JBUON 2019; 24(4): 1340-1353
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

REVIEW ARTICLE

Current and emerging first-line systemic therapies in metastatic clear-cell renal cell carcinoma

Theodoros Tegos[1], Konstantinos Tegos[2], Areti Dimitriadou[3], Georgios Dimitriadis[2]

[1]Medical Oncology Department, Evangelismos General Hospital, Athens, Greece; [2]Department of Internal Medicine, Research Institute and Diabetes Center. National and Kapodistrian University of Athens. Attikon General Hospital, Athens Greece; [3]Medical Oncology Department, Ippokratio General Hospital, Athens, Greece.

Summary

The treatment of metastatic clear-cell renal cell cancer (mccRCC) has seen substantial progress over the last decade. Until 2006, non-specific immunotherapy with high dose interleukin-2 (HD IL-2) was considered as standard therapy of mccRCC. The transition from cytokine to targeted therapy, and now to novel immunotherapeutic agents, significantly increased the overall survival (OS) of patients with mccRCC. Currently, 7 targeted agents and the combination of nivolumab/ipilimumab (immune checkpoint inhibitors, ICIs) have been approved as first-line therapy for mccRCC. Based on evidence from randomized phase III clinical trials, sunitinib and pazopanib (Tyrosine kinase inhibitors of vascular endothelial growth factor; VEGF-TKIs) are the most effective first-line options, especially in favorable and indermediate risk patients. Nivolumab/ipilimumab (dual checkpoint inhibitors) seem to be the preferred first-line therapy in poor-risk patients, although cabozantinib, temsirolimus, sunitinib and pazopanib are also recommended. HD IL-2 remains a reasonable first-line treatment option in selected, favorable-risk younger patients with good performance status. Based on data of previous phase I and II studies, several phase III trials investigating the efficacy and safety of the combination of ICI/VEGF-TKI versus sunitinib in untreated mccRCC are currently underway. These emerging therapies include the combinations of pembrolizumab/lenvatinib, pembrolizumab/axitinib, avelumab/axitinib and atezolizumab/bevacizumab and seem to introduce the mccRCC therapy in a new auspicious era. Moreover, emerging new targeted therapies and other, beyond ICIs, immunotherapies are currently underway.

Key words: *targeted therapies, metastatic renal cell carcinoma, antiangiogenic agents, immune checkpoint inhibitors. emerging first-line systemic therapies*

Introduction

Renal cell cancer (RCC) accounts for 2-3% of all adult malignancies, with a median age at diagnosis of 64 years [1]. Over 25% of patients with RCC have metastatic disease (mRCC) on presentation, while another 20-40% with localized disease will eventually develop mRCC [2]. In localized RCC, the 5-year survival has increased from 88.4% (during 1992-1995) to 92.5% (during 2006-2012) and for advanced disease from 7.3% (during 1992-1995) to 11.6% (during 2006-2012) [3]. According to the pathological classification, RCC includes a heterogeneous group of cancers with different histologic, molecular and genetic alterations [4]. Clear cell, papillary (type I and II) and chromophobe RCC are the most common histologic subtypes of RCCs and account for 85-90% of all primary renal tumours [5]. Clear cell RCC (ccRCC) is the most common subtype, occurring in 75% of the cases, and is strongly associated with alterations in von Hippel-Lindau (VHL) gene [6].

The VHL gene (chromosome 3p25) is a 2-hit tumor suppressor gene (TSG) in which, typically,

Corresponding author: Theodoros Tegos, MD, PhD. Evangelismos General Hospital, Ipsilantou 45-47. 10676, Athens, Greece. Tel: +30 6955198208, Fax: +302132041192, Email: th_tegos@yahoo.com
Received: 13/11/2018; Accepted: 20/12/2018

the first allele is inactivated through an intragenic mutation or promoter hypermethylation, and the second is lost as part of a large deletion [7]. In the absence of hypoxia, VHL protein (pVHL) typically degrades hypoxia-induced factor 1α (HIF1α) and prevents gene expression of the growth factors, including vascular endothelial growth factor (VEGF). In the tumour cell, the inactivation of pVHL prevents ubiquitination of HIF1α, allowing nuclear trafficking and subsequent intracellular HIF accumulation. This leads to overexpression of VEGF and platelet-derived growth factor (PDGF) [8]. However, evidence accumulated over the past 10 years suggests that HIF2, rather than HIF1, is the key driver of renal cancer progression [10]. VHL mutations are frequently seen in sporadic metastatic ccRCC (mccRCC), with a reported incidence ranging in several studies from 46% to 95% [9]. HIF activity is also increasing via the PI3K/AKT/mTOR (mechanistic target of rapamycin) pathway [11]. Given that a number of downstream mTOR effectors regulating angiogenesis, metabolism and cell growth have been found to be deregulated in cancers, various targeted therapies have been developed to hinder mTOR signaling.

Clinical prognostic models in mRCC

In mRCC, several clinical factors have been associated with a reduced overall survival (OS) and integrated into different risk prognostic models. These clinical models categorize patients according to expected outcomes and help risk stratification and therapy selection [12].

(a). Memorial Sloan Ketterig Cancer Center (MSKCC) model [13].

This model includes 5 variables (prognostic factors):

- Interval from diagnosis to the start of treatment < 1 year.
- Karnofsky performance status (PS) < 80%.
- Serum lactate dehydrogenase (LDH) > than 1.5 times the upper limit of normal (ULN).
- Corrected serum calcium > than ULN.
- Serum hemoglobin < than lower limit of normal (LLN).

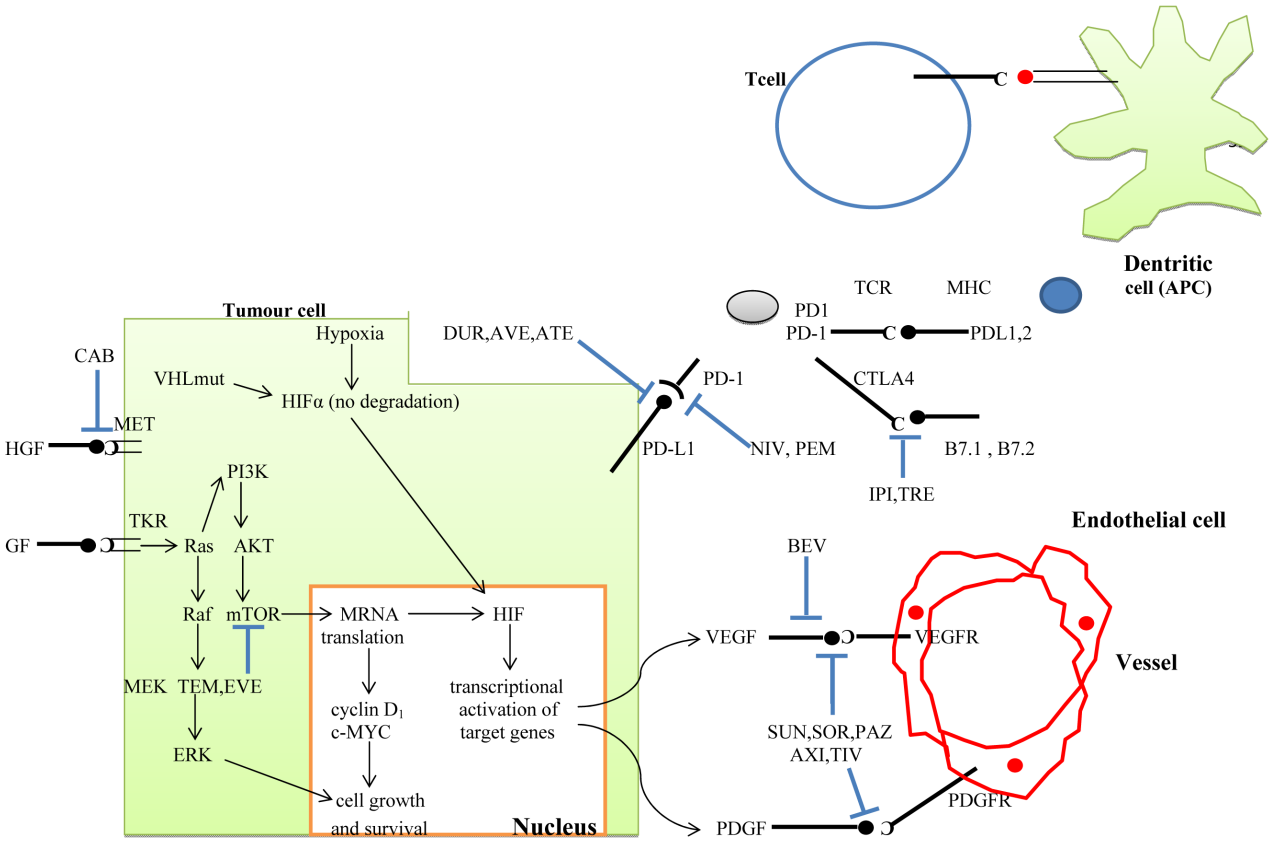

Figure 1. Molecules – targets for systemic therapies in mccRCC.
VHLmut: von Hippel-Lindau gene mutated, HIF: hypoxic induced factor, PD-1: programmed cell death 1, PD-L1: programmed cell death ligand 1, CTLA4: cytotoxic T-lymphocyte - associated antigen 4, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor, PDGF: platelet - derived growth factor, PDGFR: platelet - derived growth factor receptor, HGF: hepatocyte growth factor, MET: mesenchymal epithelial transition, TKR: tyrosine kinase receptor, TCR: T - cell receptor, APC: antigen presenting cell, NIV: nivolumab, PEM: pembrolizumab, IPI: ipilimumab, TRE: tremelimumab, AVE: avelumab, DUR: durvalumab, ATE: atezolizumab

By this model, patients were stratified into 3 prognostic risk categories, according to the number of risk factors: *favorable-risk* (0 factors), *intermediate-risk* (1-2 factors) and *poor-risk* (3-5 factors) category, with a median overall survival (mOS) of 30, 14 and 5 months (mo), respectively.

(b). International metastatic RCC database consortium (IMDC) or Heng's model [14].

This model includes 6 prognostic factors:

- Four prognostic factors similar to MSKCC model (interval from diagnosis to treatment < 1 year, Karnofsky PS < 80%, corrected calcium > ULN, hemoglobin < LLN).
- Absolute neutrophil count > ULN.
- Platelets > ULN.

In this prognostic model, patients without adverse factors were stratified as *favorable-risk category* (mOS NR, 2-year OS 75%), patients with 1 or 2 factors were in the *intermediate-risk category* (mOS 27 mo, 2-year OS 53%) and patients with 3 to 6 factors were in the *poor-risk category* (mOS 8.8 mo, 2-year OS 7%).

Until 2006, immunotherapy with interleukin-2 (IL-2) or interferon-α (IFN-α) was considered to be the standard of care for mRCC, despite modest improvements in survival and increased toxicity. The better understanding of the role of the pVHL and the molecular signaling that governs tumour growth and progression has led to the development of molecular therapies targeting the VEGF and mTOR pathways, resulting in significant improvement in overall survival and quality of life of patients with mccRCC. In the last 3 years, novel immunotherapeutic agents (immune checkpoint inhibitors), up-regulating the host immune response, have entered the field of systemic therapies for mccRCC, in order to destroy neoplastic cells that escape immune recognition (Figure 1) [15].

Current first-line systemic therapies for mccRCC

A. *High-dose interleukin-2 (HD IL-2)*

Interleukin-2 is a T cell-produced cytokine, governing the immune system through pleiotropic effects mediated by promoting activation and expansion of both cytotoxic T-cells (Tconvs) and regulatory T-cells (T-regs), through PI3K/MAPK pathways [16].

Initial studies in patients with mRCC,treated with HD IL-2, reported an objective responserate (ORR) of 14% (CR 5%), with a broad range of toxicities due to its non-specific anti-tumour activity [17]. Although IL-2 applied in low- and high-dose regimens, the FDA approved for mRCC only the high-dose regimen (1992). A retrospective analysis of 259 mRCC patients, treated with HD IL-2 between 1986 and 2006, reported an ORR of 20% (9% CR,11% PR) [18]. Recently, in the PROCLAIM study [19], 352 mccRCC patients treated with HD IL-2,between 2011 and 2015, had 4% complete response (CR), 13% partial response (PR), 39% stable disease (SD) and 43% progressive disease (PD). The mOS was not reached in patients with CR, PR or SD and was 15.5 mo in patients with PD (median follow-up 21 mo). Patient with PD, after HD IL-2, appear to benefit from follow-on targeted therapy (TT) and patients who pro-gressed on or after TT and were eligible for HD IL-2 had an ORR of 19%, with no unexpected toxicities noted. In this study, drug-related death rate was 1.4%, lower than historical experience, mainly because of improved treatments practices and better selection of patients. Addition of antiangiogenic agent (bevacizumab) to the combination of IL-2/ IFNα (low-doses, sc) did not add efficacy in mRCC [20].

Finally, since the toxicity of IL-2 is severe but predictable, administration of HD IL-2 should be restricted to younger patients with good PS (0-1) and favorable-risk category, without medical comorbidities. A significant benefit of HD IL-2 is the short duration of therapy and the potential for complete responses (5%) or long-term disease control. This characteristic is in contrast with targeted therapies, where response rates are high, but the durability of responses is quite limited.

B. *Targeted therapy (antiangiogenic agents)*

In mccRCC, molecular alterations in VHL gene lead to increased concentration of HIF and overproduction of VEGF, PDGF,mTOR, MET (mesenchymal epithelial transition), HGFR (hepatocyte growth factor receptor) and AXL tyrosine protein kinase receptors. These factors have been implicated in the tumorigenesis and metastatic potential of ccRCC. Angiogenesis is a critical process persistently present in all phases of RCC progression, which is difficult to be controlled due to VEGF signaling redundancy and alternative pathways.The elucidation of these pathways has allowed for development of targeted therapies and provided several agents for the treatment of mccRCC. Until now, 7 targeted agents have been approved as first-line therapy for mccRCC (Table 1). The small molecules tyrosine multikinase inhibitors (TKIs) against VEGFRs, PDGFRs and other kinases (sorafenib, sunitinib, pazopanib, tivozanib), the monoclonal antibody (mAb) that inhibits VEGF (bevacizumab), a mTOR inhibitor (temsirolimus) and a MET inhibitor (cabozantinib) have become the mainstay of initial therapy

in patients with mccRCC (Figure 1). The advent of antiangiogenic agents in the therapy of mccRCC was characterized as a therapeutic "revolution".

C. *Vascular endothelial growth factor receptor (VEGFR)/Tyrosine kinase inhibitors (TKIs)*

The VEGFR-TKIs constitute an important group of agents, which presently has become the mainstay of initial therapy for patients with mccRCC. The first VEGFR-TKI approved by FDA (2005) and EMA (2006) was sorafenib. Sorafenib is a multikinase inhibitor of VEGFR-1,2, PDGFR-α,β, FLT-3 (FMS-like tyrosine kinase), c-Kit (stem cell factor receptor) and RET-TKR. In the TARGET trial (Table 2), sorafenib was compared to placebo as first-line therapy in 902 patients with mccRCC. Median PFS was improved in the sorafenib arm (5.5 vs 2.8 mo, HR 0.44, p<0.01), although significant improvement in OS was found only when post-crossover placebo data censored (19.3 vs 15.9 mo, HR 0.77, p=0.02) [21,22]. In the NCT00117637 phase II trial, sorafenib was compared to IFN-α and resulted in similar PFS in patients with untreated RCC. However, sorafenib-treated patients experienced greater rates of tumor size reduction, better QoL and improved tolerability [23].

Sunitinib

Sunitinib, a multikinase inhibitor of VEGFR-1,2,3, PDGFR-α,β and c-KIT, was approved (FDA, EMA) in 2006, after a randomized trial (NCT00083889), comparing sunitinib to IFN-α as first-line therapy in 750 patients with mccRCC (Table 2). Improved median PFS (11 vs 5 mo, HR 0.42, p<0.001) and ORR (31% vs 6%, p<0.001) was demonstrated in the sunitinib arm [24]. Follow-up data also reported superior OS in the sunitinib arm (26.4 vs 21.8 mo, HR 0.82, p<0.05) [25].

Pazopanib

Pazopanib,a multikinase inhibitor of VEGFR, PDGFR, FGFR, c-KIT and RET, was approved (FDA/EMA) in 2009/2010, after a randomized trial (VEG105192) comparing pazopanib to placebo for 435 untreated mccRCC, and those pretreated with cytokines (Table 2) [26]. Median PFS was significantly prolonged with pazopanib compared to placebo in the overall study population (9.2 vs 4.2 mo, HR 0.46, p<0.0001), the treatment-naïve subpopulation (11.1 vs 2.8 mo, HR 0.40, p<0.0001), and the cytokine-pretreated subpopulation (7.4 vs 4.2 mo, HR 0.54, p<0.001). The ORR was 30% with pazopanib, compared to 3% with placebo (p<0.001). The difference in the final OS between pazopanib and placebo-treated was not statistically significant (22.9 vs20.5 mo, HR 0.91, p=0.224). However, an extensive crossover from placebo to pazopanib confounded final OS analysis. *Posthoc* analyses adjusting for crossover suggest OS benefit with pazopanib treatment for mRCC patients [27].

In order to determine the optimal first-line therapy in patients with mccRCC, *head-to-head trials*

Table 1. FDA/EMA approved targeted agents as first-line trerapy for mccRCC

Agent [ref]	*FDA/EMA* approval*	*Target*	*Dose*
Sorafenib (SOR) (Nexavar) [21,22]	Dec 2005/Jul 2006	VEGFR2, PDGFRβ1, FLT-3, c-KIT, RET	400mg x2/d, p.o
Sunitinib (SUN) (Sutent) [24,25]	Jan 2006/Jun 2006	VEGFR1-3, PDGFR, c-KIT, FLT-3	50 mg/d, p.o, for 4 wks, q6wks(4/2)
Temsirolimus(TEM) (Torisel) [43,44]	May 2007/Nov 2008	mTOR	25mg/wk, IV
Bevacizumab (BEV) (Avastin)/IFNα [35-38]	Jul 2009/Dec 2007	VEGFα	BEV: 10 mg/Kg, IV, q2wks + IFNα: 9 MIU, SC,3 times/wk
Pazopanib (PAZ) (Votrient) [26,27]	Oct 2009/Jun 2010	VEGFR1-3, PDGFR, c-KIT, RET, FGFR	800mg/d, p.o
Cabozantinib (CAB) (Cabometyx) [31]	Dec 2017/May 2018	VEGFR2,MET(HGFR), AXL	60mg/d, p.o
Tivozanib (TIV) (Fotivda) [33,34]	Aug 2017 (EMA)	VEGFR1-3, c-KIT, PDGFRβ	1.5mg/d, p.o, for 3 wk, q4wks
Nivolumab (NIV)/Ipilimumab (IPI) (Optivo/Yervoy) [47,49]	Apr 2018 (FDA)	PD-1/CTLA-4	3mg/Kg (NIV) + 1mg/Kg (IPI), q3 wks, 4c →NIV 3 mg/kg, q2wks

*FDA: US Food and Drug Administration, EMA: European Medicines Agency

were conducted.The COMPARZ trial (2013) was the first prospective direct comparison of pazopanib vs sunitinib as first-line therapy in 1110 patients with mccRCC (Table 2). Both agents demonstrated prolonged median PFS (mPFS) (8.4 vs 9.5 mo, HR 1.05) as well as mOS (28.3 vs 29.1 mo, HR 0.91, p=0.28) and ORR (31% vs 25%, p=0.03) [28,29]. In this study, pazopanib was found non-inferior to sunitinib in efficacy but had a lower incidence of reported adverse events and better quality of life [40]. Since the COMPARZ trial, many studies attempted to elucidate the preferred first-line agent, but neither has shown any consistent clinical superiority. In the PISCES trial, pazopanib rather than sunitinib performed greater patient preference and less risk of hand-foot syndrome and fatigue [30].

Cabozantinib

Cabozantinib is a potent inhibitor of VEGFR2, MET and AXL. The observation that high expres-

Table 2. Randomized clinical trials (RCTs) for first-line therapy in mccRCC

RCT [ref]	*Agent vs comparator*	*Sample size*	*Progression - Free Survival (PFS)*			*Overall Survival (OS)*			*ORR (%)*
			Median (mo)	*HR (95% CI)*	*P*	*Median (mo)*	*HR (95% CI)*	*P*	
TARGET, Escudier 2007 [21,22]	SOR vs Plac	902 (1:1)	5.5 vs 2.8	0.44	<0.01	19.3 vs 15.9	0.77	0.02	9.75 vs 1.77 (p<0.01)
NCT0083889, Motzer 2007 [24,25]	SUN vs IFNα	750 (1:1)	11 vs 5	0.42	<0.001	26.4 vs 21.8	0.82	<0.05	31 vs 6 (p<0.001)
AVOREN, Escudier 2007 [35,36]	BEV/IFNα vs Plac/IFNα	649 (1:1)	10.2 vs 5.4	0.63	0.0001	23.3 vs 21.3	0.86	0.1291	31 vs 12 (p=0.0001)
GALGB 90206, Rini 2008 [37,38]	BEV/IFNα vs IFNα	732 (1:1)	8.5 vs 5.2	0.71	<0.0001	18.2 vs 17.4	0.86	0.069	25.8 vs 13.1 (p=0.0001)
VEG105192, Sternburg 2010 [26,27]	PAZ vs Plac	435 (1:1)	9.2 vs 4.2* 11.1 vs 2.8** 7.4 vs 4.2***	0.46	<0.0001	22.9 vs 20.5	0.91	0.224	30 vs 3 (p<0.001)
COMPARZ, Motzer 2013 [28,29]	PAZ vs SUN	1110 (1:1)	8.4 vs 9.5	1.05	-	28.3 vs 29.1	0.91	0.28	31 vs 25 (p=0.03)
NCT0065468, Hudes 2007 [43]	TEM vs IFNα vs TEM/IFNα	626 (1:1:1)	5.5 vs 3.1 vs 4.7	-	<0.001	10.9 vs 7.3 vs 8.4	0.73	0.008	8.6 vs 4.8 vs 8.1
CABOZUN, Choueiri 2017[31]	CAB vs SUN	157 (1:1)	8.2 vs 5.6	0.66	0.012	30.3 vs 21.8	0.80	-	46 vs 18
TIVO-1, Motzer 2013 [33], Hutson 2015 [34]	TIV vs SOR	517 (1:1)	11.9 vs 9.1	0.797	0.042	29.3 vs 28.8	1.245	0.105	33.1 vs 23.3 (p=0.014)
INTORACT, Rini 2013 [44]	TEM/BEV vs BEV/IFNα	791 (1:1)	9.1 vs 9.3	1.1	0.8	25.8 vs 25.5	1	0.8	27 vs 27.1 (p=1)
CheckMate 214, Escudier 2017 [49]	NIV/IPI vs SUN	1096 (1:1)	11.6 vs 8.4 (I,P) 15.3 vs 25.1 (F)	0.82 2.17	0.0331 0.0001	NR vs 26 (I,P) -	0.63 -	<0.0001 -	41.6 vs 26.5 (p<0.0001) (I,P) 29 vs 52 (p=0.0002) (F)

ORR: Overall Response Rate, HR: Hazard Ratio,CI: Confidence Interval,F:Favourable – risk; I:Intermediate – risk, P:Poor – risk;*all patients;** without cytokine pretreatment; *** with cytokine pretreatment (abbreviations of targeted agents are explained in Table 1)

sion of MET and AXL are poor prognostic factors provided the biologic rationale for the CABOSUN (ALLIANCE) A031303) study (Table 2). In this randomized phase II trial, cabozantinib was compared to sunitinib as first-line therapy in 157 patients with mccRCC of poor or intermediate risk (IMDC model) [31].

Cabozantinib vs sunitinib significantly prolonged mPFS (8.2 vs 5.6 mo, HR 0.66, p=0.012) and showed a 34% reduction in rate of progression or death (HR 0.66, p=0.012). ORR was 46% (95% CI, 34-57) for cabozantinib versus 18% (95% CI, 10-28) for sunitinib. Median OS with cabozantinib was 30.3 mo versus 21.8 mo with sunitinib (HR 0.80) [32]. Analysis by tumour MET expression suggested a greater benefit with cabozantinib vs sunitinib in MET (+) patients [84]. Based on the findings of this study, FDA (2017) and EMA (2018) approved cabozantinib as first-line treatment in intermediate- and poor-risk mccRCC.

Tivozanib

Tivozanib is a potent and selective TKI of VEGFR1-3. In a phase III TIVO-1 study (Table 2), tivozanib compared with sorafenib as first-line targeted therapy in 517 patients with mccRCC. Median PFS was longer with tivozanib than with sorafenib in the overall population (11.9 vs 9.1 mo, HR 0.797, p=0.042). ORR 33.1% vs 23.3% (p=0.014). Median OS was almost similar in the 2 arms (29.3 vs 28.8 mo, HR 1.245, p=0.014) [33,34]. Tivozanib was approved by EMA (Aug 2017) as first-line treatment for mRCC, but *not* by FDA, due to the lack of significant advantage, in terms of survival, compared to sorafenib.

D. *Vascular endothelial growth factor (VEGF) inhibitor (Bevacizumab)*

Bevacizumab is a recombinant humanized mAb that binds and neutralizes circulating VEGF-A. In the AVOREN study (Table 2) [35,36], bevacizumab in combination with IFN-α was compared to placebo as first-line therapy in 649 patients with mRCC. Median PFS was significantly longer in the bevacizumab/IFN-α group than in the control group (10.2 vs 5.4 mo, HR 0.63, p=0.0001) and ORR was significantly higher in the bevacizumab/IFN-α arm (31% vs 12%, p=0.0001) [35].

A trend towards improvement in mOS was reported with the combination bevacizumab/IFN-α (23.3 vs 21.3 mo, HR 0.86, p=0.1291) [36]. The findings of this study were by the GALGB 90206 study [37,38], in which 732 patients were assigned to receive bevacizumab plus IFN-α or IFN-α alone. The GALGB study, similar to AVOREN study, also demonstrated in patients treated with bevacizumab longer mPFS (8.5 vs 5.2 mo, HR 0.71, p=0.0001) and higher ORR as compared to IFN-α (25.8% vs 13.1%, p=0.0001). The mOS time favored the bevacizumab/IFN-α arm, but did not meet the predefined criteria for significance (18.3 vs 17.4 mo, HR 0.86, p=0.069) [38]. Based on these studies, bevacizumab/IFN-α was approved by FDA/EMA (2008/2009) as first-line therapy in mccRCC. Combination therapy of bevacizumab with sunitinib was tested in two independent studies [39,40] and found suffering from dose-limiting toxicities.

E. *mTOR inhibitor (Temsirolimus)*

The mTOR has been implicated in tumorigenesis and angiogenesis in mRCC [41,42]. Temsirolimus forms a complex with FKBP-12 which then inhibits mTOR signaling. In a phase III NCT0065468 trial (Table 2), 626 untreated, intermediate or poor-risk patients (MSKCC model) with mRCC, were randomized to receive temsirolimus, IFN-α or both [43]. Temsirolimus, compared to IFN-α and temsirolimus/IFN-α, achieved longer mOS (10.9 vs 7.3 vs 8.4 mo, HR 0.73, p=0.008) and mPFS (3.8 vs 1.9 vs 3.7 mo, p<0.001). The ORR of 8.6%, 4.8% and 8.1% among patients receiving temsirolimus, IFN-α, and combination therapy, respectively, did not differ significantly. The FDA (2007) and EMA (2008) approved temsirolimus as first-line therapy in poor-risk patients with mRCC. However, temsirolimus has not been widely employed in front-line mRCC management, probably due to its toxicity and inconvenient intravenous administration. The efficacy of combination therapy with temsirolimus plus bevacizumab versus bevacizumab plus IFN-α was determined in the INTORACT trial (Table 2). Median PFS 9.1 vs 9.3 mo (HR 1.1, p=0.8), mOS 25.8 vs 25.5 mo (HR 1,p=0.8) and ORR 27% vs 27.1 (p=1) were reported in this study of 791 patients with mccRCC. Temsirolimus/bevacizumab combination therapy was not superior to bevacizumab/IFN-α for first-line treatment in mccRCC [44].

F. *Immunotherapeutic agents (immune checkpoint inhibitors, ICIs)*

Renal cell carcinoma is a highly immunogenic tumour as evidenced from response to immunotherapies. Programmed death-1 (PD-1) is a significant checkpoint molecule implicated in immunosuppression and immunotolerance. Physiologically, activated T and B lymphocytes, dendritic, natural killer and monocyte cells express PD-1 in order to restrict autoimmunity during inflammatory states. Programmed cell death ligand 1 (PD-L1) is the natural ligand to PD-1. PD-L1 is not expressed in normal kidney tissues, but is over-

expressed in approximately 30% of RCC tumors. PD-L1 expression was correlated with aggressive tumours and poorer survival [45].The interaction between PD-1 and PD-L1 negatively regulates activated T-cell effector functions. The PD-1/PD-L1 signalling pathway can be used by cancers as an adaptive evolutionary advantage to evade the immune system. Therefore, PD-1/PD-L1 pathway represents an attractive target since its inhibition can restore antitumour T-cell activity and promote immune-mediated tumour destruction. Cytotoxic T lymphocyte antigen-4 (CTLA-4) is a major immune checkpoint receptor in T-cells, that acts as a down-regulator of early immuneresponse. B7.1 (CD80) and B7.2 (CD86) molecules, expressed on the surface of immune cells, are ligands to CTLA-4 receptor. This interaction triggers down-regulation of T-cells proliferation and cytokines production leading to immunosuppression and immune tolerance [41,46,47]. The combination of PD-1 and CTLA-4 receptor blockades (dual checkpoint inhibition) results in more pronounced antitumour activity in preclinical models [48].

ICIs represent the most used by clinicians part of cancer immunotherapy and include anti-PD1 (nivolumab, pembrolizumab), anti-PDL1 (atezolizumab, avelumab, durvalumab) and anti-CTLA4 (ipilimumab, tremelimumab) mAbs (Figure 1). Checkpoint antibodies alter the interaction between immune cells and antigen presenting cells (APCs), including tumour cells. The combination of nivolumab and ipilimumab is a dual checkpoint inhibitor with selective affinity for immune cells expressing PD-1 and CTLA-4 molecules. Currently, this combination of two immune agents is the only FDA-approved (April 2018) immunotherapy for first-line treatment of intermediate- and poor-risk mccRCC, based on the findings of Checkmate214 trial (Table 2). In this phase III study, 1096 patients were randomized (1:1) to receive nivolumab/ipilimumab or sunitinib treatment [49,50]. Median PFS of 11.6 vs 8.4 mo (HR 0.68, p=0.0331), mOS was not reached with nivolumal/ipilimumab vs mOS of 26 mo with sunitinib (HR 0.63, p<0.0001) and ORR of 42% (CR 9%, PR 33%) vs 27% (CR 1%, PR 26%) were reported in intermediate- and poor-risk patients. In the favourable-risk patients, mPFS was 15.3 vs 25.1 mo (p<0.0001) and ORR 29% vs 52% (p=0.0002). In patients with a PD-L1 TPS (tumor proportion score) ≥1%, mPFS was 22.9 vs 5.9 mo (HR 0.48, p=0.0003) and in patients with a PD-L1 TPS < 1% no benefit from this combination was noticed (HR 1, p=0.9670) [49]. In conclusion, in this trial the combination of nivolumab/ipilimumab compared to sunitinib showed significantly higher ORR with 9% CR, and longer PFS in intermediate/poor-risk mccRCC, especially in those with a PD-L1 TPS ≥ 1%.

Predictive biomarkers for first-line therapy of mccRCC

Currently, there are no predictive biomarkers validated in mccRCC. PD-L1 overexpression (25% in ccRCC) appearing to predict response to ICIs, but its role as predictive biomarker is not yet clear. Increased MET expression may help predict response to cabozantinib. VHL mutational status has been assessed for VEGF targeted therapy [51]. FLT1 C/C (single nucleotide polymorphism) seems to predict inferior PFS and ORR to sunitinib therapy [52]. Other potential biomarkers for immunotherapy include factors associated with the tumour microenvironment (PD-L2 expression, IDO-1 expression, infiltration of CD8+ T-cells). Gut microbiome and tumour mutational burden have also been reported as predictive biomarkers. Moreover, loss-of-function mutations in the PBRM1 gene and heterozygosity of HLA-1 gene were recently associated with improved response to ICIs [51]. Analysis of genomic and mitochondrial circulating cell-free DNA of a patient's tumour, with a blood draw rather than a biopsy (liquid biopsy), will help guide treatment selection [2].

Selection of current first-line systemic therapy for mccRCC

Active surveillance is considered a viable option for patients with slowly progressing, asymptomatic, low volume disease, although selection criteria have not been validated. Currently, the optimal first-line therapy of mccRCC is still in evolution and research. Prior to the availability of TTs (2006), immunotherapy with cytokines was a well-established approach for thetreatment of mRCC. Thereafter, survival of patients with mRCC has significantly improved, from a mOS of approximately 12 months in the cytokines era to more than 26 months with first-line targeted agents. However, despite the success of targeted therapies, the optimal management of mRCC remains a therapeutic challenge, as complete durable tumor responses are rare and most patients will ultimately experience disease progression, due to the development of treatment resistance [53].

HD IL-2 and the combination of nivolumab/ipilimumab remain the only agents that have shown durable responses in patients with mRCC and, therefore, should be considered as anoption for front-line therapy in selected patients with appro-

priate performance status (0-1) and intermediate/poor-risk patients, respectively [19,49]. However, targeted antiangiogenic agents are widely used in first-line therapy of patients with mccRCC. FDA/EMA have approved a number of targeted agents for this setting (Table 1). In the absence of predictive biomarkers, treatment selection continues to be based on clinical evidence. MSKCC/IMDS prognostic factors are the primary selection criteria for targeted agents.

A. *First-line treatment in patients with favorable to intermediate-risk mccRCC*

Data from phase III RCSs (Table 2) support the use of sunitinib [24,25], pazopanib[26,27] and bevacizumab/IFN-α[35-38] in the first-line setting. FDA/EMA approved all three angiogenic agents as front-line treatment. The NCCN Kidney Cancer Panel [54] has listed sunitinib and pazopanib as a preferred category 1 and bevacizumab/IFN-α as category 1 in first-line treatment.

The choice between sunitinib or pazopanib currently represents the hotest topic of debate. In the first head-to-head phase III trial (COMPARZ), comparing the two alternative treatments for mccRCC, both agents demonstrated prolonged mPFS and mOS, as well as high ORR [28,29]. In this study, pazopanib was found non-inferior to sunitinib in efficacy, but had a lower incidence of reported adverse events and better quality of life. Similarly, other studies, which attempted to elucidate the preferred first-line agent, failed to show any consistent superiority [55]. As a consequence of the COMPARZ trial, which failed to conclusively demonstrate non-inferiority of pazopanib relative to sunitinib, pazopanib should remain an option for patients who prefer pazopanib over sunitinib or patients who are particularly predisposed to some of the toxicities of sunitinib (hematological toxicities, hypothyroidism, hand-foot syndrome) [30].

The combination of two ICIs, nivolumab/ipilimumab, should be considered for intermediate-risk disease for patients who cannot receive a TKI, particularly those who are younger (< 65 years) or with tumours having high PD-L1 TPS.

Bevacizumab combined with interferon-αalso represents an effective first-line alternative for mccRCC. As with sunitinib and pazopanib, longer mPFS and higherORR are reported in AVOREN [35,36] and GALGB [37,38] trials for this combination.

Although bevacizumab combined with IFN-α was characterized as category 1, the need for intravenous administration and the lack of comparative trial against sunitinib or pazopanib represent two of its drawbacks.

Sorafenib is the first VEGFR-TKI approved by FDA for initial therapy in patients with mccRCC [21,22]. However, the NCCN Kidney Cancer Panel no longer recommends sorafenib as first-line treatment. However, sorafenib is still widely used internationally due to its affordability, efficacy and safety. This targeted agent remains an appropriate option for the first-line treatment in these countries.

Tivozanib, a selective TKI, was compared with sorafenib in a Phase III TIVO-1 study. mPFS 11.9 vs 9.1 mo (p=0.042) and mOS almost similar in the two arms was reported [33,34]. Tivozanib was approved by EMA as first-line therapy in mRCC. However, there was not FDA approval due to the lack ofsignificant advantage, in terms of survival, compared to sorafenib.

Considering the adverse events of first-line agents, TKIs should not be administered to patients with severe hepatic impairment, before and following major surgery and in patients with uncontrolled hypertension, active bleeding or symptomatic cardiovascular disease. Immunotherapy is contraindicated in patients with autoimmune disease, neuromuscular disorders and patients receiving immunosuppressive treatment.

B. *First-line treatment in patients with poor-risk mccRC*

Nivolumab/ipilimumab should be considered preferred therapy for patients with poor-risk, as the combination offers durable responses and the potential for CR, which extends OS [54,56]. Dual checkpoint inhibition, with the mAbs nivolumab (anti-PD1) and ipilimumab (anti-CTLA4), was compared to sunitinib as first-line treatment in patients with mccRCC (Checkmate-224 trial) [49]. In this study, 1096 patients were stratified in favorable-(23%), intermediate-(30%) and poor-risk (47%) groups. Median PFS of 11.6 vs 8.4 mo (p=0.0331), mOS was not reached with nivolumab/ipilimumab vs mOS of 26 mo with sunitinib (p<0.0001) and ORR of 42% (CR 9%) vs 27% (CR 1%) were reported. Significantly longer mPFS (22.9 vs 5.9 mo, HR 0.48, p=0.0003) was found in patients with a PD-L1 TPS ≥ 1%. Based on these results, FDA approved (April 2018) the combination of nivolumab/ipilimumab as first-line treatment for intermediate- and poor-risk patients with mccRCC. After that, the NCCN Kidney Cancer Panel has listed nivolumab/ipilimumab as preferred category 1, for intermediate and poor-risk patients [54].

Temsirolimus, in the phase III NCT0065468 trial, which included 626 patients (69% with poor- and 31% with intermediate-risk character-

istics), achieved longer mPFS and mOS compared to IFN-α and temsirolimus/IFN-α [43]. FDA/EMA (2007) approved temsirolimus as first-line therapy for poor-risk patients with mccRCC and the NCCN Kidney Cancer Panel has listed [54] temsirolimus as category 1 for front-line therapy of poor-risk patients.

In a recent study [55], pazopanib was compared to sunitinib as first-line therapy in poor-risk mRCC. With median follow-up of 14.2 mo, mOS 14.4 vs 8.9 mo (p=0.03) and mPFS 9.8 vs 4.3 mo (p=0.04) were reported. Pazopanib and sunitinib are both active and well tolerated, but pazopanib might be more effective. Of note, 3%, 6% and 10% poor-risk patients were included in the basic trials of pazopanib [26,27], sunitinib [24,25] and bevacizumab/IFN-α [35-38], respectively.

Cabozantinib was compared to sunitinib in the phase II CABOSUN trial [31]. Significantly prolonged mPFS (8.2 vs 5.6 m, p=0.03) and ORR (46% vs 18%) were reported in intermediate- (81%) and poor-risk (19%) patients with mccRCC. Based on this trial FDA/EMA approved (2017/2018) cabozantinib for first-line treatment. NCCN Panel has included [54] cabozantinib as category 2A for first-line treatment of intermediate and poor-risk patients.

Currently, first-line treatment with sunitinib or pazopanib is suggested for favorable- and intermediate-risk mccRCC [76], as well as nivolumab/ipilimumab in selected patients with intermediate-risk disease.

For poor-risk patients, nivolumab/ipilimumab is suggested as first-line therapy, although cabozantinib, temsirolimus, sunitinib and pazopanib are also recommended. Cabozantinib is the preferred treatment for patients who are contra-indicated or who cannot tolerate ICIs. Recently, pazopanib overperformed temsirolimus in intermediate/poor-risk patients [57]. HD IL-2 treatment is only indicated in selected, favorable-risk younger patients with good performance status (Figure 2).

Emerging first-line systemic therapies for mccRCC

A. *Emerging targets for treatment of mccRCC*

Targeted therapy agents are not cytotoxic but cytostatic, and this leads to the unavoidable development of resistance and disease progression. Future research will be needed to identify collateral or alternative pathways involved in the development of resistance and to establish newly designed

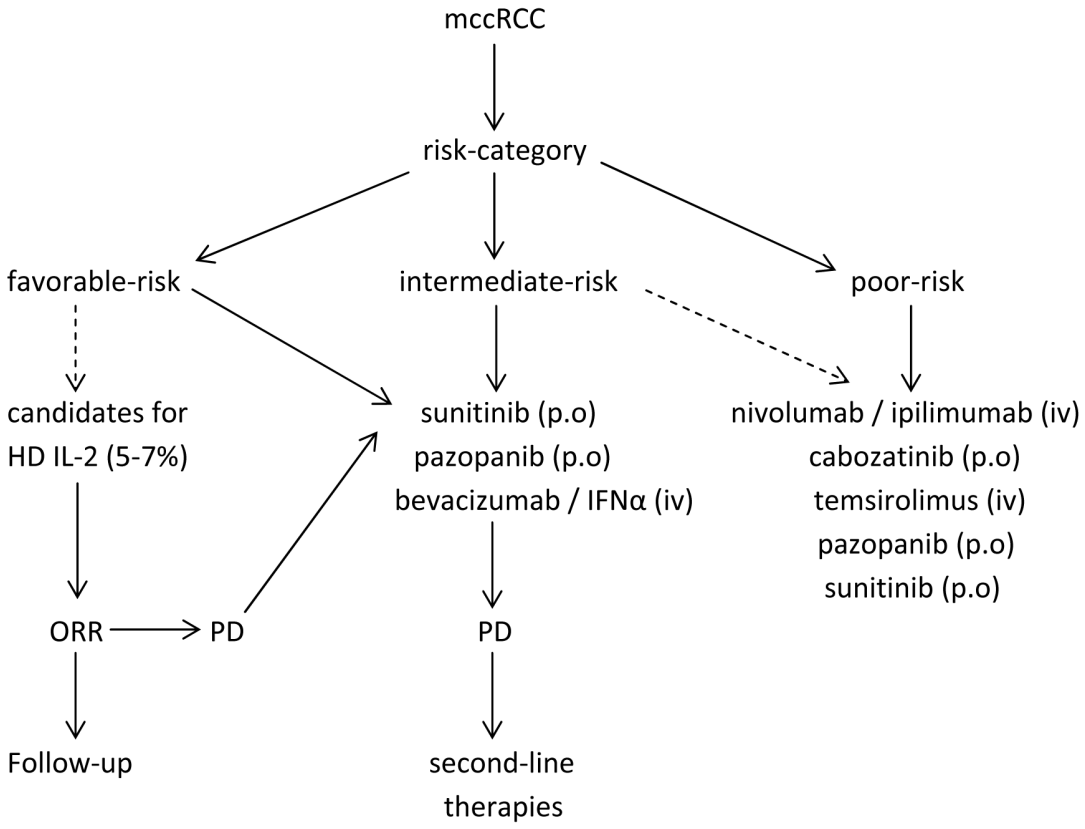

Figure 2. Front-line therapeutic algorithm in mccRCC.
Broken-line : selected patients of this risk group, PD: progressive disease, p.o: per os, iv: intravenous

Table 3. Emerging targets for antiangiogenic therapy in mccRCC

Agent[ref]	*Trial*	*Phase*	*Target*
Brivanib [77]	NCT01253668	II	VEFGR, FGFR
Dalantercept/AXI [70]	DART (NCT01727336)	II	ALK
TRC105/AXI [71]	NCT01806064	II	Endoglin
Crizotinib [72]	PAPMET (NCT02761057)	II	c-MET, ALK
Foretinib [47]	NCT00726323	II	c-MET
Savolitinib [47]	NCT03093980	III	c-MET
PT2385 [73]	NCT03108066	II	HIF-2
Moganulizumab [74]	NCT02281409	I/II	CCR

Table 4. Selected trials, investigating emerging first-line combination therapies in mccRCC

Trial [ref]	Phase	Experimental treatment	Comparator
NCT02811861 [62,63]	III	Pembrolizumab + Lenvatinib or Lenvatinib + Everolimus	Sunitinib
KEYNOTE-426 (NCT02853331) [64]	III	Pembrolizumab + Axitinib	Sunitinib
JAVELIN Renal 101(NCT02684006) [65, 67, 80]	III	Avelumab + Axitinib	Sunitinib
IMmotion–151 (NCT02420821) [75, 81, 82]	III	Atezolizumab + Bevacizumab or Atezolizumab	Sunitinib

targeted agents leading to higher response rates and longer PFS. Emerging targets for antiangiogenic treatment of mccRCC are indicated in Table 3.

B. *Emerging immune targets for treatment of mccRCC*

Naturally occurring macrophages in the tumor microenvironment (TME) (tumor-associated macrophages, TAMs) alter their phenotype and promote oncogenesis. Targeting TAMs with antisense dinucleotides, mAbs or cytokines represents a promising strategy for mRCC therapy [47].

Tumor vaccines (TVs) propagate an immunogenic response in the TME, allowing for the immune cell to evade the immunosuppressing action of RCC. Dendritic cell-based vaccines seem to be the most promising. A recently developed vaccine, IMA901, was investigated in the phase III IMPRINT trial, in which untreated mRCC patients were treated with IMA901 plus sunitinib or sunitinib alone. This study failed to demonstrate any benefit to IMA901 [58]. Another vaccine, AGS-003, used in the phase II setting, reported promising results in combination with sunitinib in unfavorable-risk patients [59].

Ongoing trials are also combining ICIs with novel/investigational immunotherapies, which include NKTR 214 (pegylated IL-2), pegylodecakin (pegyl human IL-2), CPI-444 (antagonist of adenosine A2α receptor) and epacadostat (inhibitor of indoleamine 2, 3-dioxygenase-1) [60].

C. *Selected emerging first-line combination therapies of immune checkpoint inhibitors and antiangiogenic agents in mccRCC*

Based on data of previous phase I and II studies, several phase III trials investigating the efficacy and safety of the combination of ICI with anantiangiogenic agent, in untreated mccRCC, is currently underway (Table 4). Inhibition of the VEGF pathway has been shown to increase T-cell population into the TME and to decrease the activity of T-regulatory cells and myeloid-derived suppressor cells, increasing responsiveness to immunotherapy [61].

Pembrolizumab/lenvatinib vs lenvatinib/everolimus vs sunitinib

Combination treatment with pembrolizumab (anti-PD1 mAb) plus lenvatinib showed promising antitumour activity in mRCC (ORR 63%) and manageable toxicity in the phase Ib/II study [62]. The efficacy and safety of pembrolizumab+lenvatinib and lenvatinib+everolimus versus sunitinib alone, in patients (n = 735, 1:1:1) with treatment-naïve mRCC, are under investigation in the ongoing phase III CLEAR trial (NCT028-11861) [63].

Pembrolizumab/axitinib vs sunitinib

In a phase Ib study (n=52), the combination of pembrolizumab with axitinib (VEGF inhibitor) showed substantial antitumour activity in mRCC

(ORR 71%) and manageable toxicity. The efficacy and safety of pembrolizumab + axitinib versus sunitinib alone will be evaluated in patients (n = 840, 1:1) with treatment-naïve mRCC in the ongoing phase III KEYNOTE-426 trial (NCT02853331) [64].

Avelumab/axitinib vs sunitinib

Avelumab (PD-L1 inhibitor) with axitinib, in the phase Ib JAVELIN Renal 100 trial, induced a response rate of 58.2% (CR 5.5%, PR 52.7%) and a disease control rate of 78.2% in untreated favorable- and intermediate-risk patients with mccRCC [65,66].

In this study, patients with a PD-L1 TPS >1% had ORR 67.9% and patients PD-L1 negative had ORR 50%. The safety profile of this combination therapy with avelumab plus axitinib seemed to be manageable and consistent with that of each drug alone. The promising results of this preliminary study, opened the way to the phase III JAVELIN Renal 101 trial (NCT02684006), comparing avelumab + axitinib to sunitinib monotherapy in untreated patients with mccRCC [67]. Results of this trial announced in the ESMO Congress 2018 showed PFS and ORR benefit in patients treated with avelumab/axitinib, irrespective of PD-L1 expression and across all prognostic risk groups. These results support the combination of avelumab and axitinib as a potential new first-line standard-of-care for patients with mccRCC [80].

Atezolizumab/bevacizumab vs sunitinib

Another combination therapy, involving atezolizumab (PD-L1 inhibitor) + bevacizumab (VEGF inhibitor) was compared to atezolizumab or sunitinib monotherapy, in the IMmotion 150, phase 2, trial (NCT01984242). In this study, untreated patients with a PD-L1 TPS ≥ 1% (n=164), trended towards improved mPFS with the combination of atezolizumab/bevacizumab compared to atezolizumab or sunitinib monotherapy (14.7 vs 6.1 vs 8.4 mo, HR 0.64, p=0.095). Atezolizumab versus sunitinib monotherapy produced similar mPFS (5.5 vs 7.8 mo, HR 1.03, p = 0.917). ORR in all patients was 32% vs 25% vs 29%, and in PD-L1 (+) patients it was 46% vs 28% vs 27%, respectively [68]. Atezolizumab/bevacizumab safety is consistent with the known profile of atezolizumab and bevacizumab individually. The clinical benefit of atezolizumab/bevacizumab versus sunitinib will be evaluated in the ongoing phase III IMmotion 151 (NCT02420821) trial [69]. Initial results reported that atezolizumab/bevacizumab met one of its co-primary endpoints with improved PFS versus sunitinib (11.2 vs 7.7 mo, HR 0.77, p=0.02) in patients with mccRCC and a PD-L1 TPS ≥1%. Improved PFS (11.2 vs 8.4 mo, HR 0.83, p=0.02) was also observed in ITT patients. These results support the use of atezolizumab/bevacizumab as a first-line treatment option in mRCC, irrespective of PD-L1 expression [51,75,81] Moreover, molecular correlates (angiogenesis, T-effector) differentiate response to atezolizumab/ bevacizumab vs sunitinib [82].

The aforementioned successful synergy of antiangiogenic agents and ICIs constitutes an attractive and promising combination regimen for mRCC therapy. In coming years, emerging targeted and other immune therapies, or combinations, will have a profound effect at diminishing tumour resistance to therapy and improving mRFS and OS in patients with mccRCC. Moreover, the development of RCC-specific genomic signatures, guiding selection therapy, is expected to open the way of personalized therapy in mRCC [78,79,82].

Conclusions

a. Transition from HD IL-2 to targeted therapy, and now to novel immuno-therapeutic agents significantly increased the overall survival of patients with mccRCC.
b. Sunitinib and pazopanib (VEGF-TKIs) are currently recommended as first-line therapy in mccRCC, especially in favorable- and intermediate-risk patients.
c. Nivolumab/ipilimumab (dual checkpoint inhibitor) seems to be the preferred first-line therapy in poor-risk and selected intermediate-risk patients.
d. HD IL-2 remains as first-line treatment option in selected, favorable-risk patients with good PS.
e. Emerging, promising combinations of VEGF-TKIs and ICIs, as well as emerging new targeted therapies, and other, beyond ICIs, immunotherapies are currently underway. The therapeutic algorithm of mRCC will soon be completely altered.Everything we have been doing for the last 10 years is likely to become outdated.
f. Patient selection to increase response to a specific agent is still a major challenge. Better biomarkers and predictive models are needed.
g. Soon, development of RCC-specific genomic signatures, guiding selection therapy, is expected to establish personalized therapy in mccRCC.

Conflict of interests

The authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics 2018. CA Cancer J Clin 2018;68:7-30.
2. Gill DM, Hahn AW, Hale P, Maughan BL. Overview of current and future first-line systemic therapy for metastatic clear cell renal cell carcinoma. Curr Treat Options Oncol2018;19:6-17.
3. Howlader N, Noone A, Krapcho M et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site. April 2017; National Cancer Institute. Bethesda, MD; 2017.
4. Srigley JR, Delahunt B, Eble JN et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol 2013;37:1469-89.
5. Leibovich BC, Lohse CM, Crispen PL et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol 2010;183:1309-15.
6. Nickerson ML, Jaeger E, Shi Y et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res 2008;14:4726-34.
7. Brugarolas J. Molecular genetics of clear cell renal cell carcinoma. J Clin Oncol 2014;32:1968-76.
8. Clark PE, Wong MKK, Kaufman HL et al. The role of VHL in clear-cell renal cell carcinoma and its relation to targeted therapy. Kidney Int 2009;76:939-45.
9. Network CCAR. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 2013;499:43.
10. Gossage L, Eisen T, Maher ER et al. VHL, the story of a tumour suppressor gene. Nat Rev Cancer 2015;15:55-64.
11. Thomas GV, Tran C, Mellinghoff IK et al. Hypoxia-inducible factor determines sensitivity toinhibitors of mTOR in kidney cancer. Nat Med 2006;12:122-7.
12. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376:354-66.
13. Mekhail TM, Abou-Jawde RM, Boumerhi G et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 2005;23:832-41.
14. Heng DY, Xie W,Regan MM et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141-8.
15. Xu KY, Wu S. Update on the treatment of metastatic clear cell and non-clear cell renal cell carcinoma. Biomarker Res 2015;3:5-9.
16. Amaria RN, Reuben A, Cooper ZA, Wargo JA. Update on use of aldesleukin for treatment of high risk metastatic melanoma. Immunotargets 2015;4:79-89.
17. Fyfe G, FisherRI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol 1995;13:688-96.
18. Klapper JA, Downey SG, Smith FO et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma: a retrospective analysis of response and survival in patients treated insurgery branch at the National Cancer Institute between 1986 and 2006. Cancer 2008;113:293-301.
19. Clark JI, Wong MK, Kaufman HL et al. Impact of sequencing targeted therapies with high-dose Interleukin-2 immunotherapy: an analysis of outcome and survival of patients with metastatic renal cell carcinoma from an on-going observational IL-2 clinical trial: PROCLAIM SM. Clin Genitourin Cancer 2017;15:31-41.
20. Donskov F, Jensen NV, Smidt-Hansen T, Brondum L, Geertsen P. A randomized phase II trial of interleukin-2 and interferon-α in metastatic renal-cell carcinoma (mRCC): results from the Danish Renal Cancer Group (DaRenCa) study-1. Acta Oncologica 2018. Available from https://doi/10.1080/0284186X.2018.1433324.
21. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal cell carcinoma. N Engl J Med 2007;356:125-34.
22. Escudier B, Eisen T, Stadler WM et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312-8.
23. Escudier B, Szczylik C, Hutson TE et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:1280-9.
24. Motzer RJ, Hutson TE, Pharm D et al. Sunitinib versus interferon alfa in metastatic renal cell carcinoma. N Engl J Med 2007;356:115-24.
25. Motzer RJ, Hutson TE, Tomczak P et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584-90.
26. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061-8.
27. Sternberg CN, Hawkins RE, Wagstaff J et al. A randomized double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013;49:1287-96.
28. Motzer RJ, Hutson TE, Cella D et al. Pazopanib versus sunitinib in metastatic renal cell carcinoma. N Engl J Med 2013;369:722-31.
29. Motzer RJ, Hutson TE, McCann L et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. N Engl J Med 2014;370:1769-70.
30. Escudier B, Porta C, Bono P et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol 2014;32:1412-8.
31. Choueiri TK, Haladi S, Sanford BL et al. Cabozantinib versus Sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or interme-

diate risk: The Alliance A031203 CABOSUN Trial. Ann Oncol 2016;70:7398 and J Clin Oncol 2017;35:591-7.

32. Schmidt E, Lister J, Neumann M et al. Cabozantinib vs standard-of-care comparators in the treatment of advanced/metastatic renal cell carcinoma in the treatment-naïve patients: a systematic review and network meta-analysis.Targeted Oncol 2018;13:205-206.
33. Motzer RJ, Nosov D, Eisen T et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results fron a phase III trial. J Clin Oncol 2013;31:3791-9.
34. Hutson Th, Nosov D, Tomczak P et al. Tivozanib vs sorafenib targeted therapy for advanced renal cell carcinoma: Final results of a phase III trial and efficacy results of a 2nd line tivozanib extension study. J Clin Oncol 2015;33 (Suppl 15), Abstract 4557.
35. Escudier B, Pluzanska A, Koralewski P et al. Bevacizumab plus interferon alfa-2afor treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103-11.
36. Escudier B, Bellmunt J, Negrier S et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis ofoverall survival. J Clin Oncol 2010;28:2144-50.
37. Rini BI, Halabi S, Rosenberg JE et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: GALGB90206. J Clin Oncol 2008;26:5422-8.
38. Rini BI, Haladi S, Rosenberg JE et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma:final results of CALGB 90206. J Clin Oncol 2010;28:2137-43.
39. Rini BI, Garcia JA, Cooney MM et al. A phase I study of sunitinib plus bevacizumab in advanced solid tumors. Clin Cancer Res 2009;15:6277-83.
40. Feldman DR, Baum MS, Ginsberg MS et al. Phase I trial of bevacizumab plus escalated dose of sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:1432-9.
41. Cavaliere C, D' Aniello C, Pepa CD, Pisconti S, Berretta M, Facchini G. Current and emerging treatments for metastatic renal cell carcinoma. Curr Cancer Drug Targets 2017;17:1.
42. Yuan R, Kay A, Berg WJ, Lebwohl D. Targeting tumorigenesis: development and use of Mtor inhibitiors in cancer therapy. J Hematol Oncol 2009;2:45.
43. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advancedrenal cell carcinoma. N Engl J Med 2007;356:2271-81.
44. Rini BI, Bellmunt J, Clancy J et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cel carcinoma: INTORACT trial. J Clin Oncol 2014;32:752-9.
45. Rodriguez-Vida A, Hutson TE, Bellmunt J, Strijbos MH. New treatment options for metastatic renal cell carcinoma. ESMO open 2017;2:e000185.
46. Gill D, Hahn AW, Sonpavde G, Agarwal N. Immunotherapy of advanced renal cell carcinoma: current and future therapies. Hum Vaccin Immunother 2016;12:2997-3004.
47. Zarrabi K, Wu S. Current and emerging targets for metastatic renal cell carcinoma. Curr Oncol Rep 2018;20:41-54.
48. Derosa L, Albiges L, Escudier B. Targeting the PD-1 pathway in renal cell carcinoma: a review. J OncoNephrol 2017;1:179-87.
49. Escudier B, Tannir NM, McDermott DF et al. CheckMate 214: Efficacy and safety of nivolumab+ipilimumab v sunitinib for treatment-naïve advanced or metastatic renal cell carcinoma, including IMDC risk and PD-L1 expression subgroups. ESMO 2017. Ann Oncol 2017;28 (Suppl 5), MDX440.029. Available from HTTPS://DOI.ORG/10.1093 ANNONC/MDX 440.029.
50. Hammers HJ, Plimack ER, Infante JR et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The checkmate 016 study. J Clin Oncol 2017;35:3851-8.
51. Atkins MB, Tannir NA. Current and emerging therapies for first-line treatment of metastatic clear cell renal cell carcinoma. Cancer Treatment Rev, 2018. Available from: https://doi.org/10.1016/j.ctrv.2018.07.009.
52. Beuselinck B, Jean-Baptiste J, Schoffski P et al. Validation of VEGFR1 rs9582036bas predictive biomarker in metastatic clear-cell renal cell carcinoma patients treated with sunitinib. BJU Int 2016;118:890-901.
53. Rodriquez-Vida A, Hutson TE, Bellmunt J, Trijbos MH. New treatment options for metastatic renal cell carcinoma. ESMO Open 2017;2:e000185.
54. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Kidney Cancer. Version 4.2018.
55. Kim JH, Park I, Lee JL Pazopanib versus sunitinib for the treatment of metastatic renal cell carcinoma with poor-risk features. Cancer Chemother Pharmacol 2016;78:325-32.
56. Ljungberg B, Albiges L, Bensalah K et al. EAU guidelines of renal cell carcinoma, 2018. Available from: http://uroweb.org/guideline/renal-cell-carcinoma;2018.
57. Tannir NM, Ross JA, Devine CE et al. A randomized phase II trial of pazopanib versus temsirolimus in patients with advanced clear-cell renal cell carcinoma of intermediate and poor-risk (The Tem/Pa trial). ASCO Annu Symposium, San Francisco 2018, abstract 583.
58. Rini BI, Stenzl A, Zdrojowy R et al. IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicenter, open-label, randomized, controlled, phase 3 trial. Lancet Oncol 2016;17:1599-611.
59. Amin A, Dudek AZ, Logan TF et al. Survival with AGS-003, an autologous dentritic cell-based immunotherapy, in combination with sunitinib in unfavorable risk patients with advanced renal cell carcinoma (RCC): phase 2 study results. J Immunother Cancer 2015; 3:14.
60. Moon YW, Hajjar J, Hwu P et al. Targeting the indoleamine 2,3-dioxygenase pathway in cancer. J Immunother Cancer 2015;3:51.
61. Kwilas AR, Donahue RN, Tsang KY, Hodge JW. Immune consequences of tyrosine kinase inhibitors that synergize with cancer immunotherapy. Cancer Cell Microenvironment 2015;2(1).pii:e677.

62. Lee C, Makker V, Rasco D et al. A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with renal cell carcinoma. 2017 ESMO Congress, abstract 8470.
63. Motzer RJ, Grunwald V, Hutson TE et al. A phase III to compare efficacy and safety of lenvatinib to combination with everolimus or pembrolizumab versus sunitinib alone as first-line treatment of patients with metastatic renal cell carcinoma. J Clin Oncol 2017;35(15 Suppl), abstract TPS4595.
64. Rini BI, Powles Th, Chen M et al. Phase 3 KEYNOTE-426 trial: Pembrolizumab plus axitinib versus sunitinib alone in treatment-naïve advanced/metastatic renal cell carcinoma. J Clin Oncol 2017;35 (Suppl 15):abstract TPS4597.
65. Larkin JMG, Gordon MS, Thistlethwaite F et al. Avelumab in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma. J Clin Oncol 2016;34 (Suppl 15), abstract TPS4580.
66. Choueiri TK, Larkin JMG, Oya M et al. First-line avelumab + axitinib therapy in patients with advanced renal cell carcinoma: Results from a phase 1b trial. J Clin Oncol 2017;35:abstract 4504.
67. Choueiri TK, Rini BI, Larkin JMG et al. Avelumab plus axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma: Phase 3 study (JAVELIN Renal 101). J Clin Oncol 2017;35 (Suppl 15), abstract TPS4594.
68. Atkins MB, McDermott DF, Powels T et al. IMmotion 150: A phase II trial in untreated metastatic renal cell carcinoma patients of atezolizumab and bevacizumab vs and following atezo or sunitinib. J Clin Oncol 2017;35 (Suppl 15):abstract 4505.
69. Atkins MB, McDermott DF, Powels T et al. IMmotion 150: A phase II trial in untreated metastatic renal cell carcinoma patients of atezolizumab and bevacizumab vs and following atezolizumab or sorafenib. 2017 ASCO Annu Meet, abstract 4505.
70. Voss MH, Bhatt RS, Plimack ER et al. The DART study: results from the dose-escalation and expansion cohorts evaluating the combination of dalantercept plus axitinib in advanced renal cell carcinoma. Clin Cancer Res 2017;23:3557-65.
71. Choueiri TK, Michaelson MD, Posadas EM et al. An open label phase IB dose escalation study of TRC105 (anti-endoglin antibody) with axitinib in patients with metastatic renal cell carcinoma. Oncologist 2019;24:202-10.
72. Schoffski P, Wozniak A, Escudier B et al. Crizotinib achieves long-lasting disease control in advanced papillary renal cell carcinoma type 1 patients with MET mutations of amplification. EORTC 90101 CREATE trial. Eur J Cancer 2017;87:147-63.
73. Wallace EM, Rizzi JP, Han G et al. A small-molecule antagonist of HIF2α is efficacious in preclinical modes of renal cell carcinoma. Cancer Res 2016;76:5491-5500.
74. Plitas G, Wu K, Carlson J et al. Phase I/II study of mogamulizumab, an anti-CCR4 antibody targeting regulatory T cells in advanced cancer patienrs. J Clin Oncol 2016; 34 (Suppl 15):abstract TPS3098.
75. Motzer RJ, Powles T, Atkins MB et al. IMmotion 151: a randomized phase III study of atezolizumab plus bevacizumab versus sunitinib in untreated metastatic renal cell carcinoma. J Clin Oncol 2018;36 (Suppl 6S;abstract 578):578 (GUCS 2018).
76. Kyriazoglou A, Dimitriadis I, Bamias A. Developing an algorithm for the management of renal cell carcinoma: focus on metastatic disease. Forum Clin Oncol 2017 8(1). Available at DOI:10.1515/fco-2015.0025.
77. Keefe SM, Rosen MA, Robinson J et al. Results of a feasibility study of I-124 girentuximab in metastatic clear renal cell carcinoma (MCCRCC). J Clin Oncol 2014;32:406. Available at DOI:10.1200/JCO.2014.32.4 Suppl 406.
78. Zarrabi K, Wu S. Current and emerging therapeutic targets for metastatic renal cell carcinoma. Curr Oncol Rep 2018;20:41.
79. Barata PC, Rini BI. Treatment of renal cell carcinoma: Current status and future directions. CA Cancer J Clin 2017;67:507-24.
80. Motzer RJ, Penkov K, Haanen J et al. JAVELIN RENAL 101: Randomised phase 3 trial of avelumab+axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma. ESMO Congress, Munich 2018. Ann Oncol 2018;2 (Suppl 8), abstract LBA6.
81. Escudier B, Motzer RJ, Rini BI et al. Patient-reported outcomes (PROs) in IMmotion 151: Atezolizumab + bevacizumab vs sunitinib in treatment naïve metastatic renal cell carcinoma. J Clin Oncol 2018;36:4511 (ASCO Annu Meet 2018, abstract 4511).
82. Rini BI, Huseni M, Atkins MB et al. Molecular correlates differentiate response to atezolizumab + bevacizumab vs sunitinib: results from a phase III study (IMmotion 151) in untreated metastatic renal cell carcinoma. ESMO Congress 2018. Ann Oncol 2018;29 (Suppl 8), abstract LBA31.
83. George DJ, Hessel C, Halabi S et al. Cabozantinib versus Sunitinib for previously untreated patients with advanced renal cell carcinoma of intermediate or poor risk: subgroup analysis of proggretion-free survival (PFS) and objective response rate (ORR) in the Alliance A031203 CABOSUN trial. ASCO GU 2018. J Clin Oncol 2018;36 (Suppl 6), abstract 582.