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Current and emerging therapies for first-line treatment of metastatic clear cell renal cell carcinoma

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ABSTRACT

There has been significant progress in the treatment of patients with advanced clear cell renal cell carcinoma (ccRCC), with improved knowledge of disease biology and the introduction of targeted agents and immunotherapies. In this review, we discuss current and emerging first-line treatment options, including recent approvals of the tyrosine kinase inhibitor (TKI) cabozantinib and the immunotherapy combination of nivolumab (anti-programmed cell death 1 [PD-1])/ipilimumab (anti-cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]), and initial outcomes with the combination of atezolizumab (anti-PD-ligand 1 [PD-L1])/bevacizumab (anti-vascular endothelial growth factor [VEGF]). Key clinical data are reviewed, as these novel first-line treatments offer significant improvement, particularly for patients classified as intermediate/poor risk for whom previously available therapies have demonstrated limited efficacy. Treatment recommendations based on clinical evidence and expert opinion are discussed. We also review ongoing studies investigating combinations of checkpoint inhibitors with TKIs, including cabozantinib and axitinib, and with other novel immunomodulatory agents, and the potential role of single-agent immunotherapy for select patients. With a growing treatment armamentarium, identification and validation of biomarkers will be crucial for optimizing first-line selection and treatment sequences.

Introduction

In the last update of GLOBOCAN worldwide cancer statistics, it was estimated that approximately 338,000 new cases of kidney cancer were diagnosed in 2012, with 143,000 patients succumbing to the disease [1]. Renal cell carcinoma (RCC) is the most common form of kidney cancer and accounts for 90% of all tumors, with clear cell RCC (ccRCC) being the most common histology (75%) [2,3]. The cure rate is high for patients with early, localized disease, with 5-year survival at more than 90% [4]. In contrast, 5-year survival drops to 12% for patients with distant metastatic disease. However, there has been significant progress in recent years with improved knowledge of disease biology.

ccRCC is a highly vascular tumor. The von Hippel Lindau (*VHL*) tumor suppressor gene is frequently inactivated, leading to overexpression of the hypoxia-inducible factor (HIF)-2α oncoprotein and its downstream targets, including vascular endothelial growth factor (VEGF) [5,6]. Antiangiogenic agents that target the VEGF pathway, including the tyrosine kinase inhibitors (TKIs) sunitinib and pazopanib, have been shown to improve disease control in randomized clinical trials, as have inhibitors of mechanistic target of rapamycin (mTOR); and survival data from observational studies further support their role [7–10].

Recently, the TKI cabozantinib was approved as a first-line therapy for patients with advanced ccRCC. Cabozantinib was initially approved for patients previously treated with antiangiogenic therapy based on the phase 3 METEOR study, which demonstrated a clinical benefit compared with everolimus for overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) [11,12]. Cabozantinib received an expanded indication by the US Food and Drug Administration for all patients with advanced ccRCC based on the randomized phase 2 CABOSUN study, which demonstrated prolonged PFS compared with sunitinib as initial therapy in patients with poor/intermediate-risk disease [13,14].

Immunotherapy with programmed cell death 1 (PD-1) pathway blockers has also been developed in ccRCC. The PD-1 checkpoint inhibitor nivolumab was approved for previously-treated patients with advanced ccRCC based on the phase 3 CheckMate 025 study, which demonstrated OS and ORR benefits compared with everolimus in

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patients who had prior antiangiogenic therapy [15]. However, there was no PFS advantage with nivolumab.

To improve its efficacy in solid tumors, including ccRCC, nivolumab has been partnered with other immunomodulatory agents [16,17]. In the recent phase 3 CheckMate 214 study, nivolumab was combined with ipilimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) checkpoint inhibitor, for treatment-naïve patients with advanced ccRCC. Nivolumab/ipilimumab showed a significant improvement in OS and ORR compared with sunitinib in the intention-to-treat (ITT) population, particularly for intermediate-/poor-risk patients, the population of primary clinical interest for this study [17]. Nivolumab/ipilimumab was approved by the US Food and Drug in April of 2018 as a first-line treatment for patients with intermediate or poor risk advanced RCC.

Recently, the programmed cell death-ligand 1 (PD-L1) inhibitor atezolizumab was combined with bevacizumab (anti-VEGF) and compared with sunitinib for first-line treatment of ccRCC in the phase 3 IMmotion 151 trial [18]. Studies indicate that VEGF promotes immunosuppressive cell proliferation and T-cell exhaustion and limits T-cell infiltration [19]. Initial results reported that atezolizumab/bevacizumab met one of its co-primary endpoints, with improved investigator-assessed PFS versus sunitinib in patients with advanced ccRCC and expression of PD-L1 on ≥1% of tumor-infiltrating immune cells by immunohistochemistry. Preliminary analysis indicated a trend of improved OS with updates planned.

In this review, we discuss emerging first-line treatment options in ccRCC, with a focus on cabozantinib, nivolumab/ipilimumab, and atezolizumab/bevacizumab. We review efficacy and safety data and provide treatment recommendations based on clinical evidence and expert opinion. In addition, we consider treatment sequencing and the need for biomarkers; and we look to the future as novel combinations with immunotherapy backbones come to the forefront of the treatmentparadigm.

Current treatment options for ccRCC

Prior to the introduction of targeted therapies, cytokines, including high-dose interleukin 2 (HDIL-2) and interferon (IFN)-α, were the standard of care for advanced ccRCC [20]. HDIL-2 has been shown to produce durable responses in a subset of patients [21]. However, there are currently no biomarkers to identify those most likely to respond, and HDIL-2 treatment is associated with significant toxicity. Its application is limited to younger patients with excellent performance status and normal organ function and requires treatment at specialized centers with experienced care delivery teams. Although cytokines still form part of the treatment armamentarium [20,22–24], their use has been greatly curtailed since the advent of TKIs and will likely be further diminished by checkpoint inhibitors.

The TKIs sunitinib and pazopanib are considered preferred therapies for first-line treatment based on improvements in PFS in their pivotal studies, which compared sunitinib with IFN-α and pazopanib with placebo [7,9]. A subsequent phase 3 trial, the COMPARZ study, compared pazopanib with sunitinib and demonstrated non-inferiority for PFS, with similar OS (Table 1) [25,26]. Differences were reported for safety and tolerability, with higher rates of weight loss, alopecia, and liver function abnormalities in the pazopanib arm, and higher rates of hand-foot syndrome, fatigue, and hematologic events with sunitinib (Table 2). In an analysis of OS by risk status, there was no difference between treatment arms; but OS was notably longer for favorable-risk patients (42.5 months for pazopanib and 43.6 months for sunitinib) than for intermediate-risk (26.9 and 26.1 months) or poor-risk patients (9.9 and 7.7 months).

Risk stratification is an important component of clinical trial design in ccRCC, and risk status often guides treatment selection in the first-line setting [22,23]. The two most common risk models for ccRCC were developed by the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [27,28]. These models overlap, but IMDC has been adopted more widely since the introduction of targeted therapies as it has been validated in relevant patient populations. Factors in both models include time from diagnosis to treatment, Karnofsky performance status, and hemoglobin and calcium concentrations. MSKCC also uses lactate dehydrogenase levels, whereas the IMDC uses neutrophil and platelet counts. In both models, favorable-risk patients have 0 risk factors, intermediate-risk patients have 1–2, and poor-risk patients have ≥3 [27]. Other factors have been shown to contribute to prognosis, including tumor grade, prior nephrectomy, and number and sites of metastases [29,30].

Additional first-line treatments are available, but their use is limited. These include sorafenib, bevacizumab/IFN-α, and temsirolimus [22,23]. Temsirolimus has been recommended for poor-risk patients [8]. However, in a recent randomized phase 2 trial (TemPa), first-line pazopanib was favored over temsirolimus with respect to PFS and ORR in patients with advanced ccRCC and poor-risk factors, although both agents yielded disappointing results [31].

New first-line treatment options for advanced RCC

With the addition of cabozantinib and nivolumab/ipilimumab to the first-line treatment setting, and recent outcomes with atezolizumab/bevacizumab, it is important to consider these treatments in the context of established therapies for RCC. The pivotal trials for each of these therapies used sunitinib as the control arm, but we emphasize the limitations of cross-trial comparisons because of confounding variables, such as selection criteria and treatment settings.

Cabozantinib

Cabozantinib is an oral inhibitor of multiple tyrosine kinases, including VEGF receptor (VEGFR), MET, and AXL. MET and AXL are upregulated along with VEGF following inactivation of VHL, and their expression is associated with aggressive disease and poor survival in RCC [32,33]. Targeting MET and AXL may also overcome resistance to VEGFR inhibition [34].

The randomized, phase 2 CABOSUN trial compared cabozantinib with sunitinib in treatment-naïve patients with intermediate-/poor-risk disease by IMDC [13,14,35]. The study was conducted within the Alliance Cooperative Group and enrolled a study population with a high incidence of poor prognostic features relative to other pivotal first-line trials in ccRCC, including compromised performance status, lack of prior nephrectomy, high tumor burden, and bone metastases. CABOSUN met its primary endpoint—investigator-assessed PFS was significantly improved for cabozantinib compared with sunitinib (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.46–0.95; P = 0.012) [13]. The PFS benefit was confirmed in a post hoc analysis by independent radiology committee (IRC) with extended follow-up (HR 0.48; 95% CI 0.31–0.74); and the ORR for cabozantinib was more than twice that of sunitinib (20% vs 9%; Fig. 1) [14]. In additional analyses of PFS, cabozantinib was favored over sunitinib across subgroups of clinical interest, including IMDC risk, tumor burden, metastatic site, and MET expression status [35]. The PFS benefit of cabozantinib versus sunitinib was similar for patients with (HR 0.51; 95% CI 0.26–0.99) and without bone metastases (HR 0.50; 95% CI 0.29–0.85). Analysis by tumor MET expression suggested greater benefit with cabozantinib in MET+ patients (HR 0.32; 95% CI 0.16–0.63) relative to MET− patients (HR 0.67; 95% CI 0.37–1.23) (Fig. 2). There was a trend favoring cabozantinib over sunitinib for OS (HR = 0.80; 95% CI 0.53–1.21), but this was not statistically significant; and the study was underpowered for definitive OS outcomes [14].

The safety profile of cabozantinib during CABOSUN was consistent with that of second-line cabozantinib from the METEOR trial

Table 1
Study design and survival outcomes from key studies.

Study design/treatment	Treatment arms	PFS (by IRC unless otherwise indicated)		OS	
		Median, mo	HR (95% CI)	Median, mo	HR (95% CI)
COMPARZ [25,26]					
• R, open-label ph 3; treatment-naïve pts (N = 1110)	Pazo (N = 557)	8.4	1.05	28.3	0.92
• Primary endpoint: PFS	Sun (N = 553)	9.5	(0.90–1.22)	29.1	(0.79–1.06)
• Pazo (800 mg qd) vs Sun (50 mg qd[a])					(P = 0.24)
CABOSUN [13,14]					
• R, open-label ph 2; int/poor-risk (IMDC), treatment-naïve pts (N = 157)		*Inv*			
• Primary endpoint: PFS (inv)	Cabo (N = 79)	8.2	0.66	26.6	0.80
• Cabo (60 mg qd) vs Sun (50 mg qd[a])	Sun (N = 78)	5.6	(0.46–0.95)	21.2	(0.53–1.21)
			P = 0.012		
		IRC[b]			
	Cabo (N = 79)	8.6	0.48		
	Sun (N = 78)	5.3	(0.31–0.74)		
			(P = 0.0008)		
CheckMate 214 [17]					
• R, ph 3; treatment-naïve patients stratified by IMDC risk (N = 1096)	*Int/Poor Risk*				
• Co-primary endpoints: PFS, ORR, OS in int/poor risk	Nivo/Ipi (N = 425)	11.6	0.82	NR	0.63
• Nivo/Ipi (3 mg/kg Nivo + 1 mg/kg Ipi q3w for 4 doses, then 3 mg/kg Nivo q2w) vs Sun (50 mg qd[a])	Sun (N = 422)	8.4	(0.64–1.05)[c]	26.0	(0.44–0.89)[d]
			(P = 0.03, NS)[e]		(P < 0.001)
	Favorable Risk				
	Nivo/Ipi (N = 125)	15.3	2.18	NA[f]	
	Sun (N = 124)	25.1	(1.29–3.68)[c]		
			(P < 0.001)		
	ITT				
	Nivo/Ipi (N = 550)	12.4	0.98	NR	0.68
	Sun (N = 546)	12.3	(0.79–1.23)[c]	32.9	(0.49–0.95)[d]
			(P = 0.85)		(P < 0.001)
IMmotion 151 [18]					
• R, ph 3; treatment-naïve patients (N = 915)	*PD-L1* +	*Inv*			
• Co-primary endpoints: PFS (by inv), OS	Atezo/Bev	11.2	0.74	NR[f]	0.68
• Atezo/bev (1200 mg Atezo IV q3w + 15 mg/kg Bev IV q3w) vs Sun (50 mg qd[a])	(N = 178)		(0.57–0.96)		(0.46–1.00)
	Sun (N = 184)	7.7	*P* = 0.02	23.3[f]	
	PD-L1 +	*IRC*			
	Atezo/Bev	8.9	0.93	NA[f]	
	(N = 178)		(0.72–1.21)		
	Sun (N = 184)	7.2			
	ITT	*Inv*			
	Atezo/Bev	11.2	0.83	NR[f]	0.81
	(N = 454)		(0.70–0.97)		(0.63–1.03)
	Sun (N = 461)	8.4		NR[f]	*P* = 0.09

Atezo, atezolizumab; Bev, bevacizumab; Cabo, cabozantinib; CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; int, intermediate; inv, investigator; Ipi, ipilimumab; IRC, independent review committee; ITT, intention to treat; mo, month(s); NA, not available; Nivo, nivolumab; NR, not reached; NS, non-significance; ORR, objective response rate; OS, overall survival; Pazo, pazopanib; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; ph, phase; q3w, every 3 weeks; qd, once daily; r, randomized; Sun, sunitinib; wk, week.

[a] 4 wk on/2 wk off.
[b] Follow-up for IRC was longer than for Inv.
[c] 99.1% confidence interval.
[d] 99.8% confidence interval.
[e] Between-group difference did not meet the prespecified threshold (P = 0.009) for statistical significance.
[f] Final OS analyses are pending.

[11–14]. The most common grade 3/4 adverse events (AEs; all causality) in the cabozantinib and sunitinib arms of CABOSUN were hypertension (28% vs 21%) and diarrhea (10% vs 11%). Differences (cabozantinib versus sunitinib) were noted for grade 3/4 palmar-plantar erythrodysesthesia (8% vs 4%), fatigue (6% vs 17%), and thrombocytopenia (1% vs 11%). Dose reductions were common for both cabozantinib and sunitinib (46% vs 35%), while discontinuations due to AEs (21% vs 22%) and treatment-related deaths (2 vs 4 patients) were less frequent [14].

Nivolumab/ipilimumab

Checkpoint inhibitors specifically target immune checkpoint receptors or ligands, disrupting mechanisms used by tumor cells to evade immune attack and restoring the ability of cytotoxic T cells to mount an antitumor response [36–41]. Targets include the PD-1 receptor and its ligands PD-L1/L2 and the CTLA-4 receptor and its ligands CD80/86. Upregulation of PD-L1/L2 occurs in many tumors and can contribute to inhibition of active T-cell surveillance [37,38]. Binding of PD-L1/L2 ligands to the PD-1 receptor found on T cells inhibits T-cell proliferation

Table 2
Safety data from key studies.

	COMPARZ [26]		CABOSUN [14]		CheckMate214 [17]	
	Pazo (N = 554)	Sun (N = 548)	Cabo (N = 78)	Sun (N = 72)	Nivo/Ipi (N = 547)	Sun (N = 535)
Dose reductions, %	44	51	46	35	NA	53
Discontinuation due to AEs, %	24	20	21	22	22[a]	12[a]
Treatment-related deaths, n	3	8	2	4	8	4
Immune-mediated AE, %	–	–	–	–	80[a]	–
Grade 3/4 AEs, %	Treatment emergent		Treatment emergent		Treatment related	
Hypertension	15	15	28	21	< 1	16
Fatigue	11	17	6	17	4	9
Diarrhea	9	8	10	11	4	5
PPE	6	12	8	4	0	9
Mucosal inflammation	1	3	–	–	0	3
Nausea	2	2	3	4	1	1
Vomiting	2	3	1	3	< 1	2
Stomatitis	1	1	5	6	0	3
Weight loss	1	< 1	4	0	–	–
Rash	1	1	–	–	1	0
Hypothyroidism	0	< 1	0	0	< 1	< 1
Pruritus	–	–	–	–	< 1	0
Grade 3/4 laboratory abnormalities, %						
Lymphopenia	5	14	–	–	–	–
Neutropenia[b]	5	20	0	4	–	–
Thrombocytopenia[b]	4	22	1	11	0	5
Leukopenia[b]	1	6	0	3	–	–
Anemia	2	7	1	3	< 1	4
Increased ALT	18	4	5	0	–	–
Increased AST	13	3	3	3	–	–
Hypophosphatemia	4	9	–	–	–	–

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cabo, cabozantinib; Ipi, ipilimumab; NA, not allowed; Nivo, nivolumab; Pazo, pazopanib; PPE, palmar-plantar erythrodysesthesia; Sun, sunitinib; –, not reported.
[a] Treatment-related AEs.
[b] Or decrease in counts.

and type 1 helper T-cell (Th1) cytokine production. Binding of CTLA-4 to CD80/86 results in an immune inhibitory signal; blocking this interaction has been shown to augment T-cell activation and proliferation of T-cell subsets, including tumor-infiltrating T-effector cells [39–41].

Although nivolumab demonstrated superiority over everolimus as second-line therapy for patients with ccRCC in CheckMate 025, the relatively high rate of progressive disease as best response (35% for nivolumab) supported the rationale for combining nivolumab with other immunomodulatory agents [15]. The combination of nivolumab/ipilimumab has been shown to be more efficacious than either agent alone for patients with melanoma [42]. Development of the combination in RCC was supported by preclinical and clinical studies

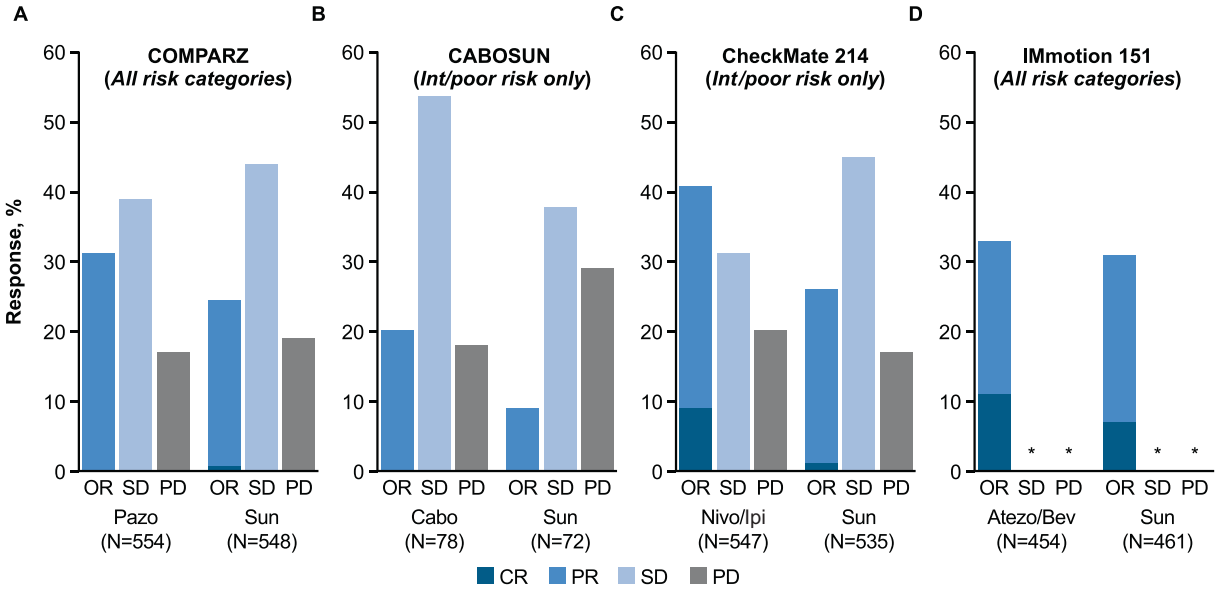

Fig. 1. Response results (assessed by IRC) from key studies [14,17,18,26]. *SD and PD data by IRC not available. Atezo, atezolizumab; Bev, bevacizumab; Cabo, cabozantinib; CR, complete response; Ipi, ipilimumab; IRC, independent review committee; Nivo, nivolumab; OR, objective response; Paz, pazopanib; PD, progressive disease; PR, partial response; SD, stable disease; Sun, sunitinib.

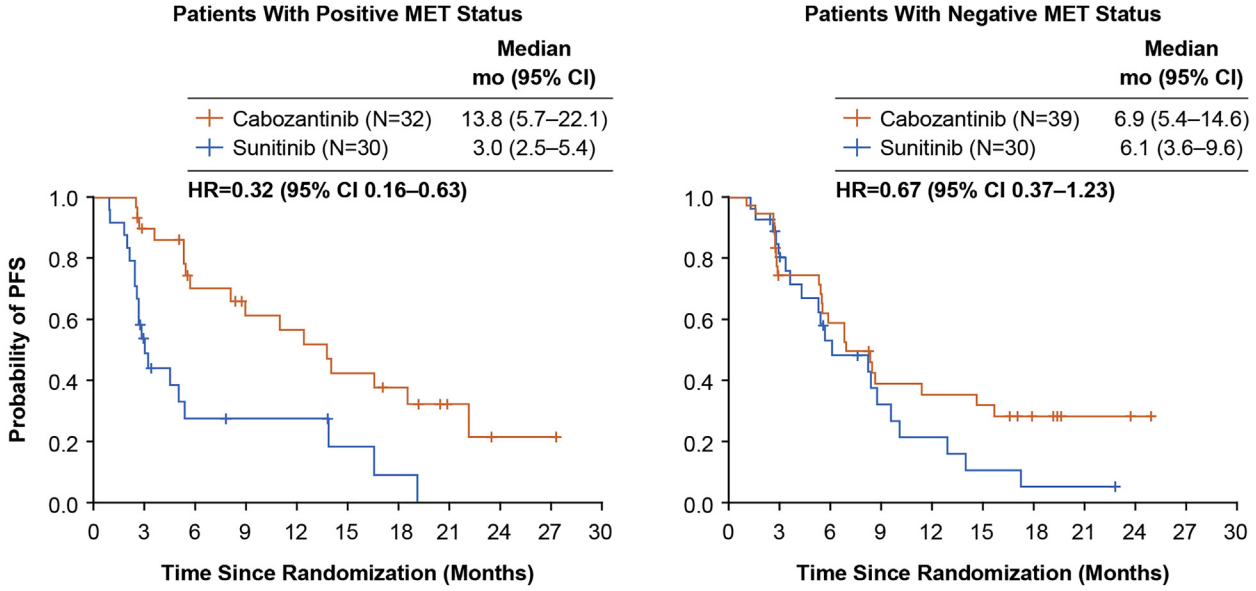

Fig. 2. Progression-free survival by MET expression in the CABOSUN study. Reproduced with permission from George et al. [35]. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

[16,43,44]. In a phase 2 study, single-agent ipilimumab demonstrated modest activity (ORR 12.5%) in patients with advanced ccRCC [43], while in the phase 1 CheckMate 016 study, nivolumab/ipilimumab produced an ORR of 40% in both treatment-naïve and previously treated patients with advanced ccRCC, with progressive disease as best response in 17% [16].

Nivolumab/ipilimumab was formally assessed in the phase 3 CheckMate 214 study, in which previously untreated patients with advanced ccRCC were randomized to the combination or sunitinib. The co-primary endpoints were OS, PFS, and ORR in the intermediate-/poor-risk disease subset. In the intermediate-/poor-risk population, the combination demonstrated improved OS compared with sunitinib (HR 0.63, 99.8% CI 0.44–0.89; $P < 0.001$). PFS was also improved, although this did not reach the pre-specified level of significance. IRC-assessed ORR was higher with the combination (42% vs 27%, $P < 0.001$), with 9% of patients achieving a complete response versus 1% with sunitinib [17]. Conversely, sunitinib was better than nivolumab/ipilimumab in the favorable-risk population for PFS (HR 2.18, 99.1% CI 1.29–3.68; $P < 0.001$) and ORR (29% vs 52%, $P < 0.001$), with OS data pending. Despite the outcomes in the favorable-risk subgroup, the overall effect size supported an OS benefit with nivolumab/ipilimumab in the ITT population (HR 0.68, 99.8% CI 0.49–0.95; $P = 0.0003$).

Subgroup analysis of intermediate-/poor-risk patients confirmed OS and ORR benefits with nivolumab/ipilimumab regardless of PD-L1 tumor expression, although patients with PD-L1 ≥ 1% responded best [17]. HR for OS with the combination compared with sunitinib was 0.45 (95% CI 0.29–0.71) for patients with PD-L1 ≥ 1% and 0.73 (95% CI 0.56–0.96) for PD-L1 < 1% (Fig. 3). Further, patients with PD-L1 ≥ 1% had improved PFS with the combination relative to sunitinib (HR 0.46, 95% CI 0.31–0.67), whereas patients with PD-L1 < 1% did not (HR 1.00, 95% CI 0.80–1.26). For intermediate-/poor-risk patients in the nivolumab arm, the CR rate was 16% for PD-L1 ≥ 1% and 7% for PD-L1 < 1%. The benefit of nivolumab/ipilimumab was generally consistent in other subgroups of interest, although subgroup analysis of OS by age indicated that younger patients (< 65 years) derived greater benefit with the combination than older patients.

The most frequent treatment-related AEs of grade ≥3 for nivolumab/ipilimumab were fatigue (4%) and diarrhea (4%) [17]. Treatment-related immune-mediated AEs were common at a rate of 80% (436/547) in the nivolumab/ipilimumab arm, with 35% of patients requiring high-dose glucocorticoids to manage these events [17], and 2% requiring secondary immunosuppression with infliximab and 1% requiring mycophenolic acid [45]. Grade 3/4 immune-mediated AEs related to nivolumab/ipilimumab treatment included events of the skin (4%), endocrine (8%), gastrointestinal (5%), pulmonary (1%), hepatic (9%), and renal systems [45]. Discontinuation due to toxicity with nivolumab/ipilimumab was 22%, and there were 8 treatment-related deaths. For perspective, discontinuation of nivolumab monotherapy due to toxicity was 8% in CheckMate 025, and there were no treatment-related deaths [15]. Despite the toxicities associated with nivolumab/ipilimumab, self-reported quality of life for intermediate-/poor-risk patients was shown to be better with the combination than with sunitinib [17].

When considering safety data across these studies, it is important to recognize differences in AE reporting—COMPARZ and CABOSUN reported all-causality AEs while CheckMate 214 reported treatment-related AEs. All-causality rates of AEs during CheckMate 214 are available in the nivolumab product label [46]. The rate of treatment-related grade 3/4 AEs was 46% [17], whereas the rate for all-causality grade 3/4 AEs was 65% [46]. Notably, the discontinuation rate from AEs (all causality) was 31% for nivolumab/ipilimumab and 21% for sunitinib [46], a rate similar to those reported in the sunitinib arms of COMPARZ (20%) [26] and CABOSUN (21%) [14].

Bevacizumab + atezolizumab

Following a phase 1 study that demonstrated the feasibility of atezolizumab/bevacizumab [47], a phase 2 trial randomized treatment-naïve patients with advanced RCC to atezolizumab/bevacizumab, atezolizumab, or sunitinib [48]. Atezolizumab/bevacizumab was favored over sunitinib for PFS in patients with PD-L1+ disease (≥1% expression on tumor infiltrating immune cells) but not in the ITT population, while there was no PFS or response benefit with atezolizumab monotherapy in either population. Based on these findings, the phase 3 IMmotion 151 study compared atezolizumab/bevacizumab with sunitinib [18]. Patients were stratified by PD-L1 status, MSKCC risk score, and presence of liver metastases. Co-primary endpoints were investigator-assessed PFS in PD-L1+ patients, and OS in the ITT population. The study met its first primary endpoint; the combination was favored over sunitinib for PFS in PD-L1+ patients (HR 0.74; 95% CI 0.57–0.96; $P = 0.02$). The PFS benefit was maintained in the ITT

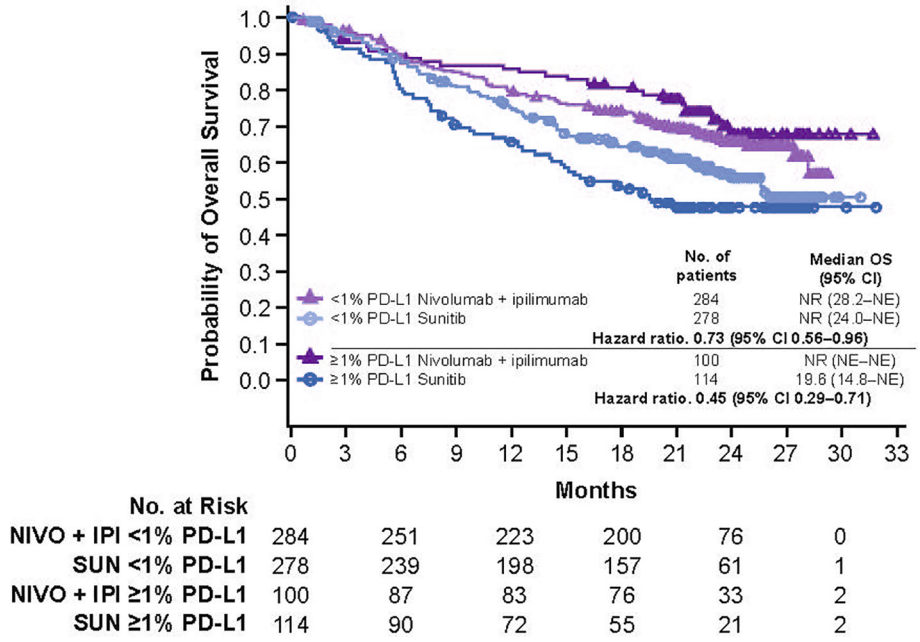

Fig. 3. Overall survival by PD-L1 expression in intermediate/poor patients (IMDC) in CheckMate 214. Reproduced with permission from Motzer et al. [17]. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NE, not estimable; NR, not reached; NIVO, nivolumab; PD-L1, programmed cell death-ligand 1; SUN, sunitinib.

population (HR 0.83; 95% CI 0.70–0.97) and across subgroups of clinical interest in the PD-L1 + population, including patients with liver metastases, sarcomatoid subtype, or favorable-risk disease. However, IRC-assessed PFS in PD-L1 + patients did not show a statistical difference between treatment arms (HR 0.93, 95% CI 0.72–1.21). Because of the discordance in PFS by investigator versus IRC, the regulatory pathway for atezolizumab/bevacizumab is uncertain without definitive OS data. Follow-up continues as only 29% of the prespecified number of deaths had occurred at data cutoff, but preliminary analyses showed trends favoring atezolizumab/bevacizumab in PD-L1 + and ITT populations.

Atezolizumab/bevacizumab was well tolerated. Patients receiving the combination had fewer treatment-related AEs relative to those receiving sunitinib (40% vs 54% for grade 3/4), particularly gastrointestinal-related events [18]. Potential immune-related AEs (any grade) included rash (19% with the combination vs 15% with sunitinib), hypothyroidism (22% v 26%), hyperthyroidism (7% vs 3%), adrenal insufficiency (2% vs 0%), colitis (2% vs < 1%), and pneumonitis (3% vs 0%). Grade 3/4 immune-related AEs were infrequent with the combination. Corticosteroids to manage AEs were required by 16% of patients receiving atezolizumab/bevacizumab. Eventually, 5% of patients discontinued atezolizumab/bevacizumab (12% discontinued at least one treatment component) because of toxicity compared with 8% for sunitinib; there were 5 treatment-related deaths with the combination and 1 with sunitinib.

Treatment selection

In the absence of predictive biomarkers, treatment selection continues to be based on available clinical evidence and expert opinion. MSKCC/IMDC risk factors are primary selection criteria [22–24,49]. Comorbidities and other disease characteristics are worth consideration, as well as accessibility, costs, and reimbursement [29,30,50]. Despite the plethora of treatment options there are important knowledge gaps and unmet needs; therefore, we strongly encourage clinicians to consider all patients for clinical trials.

Favorable-risk patients

Active surveillance is considered a viable option for patients with slowly progressing, asymptomatic, low volume disease, although selection criteria have not been validated [22,23,51,52]. For favorable-risk patients who require treatment, sunitinib and pazopanib are preferred therapies [22–24,53]. While the COMPARZ study demonstrated similar efficacy between these agents, a subsequent phase IIIb crossover study with patient preference as the primary endpoint found that both patients and physicians preferred pazopanib over sunitinib, mainly because pazopanib was associated with less fatigue and better overall quality of life [54]. Cabozantinib is an option based on the US label, but definitive data are needed in favorable-risk patients to further support its use. TKIs should not be administered to patients with severe hepatic impairment [55–57]. Studies have demonstrated the feasibility of administering TKIs to patients receiving dialysis [58], but caution is warranted given the risk of hemorrhage with antiangiogenics [55–57]. TKIs should be avoided prior to and following major surgery (from days to weeks) and in patients with uncontrolled hypertension, active bleeding or symptomatic cardiovascular disease [59,60].

Although nivolumab/ipilimumab cannot be recommended for favorable-risk patients based on PFS and ORR from CheckMate 214 [17], this will be reassessed once OS for this subgroup becomes available. We would consider nivolumab/ipilimumab for patients who cannot receive a TKI, particularly those who are younger (< 65 years), or with tumors having high PD-L1 expression or Fuhrman grade [17,61]. PFS and ORR data from IMmotion 151 suggest a role for atezolizumab/bevacizumab in favorable-risk patients, but OS data are needed given the discrepancy in PFS by investigator versus IRC [18].

Intermediate-/poor-risk patients

Nivolumab/ipilimumab should be considered preferred therapy for patients with intermediate-/poor-risk disease [22–24], as the combination offers durable responses and the potential for complete response, which can extend OS [17]. Further, checkpoint inhibitors may offer the possibility for continued response (complete or major partial response) after stopping treatment, but more data are needed before this can be

Table 3
Studies investigating checkpoint inhibitor combinations with TKIs and novel agents in advanced RCC.

Study details	Key results/completion status
TKI/anti-PD-1 checkpoint inhibitor	
• Cabozantinib/nivolumab (n = 49), cabozantinib/nivolumab/ipilimumab (n = 29) • GU tumors (N = 78), including RCC (n = 14) • 1L+, Phase 1 (NCT02496208)[94]	• ORR all evaluable pts (n = 64): 36% (3 CR, 20 PR) • RCC cohort (13 response evaluable): ORR 54% (7 PR, 6 SD); median PFS 18.4 mo (95% CI, 6.4–18.4) • Grade 3/4 AEs: 57% for cabo/nivo, 72% for cabo/nivo/ipi
• Cabozantinib/nivolumab vs sunitinib, RCC • 1L, Phase 3 (CheckMate 9ER/NCT03141177)	• Estimated primary completion date: September 2019
• Cabozantinib/pembrolizumab, RCC • 2L, Phase 1/2 (NCT03149822)	• Estimated primary completion date: June 2020
• Axitinib/pembrolizumab,RCC (N = 52) • 1L, Phase 1 (NCT02133742) [92]	• ORR: 73% (4 CR, 34 PR, 8 SD) • 12% discontinued due to treatment-related AEs
• Axitinib/pembrolizumab vs sunitinib, RCC • 1L, Phase 3 (KEYNOTE-426/NCT02853331)	• Estimated primary completion date: January 2020
• Lenvatinib/pembrolizumab, solid tumors (N = 191), including RCC • Phase 1/2 (NCT02501096) [95]	• ORR RCC cohort: 63.3% (83% in 12 treatment-naïve pts) • No new safety signals
• Lenvatinib/pembrolizumab, solid tumors including RCC • Phase 1 (NCT03006887)	• Estimated study completion date: June 2018
• Lenvatinib/pembrolizumab or lenvatinib/everolimus vs sunitinib, RCC • 1L, Phase 3 (NCT02811861)	• Estimated primary completion date: October 2019
• Tivozanib/nivolumab,RCC (N = 18) • Phase 1/2 (NCT03136627) [102]	• 5/11 evaluable pts (38%) had grade 3–4 AEs • Efficacy data pending
TKI/anti-PD-L1 checkpoint inhibitor	
• Cabozantinib/atezolizumab, solid tumors including UC/RCC • Phase 1/2 (NCT03170960)	• Estimated primary completion date: January 2020
• Cabozantinib/avelumab, RCC • Phase 1 (NCT03200587)	• Estimated primary completion date: September 2022
• Axitinib/avelumab, RCC (N = 55) • 1L, Phase 1 (JAVELIN Renal 100/NCT02493751) [93]	• ORR: 58% (3 CR and 29 PR) • Safety profile consistent with monotherapy, but with higher rates of dose reductions for axitinib
• Axitinib/avelumab vs sunitinib, RCC • 1L, Phase 3 (JAVELIN Renal 101/NCT02684006)	• Estimated primary completion date: December 2018
IL/anti-PD-1 checkpoint inhibitor	
• NKTR-214/nivolumab, solid tumors including RCC • IO-tx naïve and relapsed/refractory • Phase 1/2 (PIVOT-02/NCT02983045) [96]	• 5 initial patients: no grade 3–5 AEs, no discontinuations • Preliminary data suggest clinical activity
• Pegilodecakin (n = 19), pegilodecakin/nivolumab (n = 29) or pegilodecakin/pembrolizumab (n = 8), RCC • 2L+, anti-PD-1 naïve, Phase 1 (NCT02009449) [97]	• ORR (68 response evaluable): 25% (4 PR) pegilodecakin, 39% (10 PR) pegilodecakin/nivolumab, 50%(2 CR, 2 PR) pegilodecakin/pembrolizumab • Identified RP2D with acceptable toxicity profile
A2AR inhibitor/anti-PD-1 checkpoint inhibitor	
• CPI-444/pembrolizumab, CPI-444, solid tumors (N = 48) including RCC (n = 5) • Phase 1 (NCT02655822) [98]	• Similar disease control rate for monotherapy vs combination • 5 RCC patients: 1 PR and 3 SD • Enrollment ongoing for disease-specific cohorts
IDO inhibitor/anti-PD-1 checkpoint inhibitor	
• Epacodostat/pembrolizumab, solid tumors including RCC • Phase 1/2 (ECHO-202/KEYNOTE-037/NCT02178722) [99]	• ORR in 19 RCC pts with 0–1 prior tx: 47% (1 CR, 8 PR) • ORR in 11 RCC pts with ≥2 prior tx: 0% • Manageable toxicity; 2/30 patients discontinued due to TRAEs

1L, first-line; A2AR, adenosine A2a receptor; AE, adverse event; ave, avelumab; axi, axitinib; cabo, cabozantinib; CI, confidence interval; CR, complete response; epac, epacadostat; evero, everolimus; GU, genitourinary; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; IO, immune-oncology; ipi, ipilimumab; lenv, lenvatinib; nivo, nivolumab; ORR, objective response rate; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose; SD, stable disease; tivo; tivozanib; TKI, tyrosine kinase inhibitor; TRAE, treatment-related AE; tx, therapy; UC, urothelial carcinoma.

implemented in clinical practice [62,63]. However, immunotherapy is contraindicated in patients with autoimmune disease, neuromuscular disorders, and patients receiving immunosuppressive treatment [64–66]. More data are needed for the use of nivolumab/ipilimumab in elderly patients. The clinical benefit of the combination appeared less robust with increasing age, particularly for patients ≥75 years of age, during CheckMate 214 [17], and a similar trend was observed with single-agent nivolumab as a second-line therapy during CheckMate 025 [15]. These observations may be artifacts due the small size of the elderly subgroups in these studies, but immunosenescence could also play

a role as could tumor biology.

For patients who are contraindicated or who cannot tolerate nivolumab/ipilimumab, cabozantinib should be the preferred treatment [22–24]. We also recommend cabozantinib for patients with bone metastases given its activity in this subgroup, particularly patients with compromised performance status in whom disease control with cabozantinib could improve or help to maintain quality of life [35,67,68].

Although temsirolimus has been recommended for poor-risk disease, it should be used only if immunotherapy and TKIs are contraindicated. Pazopanib recently outperformed temsirolimus in intermediate-/poor-risk patients in the TemPa study [31]. Neither treatment was particularly efficacious—median PFS was 5.2 months for pazopanib versus 2.6 months for temsirolimus (HR 0.70; 95% CI 0.43–1.14; P = 0.16). Outcomes with pazopanib and sunitinib have been variable in patients with intermediate-/poor-risk disease [14,17,25,31]. PFS with sunitinib has ranged from 5.3 months in CABOSUN [14] to 8.4 months in CheckMate 214 [17]. These data underscore the limitations of cross trial comparisons. Notably, median PFS in the sunitinib arm of CheckMate 214 dropped to 5.9 months for patients with PD-L1 ≥ 1%, highlighting the need for biomarkers to direct treatment [17].

Predictive biomarkers

There are currently no predictive biomarkers validated in ccRCC. Although PD-L1 is overexpressed in approximately 25% of ccRCC tumors, and overexpression is associated with poor outcomes [69,70], its role as predictive biomarker is not yet clear as illustrated in a meta-analysis by Iacovelli and colleagues [70]. With nivolumab/ipilimumab, there was a trend of better outcomes for patients with PD-L1 expression ≥1% on tumor specimens in CheckMate 214 [17], but this trend was not evident with second-line nivolumab in CheckMate 025 [15]. With atezolizumab/bevacizumab, IRC analyses from IMmotion 151 showed no evidence that PD-L1 expression ≥1% on tumor-infiltrating immune cells predicted response [18]. The predictive value of PD-L1 expression appears to improve when used with immune-related RECIST rather than RECIST 1.1 and when used in conjunction with other biomarkers, such as expression of PD-1 on CD8+ tumor-infiltrating lymphocytes [71].

Studies have investigated circulating cytokines and angiogenic factors as potential biomarkers for TKIs [72]. Increased MET expression is common in ccRCC tumors and is a negative prognostic marker [32]. Results from CABOSUN suggest that MET tumor expression may help to predict response to cabozantinib [35], but this association was less evident in the METEOR study [12]. VHL mutational status has also been assessed as a predictive biomarker for VEGF-targeted therapy, but results have been inconsistent [72].

Other potential biomarkers for immunotherapy include factors associated with the tumor microenvironment, such as PD-L2 expression, IDO-1 expression, and infiltration of CD8+ T cells [72,75]. There is also evidence that the gut microbiome influences response, which may be modulated by antibiotics [76]. Tumor mutational burden has been indicated as a predictive biomarker for checkpoint inhibitors in some solid tumors, but the association has been less definitive in RCC [77,78]. Distinct genetic features may be more predictive [77–79]. Loss-of-function mutations in the PBRM1 gene, which is involved in chromatin remodeling and may regulate transcription of JAK/STAT, hypoxia, and immune signaling pathways, was recently associated with improved response to checkpoint inhibitors [79]. Germline genetics may also play a role in response to checkpoint inhibitors. In a large cohort of patients with solid tumors, heterozygosity of HLA-1 genes predicted response to checkpoint inhibitors [80].

Although the use of mTOR inhibitors as first-line therapy will further decline, data from retrospective studies do suggest a rationale for their use in select patients with activating mutations within the mTOR pathway [73,74]. It remains to be established whether these rare patients should receive mTOR inhibitors as first line therapy or only after treatment with checkpoint inhibitors and/or TKI-based therapy.

Treatment sequencing

There is no consensus on optimal treatment sequencing in ccRCC. Cabozantinib has been shown to be effective after treatment with immunotherapy or TKIs and is a preferred second-line therapy [11,12,22–24,81–83]. Nivolumab is also a preferred second-line therapy and has been shown to be effective after prior sunitinib, pazopanib, or IL-2 [22–24,83,84]. Axitinib is also an option and has been shown to be effective after cytokines, but its benefit appears less robust after TKI treatment [22,23,82,83,85]. More data are needed to understand the impact of treatment sequencing—switching from a TKI to immunotherapy and vice versa, and sequencing rather than combining immunotherapies. Although sunitinib was recently approved as an adjuvant therapy post-nephrectomy for high-risk patients, adjuvant use will likely be limited given its toxicity and lack of OS benefit [55]. The treatment paradigm will continue to evolve as biomarkers are developed and results from a number of ongoing pivotal studies in RCC become available.

Future directions

Concerns over incremental toxicity with checkpoint inhibitor combinations have prompted investigations of other potential partners, including TKIs, where there is a biological and clinical rationale (Table 3) [86]. Inhibition of the VEGF pathway has been shown to increase T-cell production and infiltration into the tumor microenvironment and to decrease the activity of T-regulatory cells and myeloid-derived suppressor cells [87–89]. Inhibition of the VEGF pathway and other targets of TKIs could attenuate tumor immunosuppression, increasing responsiveness to immunotherapy [90].

Immunotherapy-TKI combinations

Although early studies of immunotherapy in combination with sunitinib or pazopanib were disappointing because of intolerable toxicity [91], combinations with other TKIs have proven feasible and active.A phase 1 study demonstrated the safety and tolerability of first-line axitinib/pembrolizumab in patients with advanced RCC, with an ORR of 73% (8% CR) and a median PFS of 20.9 months [92]. These results supported a phase 3 study to assess the combination versus sunitinib in treatment-naïve patients (NCT02853331). In a separate phase 1 study of RCC patients, first-line axitinib/avelumab had an ORR of 58% in patients with ccRCC [93].

Cabozantinib/nivolumab with or without ipilimumab demonstrated acceptable tolerability in a phase 1 study of heavily pretreated patients with genitourinary tumors, with an ORR of 54% for the RCC cohort [94]. A phase 3 study of cabozantinib/nivolumab versus sunitinib in patients with ccRCC is underway (NCT03141177); and cabozantinib is also being combined with atezolizumab (NCT03170960), pembrolizumab (NCT03149822), and avelumab (NCT03200587) in phase 1/2 studies.

Studies are also investigating combinations with lenvatinib. Interim analysis of a phase 1/2 study in treatment-naïve and pretreated patients with ccRCC reported an overall ORR of 63% at Week 24 with lenvatinib/pembrolizumab (83% in 12 treatment-naïve patients) [95]. A phase III trial of lenvatinib/pembrolizumab, lenvatinib/everolimus, and sunitinib has been initiated (NCT02811861).

Novel immunotherapy combinations

Ongoing trials are also combining checkpoint inhibitors with novel/investigational immunotherapies. These include: NKTR 214 (pegylated IL-2), an agonist of CD-122 that stimulates CD-8+ and NK cells [96]; pegilodecakin, a pegylated human IL-10, as IL-10 receptors are expressed on activated CD8+ cells [97]; CPI-444, an oral adenosine A2a receptor antagonist [98]; and epacadostat, an inhibitor of indoleamine

2,3-dioxygenase 1, a tryptophan-catabolizing enzyme that induces immune tolerance by T-cell suppression [99]. Preliminary results from a phase 1/2 study for epacadostat combined with pembrolizumab in advanced RCC reported an ORR of 47% [99]; however, a recent phase 3 trial of this combination in patients with melanoma failed to meet its primary endpoint of improved PFS relative to pembrolizumab monotherapy [100].

Checkpoint inhibitor monotherapy

Few studies have investigated first-line checkpoint inhibitor monotherapy in ccRCC. We do not know the contribution of ipilimumab to the nivolumab/ipilimumab combination and whether some patients could derive the same benefit from nivolumab monotherapy. The HCRN: GU16-260 trial (NCT03117309) is investigating nivolumab monotherapy in patients with treatment-naïve RCC of any histology, with the addition of ipilimumab as salvage therapy, and pembrolizumab monotherapy is being studied in an ongoing phase 2 trial in RCC of any histology (NCT02853344). Both studies involve intensive biomarker analyses. The lack of broad activity with checkpoint inhibitor monotherapy in ccRCC highlights the need for biomarkers to improve patient selection and outcomes [15,101].

Summary/conclusion

The frontline treatment paradigm for ccRCC has evolved, particularly for intermediate-/poor-risk patients, with the recent addition of cabozantinib and nivolumab/ipilimumab. Atezolizumab/bevacizumab, as well as nivolumab/ipilimumab, may be relevant options for favorable-risk patients in the near future, but OS data are needed to understand their benefit-to-risk profiles compared with established therapies. It will be important to evaluate cabozantinib in favorable-risk patients, and to investigate the potential role of immunotherapy as a monotherapy or in combination with other immunomodulatory agents, including TKIs. Prospectively validated biomarkers are needed to match patients to single-agent treatment with TKIs or immunotherapy, or to combinations of immunotherapies with TKIs or novel agents. As novel treatments come to the clinic, there is a need to develop strategies for sequencing new and established therapies.

Conflict of interest

The authors declared that there is no conflict of interest.

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