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Euo Collaborative Review – Kidney Cancer

Sequencing and Combination of Systemic Therapy in Metastatic Renal Cell Carcinoma

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Abstract

Context: Introduction of additional new agents targeting the vascular endothelial growth factor receptor (VEGFR) and immune checkpoint inhibitors (ICIs) has completely modified the systemic treatment of metastatic renal cell carcinoma (mRCC) during the last years.

Objective: A comprehensive (nonsystematic) review to determine the suggested sequence or combinations for the systemic treatment of mRCC.

Evidence acquisition: PubMed and abstracts from main conferences up to December 2018 were reviewed to retrieve the current evidence for treatment of mRCC. Search terms included renal cell carcinoma, systemic therapy, targeted therapy (TT), and immunotherapy.

Evidence synthesis: Marked advances in the treatment of mRCC have been made with novel VEGFR tyrosine kinase inhibitors and multiple ICIs that have been included in the current treatment paradigm of mRCC. Remarkable advance has been made with the combination of double checkpoint blockade. The combination of ipilimumab and nivolumab compared with sunitinib has shown to increase the overall survival in the intermediate- and poor-risk patients based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model.

Conclusions: Double checkpoint blockade with ipilimumab and nivolumab has reported overall survival benefit in IMDC intermediate- and poor-risk patients, providing a durable response for a subset of patients. VEGF inhibitors remain the standard of care for favorable-risk patients in the first line. In the immediate future, more consolidated data on combination of VEGF-TT plus ICIs may show similar robust benefit with different safety profiles.

Patient summary: Multiple drugs and sequences are now accepted as effective treatment for metastatic renal cell carcinoma (mRCC). Combination of immune checkpoint inhibitors has shown to increase the overall survival in treatment-naïve mRCC patients. Combinations of immunotherapy and antiangiogenics may be another option in the near future. Outcomes of the first line will determine the sequence, although the best sequence has yet to be defined.

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1. Introduction

Introduction of additional new agents targeting the vascular endothelial growth factor receptor (VEGFR) and immune checkpoint inhibitors (ICIs) has completely modified the systemic treatment of metastatic renal cell carcinoma (mRCC) during the last years. Previously, several drugs targeting the VEGF pathway (axitinib, bevacizumab, pazopanib, and sunitinib) or the mammalian target of rapamycin (mTOR) pathway (everolimus and temsirolimus) have increased the overall survival (OS) of mRCC patients during more than a decade [1–3].

Recent treatment advances include T-cell checkpoint blockade with Programmed Cell Death protein 1 (PD-1) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies (Abs) as well as the most recent generation of VEGF tyrosine kinase inhibitors (TKIs). This article will review new therapeutic options available for the treatment of advanced renal cell carcinoma (RCC). Most strategies have seen only a small percentage of patients to achieve a durable response to these drugs as monotherapy. Lately, some strategies have combined different mechanisms of action of these agents to enhance outcomes and durable responses. Herein, we have performed a comprehensive (nonsystematic) review to determine sequence and combinations for the systemic treatment of mRCC.

2. Evidpasse acquisition

PubMed and abstracts from main conferences up to December 2018 were reviewed to retrieve the current evidence for the treatment of mRCC. Search terms included renal cell carcinoma, systemic therapy, targeted therapy (TT), and immunotherapy.

3. Evidence synthesis

3.1. Systemic therapy in sequence

First VEGFR-TKIs were approved following progression after cytokines [4]. Subsequently, the approval of VEGF/VEGFR inhibition as first-line treatment in mRCC led to the development of studies designed to assess both mTOR and VEGFR inhibition, mainly in the post-VEGF/VEGFR inhibition setting. In this review, the sequence of cytokines-VEGFR-TKIs will not be discussed.

3.2. First-line VEGF-TT

Sunitinib, pazopanib, tivozanib, and bevacizumab-interferon (IFN) are available VEGF-TTs in the first-line setting for mRCC. Pazopanib was noninferior to sunitinib with respect to progression-free survival (PFS), and OS was similar in a phase 3 clinical trial (COMPARZ trial) [5,6]. A cross-over study (PISCES trial) demonstrated a significant patient preference for pazopanib over sunitinib, with quality of life and safety as key influencing factors [7]. Both drugs have been the main choice for oncologists worldwide during the last decade. Bevacizumab-IFN showed benefit in OS, but due to toxicity the regimen has been less used commonly [8]. Tivozanib is an inhibitor of VEGFR 1, 2, and 3 [9]. The main clinical evidence for tivozanib comes from TIVO-1, a randomized controlled trial that showed that tivozanib prolongs PFS (12.7 mo) compared with sorafenib (9.1 mo; hazard ratio [HR], 0.76, 95% confidence interval [CI], 0.58–0.99; Table 1) [9].

3.2.1. Intermediate/poor-prognosis group

Cabozantinib is an oral TKI that targets cMet, VEGFRs, and AXL. Cabozantinib compared with sunitinib significantly increased median PFS (8.2 vs 5.6 mo) across subgroups of treatment-naïve patients with intermediate and poor International Metastatic RCC Database Consortium (IMDC) risk [10,11]. Cabozantinib was associated with a 34% reduction in the rate of progression or death (adjusted HR, 0.66; 95% CI, 0.46–0.95; $p = 0.012$) [12]. Despite this single phase 2 randomized controlled trial being the only evidence, cabozantinib has been approved for the first-line treatment of mRCC [13].

3.2.2. Second line after first-line VEGF-TT monotherapy

Based on the available data, up to four different strategies may be used to treat mRCC, which progressed after VEGF-TT (Fig. 1): immunotherapy, VEGFR-TKI, and the combination of VEGFR-TKI and an mTOR inhibitor.

3.2.3. Immunotherapy

Cytotoxic CTLA-4 and PD-1 are immune checkpoint molecules implicated in immune control [14]. PD-1 binds to two ligands, PD-L1 and PD-L2 [15]. The interaction between PD-1 and PD-L1 negatively regulates activated T-cell effector functions. PD-L1 is overexpressed in up to 30% of RCC tumors, and its expression is correlated with advanced tumor stage, higher Fuhrman grade, sarcomatoid

Table 1 – Summary of OS and PFS for selected TKIs in treatment-naïve mRCC patients

All groups	Median PFS (mo)	Median OS (mo)
Tivozanib vs sorafenib (TIVO-1) [9]	12.7 vs 9.1 ($p = 0.037$)	28.8 vs 29.3 (p = NS)
Sunitinib vs pazopanib (COMPARZ) [5]	9.5 vs 8.4 (p = NS)	29.3 vs 28.4 (p = NS)
Axitinib vs sorafenib [48,49]	10.1 vs 6.5 (p = NS)	21.7 vs 23.3 (p = NS)
Intermediate/poor risk groups	**Median PFS (mo)**	**Median PFS (mo)**
Cabozantinib vs sunitinib (CABOSUN) [10,12]	8.2 vs 5.6 ($p = 0.0008$)	26.6 vs 21.2 (p = NS)

mRCC = metastatic renal cell carcinoma; NS = not significant; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

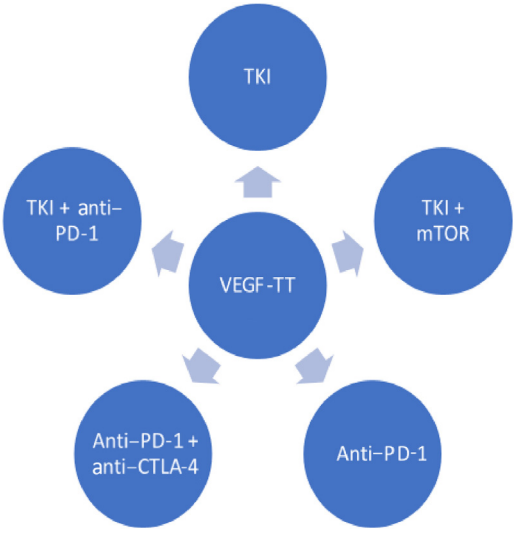

Fig. 1 – Emerging potential sequential treatments after first-line VEGF-TT. CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; mTOR = mammalian target of rapamycin; PD-1 = Programmed Cell Death protein 1; TKI = tyrosine kinase inhibitor; VEGF-TT = vascular endothelial growth factor-targeted therapy.

differentiation, and poorer survival [16]. CTL-4 displaces CD28 from B7, which ensues T-cell suppression as well as enhances activation of T-regulatory cells [17].

3.2.3.1. Nivolumab. Nivolumab is an ICI Ab that selectively blocks the interaction between PD-1 and PD-L1 and PD-L2. Nivolumab has been shown to improve the OS (25.0 vs 19.6 mo) compared with everolimus in advanced clear cell RCC (ccRCC) patients progressed to one or two regimens of VEGF-TT [18]. The HR for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57–0.93; $p = 0.002$). The OS benefit was observed irrespective of the prognostic group, number of prior antiangiogenic therapies, and PD-L1 expression. Nivolumab was superior in terms of objective response (25% vs 5%; $p < 0.001$). The median PFS was 4.6 mo (95% CI, 3.7–5.4) with nivolumab and 4.4 mo (95% CI, 3.7–5.5) with everolimus (HR, 0.88; 95% CI, 0.75–1.03; $p = 0.11$). Grade 3 or 4 treatment-related adverse events (AEs) occurred in 19% of patients receiving nivolumab and in 37% of patients receiving everolimus (8%).

3.2.3.2. Nivolumab and ipilimumab. In a phase I (CheckMate-016) study [19], nivolumab plus ipilimumab in combination was assessed in patients with mRCC. Patients received IV nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, or nivolumab 3 mg/kg plus ipilimumab 3 mg/kg every 3 wk for four doses, followed by nivolumab monotherapy 3 mg/kg every 2 wk until progression or toxicity. The confirmed overall response rate (ORR) was 40.4% in both treatment arms. Five (10.6%) patients achieved complete response and 14 (29.8%) a partial response in the N3I1 arm. In this study, nearly half of the patients had prior treatment. Although small, this is the only evidence of the combination of ipilimumab and nivolumab after prior treatment.

3.2.3.3. Duration of immunotherapy. The optimal duration of treatment with PD-1/PD-L1 inhibitors remains unclear. The different patterns of response highlight the relevance of characterizing the type and duration of response [20]. Measurement of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 may not adequately reflect patient benefit from anti-PD-1 therapy. Some randomized clinical trials investigating anti-PD-1 therapy have allowed for treatment beyond first progression provided that patients continued to exhibit investigator-assessed clinical benefit (Supplementary Table 2). In fact, there is a subset of patients who after disease progression may experience postprogression tumor reduction with nivolumab, which has an acceptable safety profile.

3.2.4. *VEGFR-TKI*

3.2.4.1. Cabozantinib. Upregulation of cMet and AXL has been described as a resistance mechanism to VEGFR inhibitors in preclinical models of RCC [21]. In a phase 3 clinical trial (METEOR), 658 ccRCC patients who progressed to VEGF-TT were randomized to receive cabozantinib at a dose of 60 mg daily or everolimus at a dose of 10 mg daily [22]. Median PFS was 7.4 mo with cabozantinib and 3.8 mo with everolimus (HR, 0.58; 95% CI, 0.45–0.75; $p < 0.001$). Median OS was 21.4 mo (95% CI, 18.7–not estimable) with cabozantinib and 16.5 mo (14.7–18.8) with everolimus (HR, 0.66 [95% CI, 0.53–0.83]; $p = 0.00026$) [12]. This study led to the approval in second line (Table 2).

Table 2 – Selected randomized clinical trials in the postvascular endothelial growth factor inhibition setting

Clinical trial	Phase	*N*	PFS (mo)	OS (mo)
VEGF inhibition refractory				
Everolimus vs placebo [34]	Phase 3	416	4.6 vs 1.8	14.8 vs 14.4
Axitinib vs sorafenib [28,50]	Phase 3	723	8.3 vs 5.7	20.1 vs 19.2
Temsirolimus vs sorafenib [51]	Phase 3	512	4.3 vs 3.9	12.3 vs 16.6
Sunitinib/everolimus vs everolimus/sunitinib [52]	Phase 3	471	su-eve: 21.7	su-eve: 29.5
			eve-su: 22.2	eve-su: 22.4
Dovitinib vs sorafenib (3rd line) [53]	Phase 3	570	3.7 vs 3.6	11.1 vs 11.0
Nivolumab vs everolimus [18]	Phase 3	658	4.6 vs 4.4	25 vs 19.6
Cabozantinib vs everolimus [22]	Phase 3	375	7.4 vs 3.8	21.4 vs 16.5
Lenvatinib/everolimus vs everolimus vs lenvatinib [37,54]	Phase 2	153	12.8 vs 5.6 vs 9	25.5 vs 15.4

eve = everolimus; OS = overall survival; PFS = progression-free survival; su = sunitinib; VEGF = vascular endothelial growth factor.

3.2.4.1.1. Selection of second-line therapy by subgroup analysis. Cabozantinib and nivolumab are the two drugs that have been shown to increase OS in phase 3 clinical trials at second line. Despite not having been compared in head-to-head trials, there are some similarities and differences. In this section, subgroup analyses are discussed as hypothesis generating, since post hoc subgroup analyses are usually flawed and may direct management wrongfully.

3.2.4.1.2. Specific prior therapy.

1. In the METEOR trial, patients who had prior sunitinib, median OS was 21.4 mo for cabozantinib versus 16.5 mo for everolimus (HR, 0.66 [95% CI, 0.47–0.93]); in those who had prior pazopanib, median OS was 22 mo for cabozantinib versus 17.5 mo for everolimus (HR, 0.66 [95% CI, 0.42–1.04]) [23].
2. In the CheckMate-025 trial, patients who had prior sunitinib, median OS was 23.6 mo for nivolumab versus 19.8 mo for everolimus (HR, 0.60 [95% CI, 0.42–0.84]); in those who had prior pazopanib, median OS was not estimable for nivolumab versus 17.6 mo for everolimus (HR, 0.81 [95% CI, 0.64–1.04]) [24,25].
3. Of note, the number of prior therapies does not seem to affect the relative efficacy of cabozantinib or nivolumab.

3.2.4.1.3. Bone metastases.

1. In the METEOR trial, patients with bone metastases at baseline (cabozantinib [n = 77]; everolimus [n = 65]), median PFS was 7.4 mo for cabozantinib versus 2.7 mo for everolimus (HR, 0.33 [95% CI, 0.21–0.51]). Median OS was longer with cabozantinib (20.1 vs 12.1 mo; HR, 0.54 [95% CI, 0.34–0.84]) [26]. In the CABOSUN trial, the presence of bone metastases favored cabozantinib compared with sunitinib: HR, 0.54 (95% CI, 0.31–0.95). However, there was also a benefit for patients without bone metastases (HR for PFS, 0.78; 95% CI, 0.48–1.21) [12].
2. In the CheckMate-025 trial, for patients with bone metastases at baseline (nivolumab [n = 76]; everolimus [n = 70]), median OS was 18.5 mo for nivolumab versus 13.8 mo for everolimus (HR, 0.72; 95% CI, 0.47–1.09).

3.2.4.1.4. Memorial Sloan Kettering Cancer Center risk group.

1. In the METEOR trial, cabozantinib showed consistently higher PFS than everolimus in patients with good Memorial Sloan Kettering Cancer Center (MSKCC) risk (HR = 0.54), intermediate MSKCC risk (HR = 0.56), or poor MSKCC risk (HR = 0.8) [22]. OS results for intermediate/favorable-prognosis patients seem to be superior to those for poor-risk patients.
2. In the CheckMate-025 trial, OS benefit with nivolumab versus everolimus was seen across prognostic groups: good (HR, 0.80 [0.52–1.21]), intermediate (HR, 0.81 [0.61–1.06]), or poor MSKCC risk factors (HR, 0.48 [0.32–0.70]) [25]. However, in poor-prognosis patients, nivolumab seem to have greater efficacy than everolimus.

Nivolumab and cabozantinib are the first approved therapies in this setting to confer a significant OS benefit (Fig. 2). Based on the ESMO-Magnitude of Clinical Benefit Scale, nivolumab should be considered a second-line option for most patients [27]. The main drawback of nivolumab is the lack of PFS benefit. Unmet needs and questions remain in the second-line treatment setting, including primary and acquired resistance to TKIs. Head-to-head comparisons are needed to understand treatment selection. Subgroup analyses are usually hypothesis generating. However, the magnitude of benefit with cabozantinib in patients with

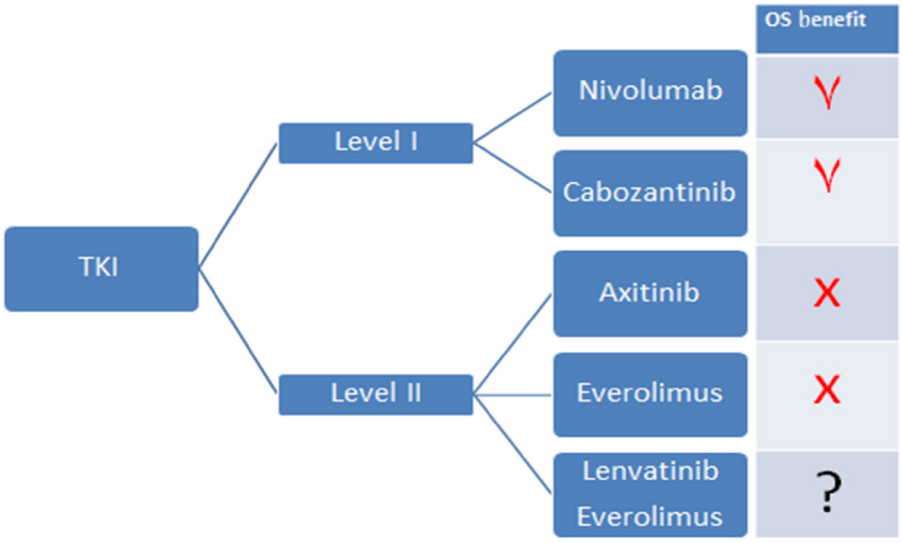

Fig. 2 – Level of evidence after TKIs (nivolumab and cabozantinib have the highest level of evidence). OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor. ** Combination of lenvatinib and everolimus has shown OS in a small phase 2 randomized clinical trial powered to study PFS.

bone metastases seems to be clinically meaningful. In addition, patients with poor IMDC risk features seem to have higher benefit with nivolumab, and on the contrary, the benefit with cabozantinib seems to be higher in patients with less adverse risk features.

3.2.4.2. Axitinib. Axitinib was compared with sorafenib in the AXIS trial. There was better PFS for axitinib (6.7 mo for axitinib compared with 4.7 mo for sorafenib [HR, 0.67; 95% CI, 0.54–0.81]), but there was no significant OS benefit (20.1 mo for axitinib vs 19.2 mo for everolimus) [28]. Axitinib may still be considered an option in the second line based on the good safety profile. In addition, axitinib is probably the TKI with more data in mRCC supporting increased efficacy with dose titration [29–31].

3.2.4.3. Tivozanib. The TIVO-3 trial enrolled patients with mRCC who have failed at least two prior regimens. The trial met its primary endpoint of demonstrating a statistically significant benefit in PFS [32]. Tivozanib demonstrated 44% improvement in median PFS and 26% reduction in the risk of progression or death (HR, 0.74; $p = 0.02$) compared with sorafenib. Median PFS was 5.6 mo for tivozanib compared with 3.9 mo for sorafenib. Among these, approximately 26% of patients received checkpoint inhibitor therapy in earlier lines of treatment [33].

3.2.5. *mTOR inhibitors*

Everolimus is an mTOR inhibitor that was showed to increase the median PFS (4.6 mo) compared with placebo (1.8 mo) after VEGF inhibition [34]. Nivolumab and cabozantinib have been shown to increase OS compared with everolimus; therefore, it does not seem to be a preferred option after VEGF-TT. Some studies have shown that there might be a better response in patients harboring mutations of mTOR, TSC1, and TSC2 [35,36]. Currently, there is not enough evidence to fully support these genomic alterations for treatment selection.

3.2.6. *Combination of mTOR inhibitors and VEGF-TKI*

Combination of different approved drugs to get synergistic activity has long been a classic treatment strategy in mRCC. Targeting both VEGFR and mTOR pathways has been considered an attractive strategy. Unfortunately, most trials testing this combination failed to show a strong signal of synergy, and the toxicity clearly outranged the benefits.

3.2.6.1. Lenvatinib/everolimus. Lenvatinib is a multi-TKI of VEGFR1-3, with inhibitory activity against fibroblast growth factor receptors (FGFR1–4), PDGFRα, RET, and KIT. In a phase 2 trial, 153 patients with mRCC previously treated with VEGF-TT were randomized to lenvatinib (24 mg/d, $N = 52$), everolimus (10 mg/d, $N = 50$), or lenvatinib plus everolimus (18 and 5 mg/day, $N = 51$) administered orally in continuous 28-d cycles [37]. Lenvatinib plus everolimus prolonged PFS compared with everolimus (median 14.6 vs 5.5 mo; HR, 0.40; 95% CI, 0.24–0.68), but not compared with lenvatinib alone (7.4 mo; HR, 0.66; 95% CI, 0.30–1.10). Single-agent lenvatinib prolonged PFS compared with everolimus (HR, 0.61; 95% CI, 0.38–0.98; $p = 0.048$). Grade 3–4 AEs were more common with the combination arm (71%) than with single-agent everolimus (50%). Of the patients, 24% discontinued treatment due to AEs with lenvatinib/everolimus compared with only 12% with everolimus. Despite the small sample size of the study, the Food and Drug Administration, as well as the European Medicines Agency, approved the combination of lenvatinib plus everolimus after VEGF-TKI.

3.3. *First-line anti-PD-1/anti-CTLA-4 combination (nivolumab/ipilimumab)*

3.3.1. *Nivolumab/ipilimumab*

In a phase 3 clinical trial (CheckMate-214), mRCC patients were randomized to receive either nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) IV every 3 wk for four doses, followed by nivolumab (3 mg/kg) every 2 wk, or sunitinib (50 mg) [38]. A total of 1096 patients were included; 550 received nivolumab plus ipilimumab, and 546 sunitinib. At a median follow-up of 25.2 mo in intermediate- and poor-risk patients, the median OS was not reached with nivolumab plus ipilimumab versus 26.0 mo with sunitinib (HR for death, 0.63; $p < 0.001$). The median PFS was 11.6 and 8.4 mo, respectively. Of the patients, 9% achieved a complete response with the combination. Grade 3/4 events occurred in 250 (46%) and 335 (63%) patients, respectively. Treatment-related AEs leading to discontinuation occurred in 22% and 12% of the patients in the respective groups. Based on these excellent outcomes (Supplementary Table 1), this combination is changing the current landscape of mRCC, becoming the standard of care, especially for patients with intermediate and poor risk.

3.3.2. *Second line after anti-PD-1/anti-CTLA-4 (nivolumab/ipilimumab)*

The subsequent therapy that should be offered after anti-PD-1/anti-CTLA-4 failure has yet to be defined. As the tumor is still VEGF-TT naïve, any TKI approved for the first line may have a role (Fig. 3). Arguments could also be made that because this is the second-line setting, patients could receive axitinib, cabozantinib, or the combination of lenvatinib + everolimus as well. However, these choices are very much dependent on reimbursement regulations in each jurisdiction. A phase 2 nonrandomized trial ($n = 38$) has shown that axitinib on an individualized titration schema may provide clinical efficacy (PFS 9.2 mo, ORR 40%) after checkpoint inhibitor therapy, including patients treated after ipilimumab/nivolumab [39]. In addition, small retrospective studies have reported median PFS of 8 mo (95% CI, 5–13) using TKI after dual checkpoint blockade. As mRCC patients progressing to nivolumab/ipilimumab would have intermediate- and poor-risk IMDC factors, cabozantinib may have a special role in this specific population compared with sunitinib. However, time to treatment failure with first-generation TKI (sunitinib/pazopanib) and second-generation TKI (axitinib/cabozantinib) was reported to be 8 (5–16) and 7 (5–not available) mo, respectively, in a small retrospective multicenter study.

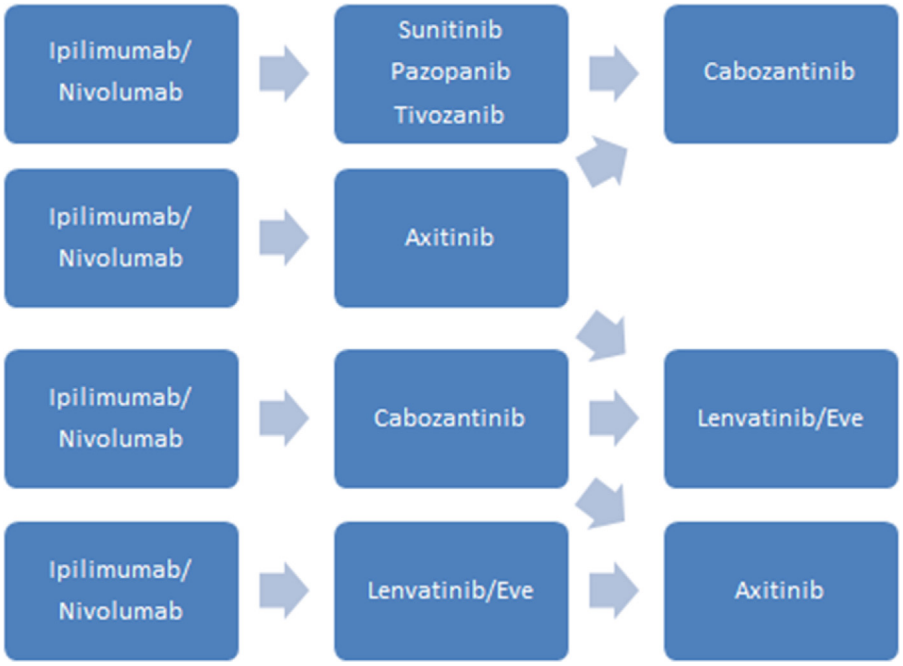

Fig. 3 – Panel of options for the second and third lines after ipilimumab-nivolumab. Eve = everolimus. ** Tivozanib could also be an option for the third and fourth lines, but data are still unpublished.

3.4. *Anti-PD-1 monotherapy as first line*

Pembrolizumab is a monoclonal Ab (mAb) against PD-1. In a phase 2 nonrandomized trial, treatment-naïve mRCC patients (clear cell, cohort A) received pembrolizumab 200 mg IV every 3 wk for 2 yr. A total of 110 patients were included. Interim data showed an ORR of 38.2% [40]. Median PFS was 6.9 (95% CI, 5.1–not reported) mo. Based on PD-L1 status, ORR was 50.0% in patients whose tumors expressed PD-L1, with a complete response rate of 6.5% and a partial response rate of 43.5%. OS rates at 3 and 6 mo were 97.2% and 92.4%, respectively. Of the patients, 73.6% had a treatment-related AE [41]. These are the first data with anti-PD-1 monotherapy as first-line treatment, but more mature and randomized data are required.

3.4.1. *Second line after first-line anti-PD-1 monotherapy*

3.4.1.1. VEGF-TT. Any TKI may have a role after anti-PD-1 therapy.

3.4.1.2. Combination of VEGF-TT and anti-PD-1 therapy. IMmotion150 was the first randomized study of PD-1/PD-L1–directed therapy and VEGF pathway inhibition in the first-line setting of mRCC. A total of 305 treatment-naïve mRCC patients were randomly assigned to receive bevacizumab plus atezolizumab, atezolizumab monotherapy, or sunitinib. A stratified analysis in the intention-to-treat population showed median PFS of 11.7 mo (95% CI, 8.4–17.3) with atezolizumab/bevacizumab versus 8.4 mo with sunitinib (HR, 1.00), and 6.1 mo with atezolizumab monotherapy (HR, 1.19) versus sunitinib. In the PD-L1+ population, the median PFS was 14.7 mo with atezolizumab/bevacizumab versus 7.8 mo with sunitinib (HR, 0.64; 95% CI, 0.38–1.08), and 5.5 mo (95% CI, 3.0–13.9) with atezolizumab monotherapy (HR, 1.03) versus sunitinib. Patients receiving atezolizumab were able to receive the combination of atezolizumab and bevacizumab after progression on atezolizumab. These specific data have not yet been published [42].

3.4.1.3. Combination of anti-PD-1 and anti-CTLA-4. Several ongoing studies are trying to answer whether the addition of anti-CTLA-4 Ab may revert the resistance to anti-PD-1 monotherapy (Supplementary Table 3). In these studies, nivolumab monotherapy is started with additional nivolumab/ipilimumab "boost" cycles if there is no response or progression to monotherapy.

3.5. *First-line VEGF-TT combined with anti-PD-1/PD-L1 mAbs*

VEGF-TT may modulate immune responses by increasing trafficking of T cells into the tumor, and reducing suppressing cytokines and infiltrating T regs [43]. Targeting the VEGF pathway may diminish tumor-induced immunosuppression, allowing the tumor to become more responsive to immunotherapy [44]. Different combinations have been evaluated, and some are still under investigation.

3.5.1. *Atezolizumab/bevacizumab*

IMmotion151 was a phase 3 clinical trial in which atezolizumab/bevacizumab was compared with sunitinib in treatment-naïve mRCC patients [45]. Although OS is still immature, the PFS benefit was consistent across analyzed subgroups, including MSKCC risk, liver metastases, and sarcomatoid histology (Table 3). Of note, in this study, there were substantial discrepancies between central and investigator reviews.

Table 3 – Outcomes in the intention-to-treat and PD-L1+ population

	Median progression-free survival (mo)			
	IMmotion150		IMmotion151	
	Intention to treat	PD-L1 (≥1%)	Intention to treat	PD-L1 (≥1%)
Atezolizumab	6.1 (5.4, 13.6)	5.5 (3.0, 13.9)		
Sunitinib	8.4 (7.0, 14.0)	7.8 (3.8, 10.8)	8.4	7.7
Atezo-Beva	11.7 (8.4, 17.3)	14.7 (8.2, 25.1)	11.2	11.2

Atezo-Beva = atezolizumab-bevacizumab; PD-L1 = Programmed Cell Death protein ligand 1.

Table 4 – Outcomes of early trials of combinations of VEGFR-TKI + anti-PD-1/PD-L1 mAbs in mRCC

	Axitinib, pembrolizumab [55] *N* = 52	Axitinib, avelumab [56] *N* = 55	Lenvatinib, pembrolizumab [57] *N* = 30	Cabozantinib, nivolumab [58,59] *N* = 13	Tivozanib, nivolumab [60] *N* = 14
ORR (%)	73	58	63	54	64
CR (%)	8	6	–	0	0
PFS (mo)	20.9		NR	18.4	–

CR = complete response; mAb = monoclonal antibody; mRCC = metastatic renal cell carcinoma; NR = not reported; ORR = overall response rate; PD-1 = Programmed Cell Death protein 1; PD-L1 = Programmed Cell Death protein ligand 1; PFS = progression-free survival; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

3.5.2. Other combinations under development

Multiple combinations of VEGFR-TKI + anti-PD-1/PD-L1 mAbs are under development. For the time being, the preliminary results are encouraging (Table 4). The safety profile of the combinations in treatment-naïve mRCC patients seemed to be manageable and consistent with that of each drug alone. In addition, the efficacy seems to be promising. Several phase 3 trials are assessing these combinations compared with sunitinib monotherapy. Depending on the results of all these trials, the landscape of management of mRCC patients may evolve rapidly.

The JAVELIN Renal 101 trial is the first phase 3 clinical trial providing results of VEGFR-TKI + anti-PD-1/PD-L1 therapy. This study has shown that the combination of avelumab and axitinib significantly improves PFS compared with sunitinib in treatment-naïve mRCC patients, irrespective of the PD-L1 status. A total of 886 patients were randomly assigned to receive either avelumab 10 mg/kg every 2 wk with axitinib 5 mg twice daily in 6-wk cycles or sunitinib. The coprimary endpoint of independent review-assessed PFS in the PD-L1–positive subgroup (63.2%, $N = 560$) was a median of 13.8 mo with avelumab/axitinib compared with 7.2 mo for sunitinib (HR = 0.61; $p < 0.0001$) in favor of the combination. Median PFS in patients in the overall population and irrespective of PD-L1 expression was 13.8 versus 8.4 mo (HR = 0.69; $p = 0.0001$). OS data are still immature. The incidence of grade 3/4 treatment-related AEs was similar (71.2% vs 71.5%) in the combination and sunitinib arms [46].

3.5.3. Second line after VEGF-TT/PD-1–PD-L1 mAbs

The current landscape after first-line VEGF-TT/PD-1/PD-L1 is extremely uncertain. Several studies are ongoing (Supplementary Table 4), but the only information available has low evidence since most data for it are obtained from retrospective studies.

3.5.3.1. VEGFR-TKIs after VEGF-TT/PD-1–PD-L1 combination. Evidence from clinical trials is still very limited. Some patients from clinical trials and data from retrospective studies have shown that both VEGF/VEGFR and mTOR inhibitors demonstrate antitumor activity following PD-1/PD-L1 blockade [39,47].

3.5.3.2. Ipilimumab/nivolumab could be also considered. No data are available regarding ipilimumab/nivolumab.

4. Conclusions

Over the last 5 yr, marked advances in the treatment of mRCC have been made, with novel VEGFR-TKI and multiple ICIs having been included in the current landscape of mRCC.

At this time, based on approvals and follow-up, double checkpoint blockade with ipilimumab and nivolumab has reported the best data at the first line in terms of OS (especially for patients with intermediate and poor IMDC risks), providing a long durable response for a subset of patients. In the immediate future, more consolidated data on the combination of VEGF-TT plus ICI may show similar robust benefits with different safety profiles. These differences will probably shape the treatment selection for first-line therapy.

Currently, it is uncertain whether a subset of patients will be cured by immunotherapy combination. Therefore, the need for sequencing will remain, and treatment management should focus on efficacy as well as safety profile. At

this point, control of disease remains important, but quality of life emerges as an extremely relevant factor for treatment selection. This exciting era is characterized by the lack of a solid molecular biomarker to select treatment, although multiple options, including VEGF-TT, mTOR inhibitors, immunotherapy, or their combinations, are available. Unfortunately, this era is still characterized by lower levels of evidence to select the best sequence for each patient.

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Study concept and design: Escudier, de Velasco.
Acquisition of data: Escudier, de Velasco.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: de Velasco.
Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

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