744$) [21].

Cabozantinib is the only TKI to show a benefit of ORR, PFS, and OS after VEGF treatment failure. In METEOR, a phase 3 randomized trial, 658 VEGF-refractory patients with ccRCC were randomized to cabozantinib 60 mg daily or everolimus 10 mg daily. In an independent review, cabozantinib extended PFS (primary endpoint) from 3.9 to 7.4 mo (HR 0.51, 0.41–0.62, $p < 0.0001$) and the ORR was also improved at 17% versus 3% ($p < 0.001$). Benefit extended across all subgroups [6]. There was an improvement in OS from 17.1 to 21.4 mo with cabozantinib versus everolimus (HR 0.7, 0.58–0.86, $p = 0.0002$) [22]. The most common grade 3 or 4 AEs associated with cabozantinib were hypertension (15% vs 4%), diarrhea (13% vs 2%), fatigue (11% vs 7%), and hand foot syndrome (8% vs 1%), while anemia (6% vs 17%) and hyperglycemia (1% vs 5%) were more commonly seen with everolimus [6].

Given poor response rates with single-agent mTOR inhibition, addition of a TKI was studied in a randomized phase 2 trial of 153 patients with VEGF-refractory ccRCC randomized in 1:1:1 fashion to everolimus 10 mg daily, lenvatinib 24 mg daily, or everolimus 5 mg daily with lenvatinib 18 mg daily. Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone (14.6 vs 5.5 mo; HR 0.40, 0.24–0.68, $p = 0.0005$), but not compared with lenvatinib alone (7.4 mo; HR 0.66, 0.30–1.10, = 0.12). Grade 3 and 4 events occurred in fewer patients allocated single-agent everolimus (50%) compared with those assigned lenvatinib alone (79%) or in combination (71%), with diarrhea, proteinuria, and hypertension being more common with lenvatinib alone or in combination. ORRs were 43%, 27%, and 6% for the combination, single-agent lenvatinib, and everolimus, respectively. Median OS was 25.5 mo with the combination versus 15.4 mo with everolimus (HR 0.51, 0.30–0.88, $p = 0.024$) [23].

3.2. Immunotherapy

3.2.1. Historical cytokines

Cytokines such as interleukin-2 (IL-2) and IFN-α have had a historical presence in the treatment of mRCC; however, in the context of contemporary options with less toxicity, current use has generally fallen out of favor and high-dose IL-2 is offered only to a small percentage of patients in few centers. Over 20 yr ago, Fyfe et al. [24] reported on a pooled study of 255 mRCC patients treated with IL-2 and showed a response rate of 14%, countered by a treatment-related death rate of 4%. More recently, IFN has been evaluated in combination with bevacizumab versus IFN alone (±placebo). Escudier et al. [25,26] evaluated the combination versus IFN with placebo in 649 treatment-naïve patients with predominantly (>50%) ccRCC, where <10% had poor-risk disease by MSKCC criteria. While PFS was improved with bevacizumab plus IFN (median PFS 10.2 vs 5.4 mo), the primary endpoint of OS was not significantly improved compared with IFN and placebo (median OS 23.3 vs 21.3 mo; stratified HR 0.86, 0.72–1.04, $p = 0.13$). Rini et al. [27,28] studied the combination of bevacizumab plus IFN versus IFN alone in 732 untreated mRCC patients. Similarly, they reported improved PFS with the combination (median PFS 8.5 vs 5.2 mo), but the primary endpoint of OS was not significantly different compared with IFN (median OS 18.3 vs 17.4 mo; stratified HR 0.86, 0.73–1.01, $p = 0.07$). There was significantly more grade 3–4 hypertension (11% vs 0%), anorexia (17% vs 8%), fatigue (37% vs 30%), and proteinuria (15% vs <1%) with the treatment combination [28].

3.2.2. Vaccine-based therapies

Vaccine-based regimens have generated continued interest in mRCC but to date have not permeated into established care options. In a phase III study of good- or intermediate-risk mRCC patients (MSKCC criteria) with prior nephrectomy, Amato et al. [29] evaluated MVA-5T4 ($n = 365$) or placebo ($n = 368$) in combination with sunitinib, IL-2, or IFN (termed standard–of-care options at trial design). Median OS was no different between both groups at 20.1 and 19.2 mo for MVA-5T4 and placebo-treated patients, respectively (HR 1.07, 0.86–1.32, $p = 0.55$). Rini et al. [30] reported on the phase III IMPRINT study, which randomized 339 HLA-A*02–positive patients 3:2 to receive IMA901 vaccinations plus sunitinib ($n = 204$) or sunitinib alone ($n = 135$). Median OS did not differ between the two arms (HR 1.34, $p = 0.087$), and grade ≥3 treatment-related AEs (TRAEs) were noted in 57% and 47% of patients, respectively.

The phase III ADAPT study randomized 462 untreated mRCC patients 2:1 to receive rocapuldencel-T (AGS-003), an autologous dendritic cell vaccine, plus sunitinib versus sunitinib alone. This trial includes intermediate- (77%) and poor-risk (23%) patients. While the interim analysis showed the combination arm having a survival HR greater than the predefined futility boundary, the trial was kept open after discussion with the US Food and Drug Administration (FDA) based on the rationale of a delayed treatment effect and the safety profile. At ESMO 2017, Figlin [31] reported a trend to an OS benefit for the combination in patients with the longest follow-up and least censored data. These data are currently unpublished and final results are pending (NCT01582672).

3.2.3. Immune checkpoint inhibitors

Recent evaluations of ICIs have shifted the treatment paradigm of mRCC to include contemporary immunotherapy in both the subsequent- and the first-line setting. The phase III study CheckMate-025 randomized 821 previously treated patients to receive nivolumab (3 mg/kg) or everolimus. Median OS was 25 versus 19.6 mo favoring nivolumab (HR 0.73, 98.5% confidence interval [CI] 0.57–0.93), and benefits were seen regardless of programmed death-ligand 1 (PD-L1) expression [7]. Importantly, the side-effect profile favored patients treated with nivolumab (grade 3–4 TRAEs 19% vs 37%). Further, more patients had clinically meaningful improvement in health-related QoL scores with nivolumab [32].

Provocative data for ICIs in the front-line mRCC setting have been reported in two combination trials thus far. The CheckMate-214 study evaluated the combination of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg, combination every 3 wk for four doses and then nivolumab every 2 wk) versus sunitinib (4/2 schedule). The coprimary endpoints were OS (alpha assigned 0.04), PFS (alpha 0.009), and ORR (alpha 0.001) among patients with a intermediate- or poor-risk prognosis by IMDC criteria. The median OS was not reached in the combination arm versus 26 mo with sunitinib (HR 0.63, 99.8% CI 0.44–0.89, $p < 0.001$), and 18-mo OS was also better (75% vs 60%) [8]. PFS was numerically improved with the combination (median PFS 11.6 vs 8.4 mo) but did not meet the prespecified threshold for statistical significance (HR 0.82, 99.1% CI 0.64–1.05, $p = 0.03$). Nivolumab and ipilimumab also impressively had a CR rate of 9% compared with just 1% with sunitinib, in the context of an improved ORR with the combination (42% vs 27%, $p < 0.001$). An exploratory analysis of favorable-risk patients, however, revealed that PFS (15.3 vs 25.1 mo) and ORR (29% vs 52%) favored sunitinib in this subgroup. With only 37 deaths at initial database lock, the HR for death also favored sunitinib (HR 1.45, $p = 0.27$) in these patients. The benefit of OS with the ICI combination was also seen regardless of PD-L1 expression, although the magnitude was more pronounced in patients with PD-L1 ≥1% compared with those with PD-L1 <1% (HRs for death 0.45 and 0.73, respectively). Further, the CR rate was 16% in intermediate- and poor-risk patients treated with the ICI combination. In terms of toxicity, TRAEs leading to discontinuation occurred in 22% in the combination group and 12% in the sunitinib group. Of those receiving nivolumab and ipilimumab who had immune-mediated TRAEs, 35% were treated with high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent). This study has lead to US FDA approval of the combination in untreated patients with mRCC having intermediate- or poor-risk disease; decision of the European Medicines Agency is pending.

The IMmotion 151 study was the next front-line, phase III combination trial to have data presented. A total of 915 patients were randomized to treatment with atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) every 3 wk versus sunitinib (4/2 schedule). Coprimary endpoints were PFS by investigator assessment in PD-L1+ patients, defined as ≥1% expression on tumor-infiltrating immune cells (alpha assigned 0.04), and OS in the intention-to-treat (ITT) population (alpha 0.01). Median PFS in the PD-L1+ group was 11.2 mo in the combination group versus 7.7 mo in the sunitinib arm (HR 0.74, 0.54–0.96, $p = 0.02$), and similar results were seen for PFS in the ITT population [33]. The combination of atezolizumab plus bevacizumab had an ORR of 43% compared with 35% in the PD-L1+ group, where CRs were seen in 9% versus 4%, respectively. However, according to an assessment by the Independent Radiology Committee (IRC), no significant improvement was seen in PFS in the PD-L1+ patients (HR 0.93, 0.72–1.21) or the ITT population (HR 0.88, 0.74–1.04), although CRs were seen in both subgroups (15% PD-L1+ and 11% ITT by IRC). OS data were immature at the first readout. The combination of atezolizumab and bevacizumab was well tolerated with a favorable toxicity profile compared with sunitinib, and only 16% of patients treated with the combination required corticosteroids within 30 d of an immune-mediated AE.

3.3. *Future combination strategies*

Several early-phase combination studies in mRCC have displayed encouraging initial findings, which have formed the basis of subsequent evaluations in the phase III setting (Table 2). The JAVELIN 100 study was a dose-finding, dose-expansion phase Ib trial evaluating avelumab (a human anti-PD-L1 IgG1 monoclonal antibody) plus axitinib in 55 untreated mRCC patients. Preliminary results showed a confirmed ORR of 58% with three patients experiencing a CR [34]. Using the Ventana SP263 assay, PD-L1 expression ≥1% (on immune cells) was associated with an ORR of 66% compared with 36% for expression <1%. Thirty-two patients experienced grade 3–4 combination TRAEs, the most frequent being hypertension, palmar-plantar erythrodysesthesia syndrome, and increased levels of ALT, amylase, and lipase. Seventeen patients experienced an immune-related AE (iRAE) of any grade, with three patients experiencing a grade 3 event and immune-related myocarditis leading to death in one patient.

Atkins et al. [35] reported on an open-label phase Ib trial evaluating pembrolizumab (a humanized anti-PD-1 monoclonal antibody) with axitinib in 52 untreated mRCC patients. With a median follow-up of 20 mo, the ORR was 73%, with four patients displaying CRs. Using the 22c3 Dako assay, nine patients had PD-L1 ≥1% (tumor cells) and 89% of these patients displayed PR. Median PFS was 20.9 mo (15.4—NE) and median OS was not reached at the last follow-up. Thirty-four patients had grade 3 or worse TRAEs, most commonly hypertension, diarrhea, fatigue, and increased ALT. The most common iRAEs were diarrhea, increased ALT or AST, hypothyroidism, and fatigue, with 10 patients experiencing grade 3 or more, and no treatment-related deaths were noted.

Lee et al. [36] presented updated results of a phase Ib/II trial evaluating lenvatinib with pembrolizumab in previously treated or untreated patients with mRCC. The ORRs at 24 wk was 63% for the overall population ($n = 30$) and 83% for treatment-naïve patients ($n = 12$). Using an investigational version of the 22c3 pharmDx assay, PD-L1 status was determined by a combined positive score of the number of staining tumor and immune cells relative to total tumor cells. Of the PD-L1–positive patients ($n = 12$), the ORR at 24 wk was 58% compared with 71% in those with a PD-L1–negative status. Eighteen patients experienced grade 3–4 TRAEs, most commonly hypertension, proteinuria, fatigue, diarrhea, and elevated lipase levels, and two patients experienced grade 5 events related to disease progression.

Lara et al. [37] presented results from the ECHO-202/KEYNOTE-037 phase Ib/II trial evaluating the combination of epacadostat (a selective inhibitor of indoleamine 2,3-dioxygenase-1) with pembrolizumab across a variety of tumors, with 46 patients having untreated or treated mRCC. For patients receiving zero to one prior line of therapy, the ORR was 47% (one patient with a CR) compared with 9% for those with two or more treatments. However, due to the phase 3 ECHO-301/KEYNOTE-252 study failing to meet its primary endpoint of PFS in unresectable or metastatic melanoma patients, further phase III evaluations of this combination strategy in mRCC (and other solid tumors) has been halted as of this writing.

Nadal et al. [38] presented updated results of a phase I plus expansion cohort of 78 patients with metastatic treatment-refractory genitourinary malignancies treated with either cabozantinib plus nivolumab (CaboNivo) or both medications plus ipilimumab (CaboNivoIpi). For the 13/14 mRCC patients (most with sarcomatoid differentiation) who had at least one radiological assessment, the ORR was 54% and 12-mo PFS and 12-mo OS were 73% and 50%, respectively. Overall, 57% of patients treated with CaboNivo and 72% treated with CaboNivoIpi experienced grade 3–4 TRAEs, most common being hypertension, infection, colitis, diarrhea, fatigue, hypophosphatemia, elevated lipase, and elevated AST/ALT.

Escudier et al. [39] presented preliminary results of a phase Ib/II study on the combination of tivozanib and nivolumab in 27 mRCC patients, of whom 44% were previously untreated. In the evaluable cohort (n = 14), the ORR was 64%. Fifty-two percent of patients experienced a grade 3/4 AE, the most common of which was hypertension.

4. Discussion

Since the approval of sunitinib over 11 yr ago, therapy for mccRCC has greatly evolved. With the prospects of combination therapies appearing on the horizon, the precise role of a single-agent TKI requires some refinement. In the current landscape, TKI monotherapy still plays a role in the front-line management of mRCC. Results from CheckMate-214 showed superior PFS and ORR with sunitinib compared with nivolumab and ipilimumab in IMDC good-risk patients, suggesting that there are populations potentially better served with a TKI in the front-line therapy [8]. Further, with data from CABOSUN showing improved ORR, PFS, and trend toward OS, cabozantinib has emerged as an effective front-line TKI and has been granted FDA approval for untreated mRCC [40]. While the trial included only those with poor- and intermediate-risk disease, its unique mechanism of action with VEGF, MET, and AXL inhibition may suggest plausible effectiveness in patients with good-risk disease as well. Additionally, it may have a place in patients with bone metastases given its activity in the setting of skeletal disease, which is historically associated with a worse outcome [41]. There are several retrospective analyses exploring TKI therapy following an ICI; additionally, a phase 2 prospective trial of axitinib employing an individual dosing strategy showed response rates nearing 40% [42]. With continued emerging data for TKI benefit following previous ICIs, TKI monotherapy will plausibly become the standard second-line therapy for the foreseeable future as immunotherapy moves into the front-line setting.

While nivolumab monotherapy has been studied most prominently in the pretreated setting, pembrolizumab has recently been assessed in the untreated setting. Phase II data from cohort A (ccRCC) of the KeyNote-427 trial showed an impressive ORR of 38%; encouraging activity was also noted in the PD-L1+ subgroup (ORR 50%) [43]. Moreover, the IMmotion 150 study reported an ORR of 25% (including 11% CR rate) in 103 treatment-naïve patients who received atezolizumab monotherapy [44]. An ensuing priority is to build upon an ICI backbone in the front line with the aim of developing safe and efficient combination strategies with a synergistic effect. The growth potential for combinations was rooted in a deeper understanding of the stimulatory and inhibitory factors in the cancer-immunity cycle [45]. For example, biological rationale supported the synergy of CTLA-4 inhibition, which influences the development of an active immune response at the level of T-cell proliferation, with PD-1 inhibition, which modulates the immune response at the level of the tumor bed. On this basis, clinical outcomes from CheckMate-214 showed improved survival with combination ICIs in untreated mRCC patient with intermediate- and poor-risk disease, developing a new standard of care in this setting [8]. Significant efforts have also been directed into strategies that enhance T-cell trafficking and/or infiltration into tumors, for example, with VEGF- or VEGFR-directed therapy, in addition to PD-1/PD-L1 inhibition [45]. To that end, the phase III IMmotion 151 study has displayed promising initial data on the combination of bevacizumab plus atezolizumab in terms of improved PFS for both the PD-L1–positive and the ITT population [33]. Furthermore, there will be readout from multiple phase III trials exploring ICI plus VEGFR inhibition (Table 2). The degree to which these highly anticipated results also inform the treatment landscape, given the promising data from earlier phase studies, will depend upon the measures of added efficacy and the extent of (potentially higher) toxicity, compared with VEGF-TKI monotherapy. Promising directions for future combination strategies may also include CD-122-receptor–directed therapies (NKTR-214), small-molecule agonists of toll-like receptors (NKTR-262), or pegylated IL-10 (pegilodecakin)—these are currently being explored in combination with PD-1 inhibition in early-phase studies (NCT02983045, NCT03435640, NCT02009449).

With the potential availability of numerous effective combinations in the future, biomarkers to guide therapeutic decisions will be critical. The utility of PD-L1 expression in mRCC continues to evolve with the shifting treatment landscape. Analysis of samples from the COMPARZ trial showed that higher tumor cell PD-L1 expression (via H-score) was associated with shorter OS in patients treated with sunitinib or pazopanib [46], and in CheckMate-025, PD-L1 was a poor prognostic marker irrespective of therapy [7]. Interestingly, when assessing outcomes by PD-L1 status in the CheckMate-214 and IMmotion 151 trials, only the PD-L1–positive group treated with sunitinib had reached median OS, with the respective ICI arms (and PD-L1–negative sunitinib arm) remaining not evaluable—again validating its role as a poor prognostic marker. However, its role as a predictive marker is less clear. The combination of nivolumab and ipilimumab was shown to improve survival regardless of the PD-L1 status for the intermediate/poor-risk groups, although the magnitude of OS benefit was greater for PD-L1–positive patients (HR 0.45) compared with PD-L1–negative patients (HR 0.73). Further, good-risk patients were more likely to be PD-L1 negative than their intermediate/poor-risk counterparts. While the sunitinib arm displayed better PFS and ORR in this subset, it is important to note that the CR rate was better with the ICI combination (11% vs 6%). The challenge of interpreting PD-L1 requires sage understanding of the nuances of different companion assays in different trials using different positivity cutoffs, notwithstanding other inherent issues with PD-L1 analysis: specimen “age” in temporal relation to treatment, cell localization, primary versus metastatic site, technical variability, and even discordance of assays among expert pathologists [47]. Ultimately, the quest for optimal methods to select patients for ICI-based treatments may involve refinement of tissue-based analysis [48], integrative genomics [49], angiogenesis and inflammatory gene expression signatures [44], blood-based biomarkers [50], and assessment of the microbiome [51] among others. Currently, PD-L1 is not ready for implementation into routine practice, and there is not a "one size fits all" biomarker in mRCC yet.

Given the evolving treatment options and ongoing trials, an important reflection is how best to measure or evaluate "efficacy" of emerging therapeutic strategies. With head-to-head comparisons of the different combinations unlikely to materialize, patients and clinicians will be left with cross trial comparisons to determine the optimal treatment regimen. Particularly in the context of subsequent therapies now available for control arms on clinical trials, one consideration is that the magnitude of difference in OS, if present in future results, may not be a reliable outcome. CheckMate-214 revealed an impressive improvement in survival in those with poor- or intermediate-risk disease, independent of the PD-L1 status. However, this trial was completed prior to the approval of nivolumab, and as such only 27% of patients assigned to the sunitinib arm received nivolumab in the second line [8]. In addition to prolonged survival, the pursuit of CR is a motivating goal and may justify the potential for increased toxicities with combination therapies. Rates of CR with prolonged duration of response may therefore become even more informative benchmarks. A recent meta-analysis suggests that for early-phase studies with ICIs, 6-mo PFS may be a more representative surrogate for OS (correlation coefficient 6-mo PFS with 12-mo OS $r = 0.74$) compared with historical associations such as ORR [52]. Therefore, as the standard of care in the front-line setting moves away from TKI monotherapy for most mRCC patients, these alternate endpoints may play an increasing role as we continually seek the optimal therapy for the right patient.

5. Conclusions

The treatment landscape for mccRCC has evolved since the introduction of oral VEGF inhibition in 2007. Several other TKIs continued to show activity with cabozantinib, the only TKI to offer a PFS advantage versus sunitinib in the front-line setting. Both cabozantinib and nivolumab offered a survival advantage of nearly 6 mo in the second-line setting following TKI therapy, while the combination of lenvatinib and everolimus has shown promise in a phase 2 trial. While TKI and ICI monotherapy continue to play a role, combination therapies are promising as a new standard of care in the untreated setting. Nivolumab plus ipilimumab is the first combination to show an improvement in survival compared with sunitinib in intermediate- and poor-risk patients, with several other combinations showing promising results in early data (Tables 1 and 2). Improved OS appears to be a new benchmark; however, it remains to be seen in ongoing trials given greater availability of ICIs in the second line. With intensification of front-line therapy with synergistic combinations, there is hope for durable CRs and potential cure.

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Study concept and design: All authors.
Acquisition of data: Lalani, McGregor.
Analysis and interpretation of data: Lalani, McGregor, Bex.
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Appendix A. Supplementary data

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