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Review

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Individualized therapy for metastatic renal cell carcinoma

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Abstract

Metastatic Renal Cell Carcinoma (mRCC) is a highly heterogeneous disease that is notoriously difficult to treat successfully. However, the discovery of novel, targeted therapies over the last decade has revolutionized its management. As the therapeutic options continue to evolve, developing a more individualized treatment strategy is of paramount importance. The International mRCC Database Consortium (IMDC) is a prognostic model that is commonly used in trials and clinical settings to risk stratify patients. This allows for optimal therapy selection on a more individual basis. However, the distinct lack of validated predictive biomarkers in mRCC renders it difficult to assess therapy response. An improved understanding of tumor biology and genetics has prompted a shift from cytokine therapy to the use of vascular endothelial growth factor (VEGF) inhibitors, tyrosine kinase Inhibitors, immune checkpoint inhibitors or combination strategies. Studies have identified some putative markers and genetic mutations as potential predictors of therapy response. Early results are promising, and there are many ongoing trials further assessing their suitability for clinical use. This review will evaluate the current treatment landscape and molecular biology of mRCC, with a specific focus on the prognostic and predictive markers available to guide treatment options and further improve patient outcomes.

Keywords: Metastatic renal cell carcinoma, IMDC, predictive biomarker, individualized therapy, immunotherapy, VEGF, prognosis

INTRODUCTION

Renal Cell Cancer (RCC) represents 2%-3% of global cancer diagnoses[1]. However, its incidence in the developed world has doubled over the past half-century and is projected to increase[2]. It is the 7th most common cancer in the UK, with around 13,100 new diagnoses each year[3]. About 30% of patients present with metastatic disease at the time of diagnosis and an additional 30% of patients undergoing curative surgery for localized RCC, will develop recurrence or metastases[4].

The systemic treatment for mRCC has evolved substantially over the last decade owing to a better understanding of the underlying biology of RCC. The discovery of the significance of the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways has radically shifted RCC management from interferons in the mid-2000s to novel, targeted agents. More recently, several immune checkpoint inhibitors (ICIs) have joined the therapeutic options of mRCC. The spectrum of overall survival in a vastly heterogenous disease such as mRCC ranges from a few months to many years. Therefore, a risk stratification tool is of paramount importance to guide future individualized treatment decision-making. In addition, predictive biomarkers are critical for developing personalized care in oncology; examples include anti-HER2 antibody in HER2-positive breast cancer and BRAF inhibitors in BRAF mutant melanomas[5]. Unfortunately, no biomarkers currently have equivalent utility in mRCC despite the obvious dependence of this disease on the VEGF pathway.

This article will review the treatment landscape of mRCC, evaluate the available risk prognostication tools and explore potential predictive markers that may help achieve the goal of personalized systemic therapy in kidney cancer.

PROGNOSTIC CLINICAL MODELS

Appropriate treatment selection in clinical practice is facilitated by prognostic stratification. The era of VEGF-targeted therapy saw the development of the International mRCC Database Consortium (IMDC), a clinical model that integrates six variables to stratify patients with mRCC into three prognostic groups (favorable, intermediate and poor-risk) [Table 1]. It incorporates six prognostic factors that correlate independently with overall survival (OS): Karnofsky performance status score of less than 80%, an interval of less than 1 year between diagnosis of RCC and initiation of treatment, corrected serum calcium level greater than 10mg/dL, hemoglobin levels below the lower limit of normal, high absolute neutrophil and platelet count. This has largely superseded the Memorial Sloan Kettering Cancer Centre (MSKCC) model, commonly used in the era of interferon therapy[6,7]. The median OS associated with each prognostic group is 43 months, 23 months, and 8 months in the favorable, intermediate and poor-risk groups, respectively[8]. The IMDC has not only been shown to profile risk using VEGF-targeted agents in the first-line setting, but also in the second and third-line settings[9,10]. Although the IMDC was specifically applicable to anti-VEGF therapy, its positive value has also been demonstrated in patients receiving single or combination immunotherapy[11-13].

THE USE OF PREDICTIVE BIOMARKERS IN METASTATIC RENAL CELL CARCINOMA

There are various histological subtypes of renal cell carcinoma; the most common of these being clear cell RCC (ccRCC), which accounts for over 75% of diagnoses[14]. The molecular heterogeneity within each subtype has affected the success of biomarker discovery and may explain the variable responses to systemic therapies[5]. Therefore interpretation and validation of certain molecular markers will be key to further enhancing the individualized management of RCC.

Table 1. Differences between the MSKCC and IMDC risk prognostication tools for mRCC[6-8]

	MSKCC	IMDC
Prognostic factors		
Low Karnofsky performance (< 80%)	√	√
Time from diagnosis to treatment < 1 year	√	√
Low haemoglobin (< LLN)	√	√
High corrected calcium (> ULN)	√	√
High neutrophils (> ULN)		√
High platelets (> ULN)		√
High LDH (> 1.5 times ULN)	√	
Entry population criteria		
MRCC patient	Interferon as frontline therapy	First-line TKI therapy
Median OS (by risk groups)		
0 criteria (favorable)	29.6 months (95%CI: 20.9-37.8 months)	43.2 months (95%CI: 31.4-50.1 months)
1-2 criteria (intermediate)	13.8 months (95%CI: 12.4-15.9 months)	22.5 months (95%CI: 18.7-25.1 months)
≥ 3 criteria (poor)	4.9 months (95%CI: 4.3-6.3 months)	7.8 months (95%CI: 6.5-9.7 months)

The inactivation of von Hippel-Lindau (VHL) is the most common mutation observed in ccRCC[15]. The loss of VHL leads to hypoxia-inducible factor (HIF) accumulation, which in turn results in the overexpression of pro-angiogenic VEGF and platelet-derived growth factor (PDGF)[15,16]. Sunitinib, a tyrosine kinase Inhibitors (TKI), blocks VEGF and PDGF receptors [Figure 1][17]; it is used as a first or second-line therapy in ccRCC. Research suggests that the loss of VHL is not sufficient to promote oncogenesis, and that mutations of epigenetic regulators such as PBRM1 and BAP1 are required to drive the development of ccRCC[18]. Studies indicate that tumors with *BAP1* mutations are correlated with unfavorable outcomes in both local and metastatic disease[19,20].

The PI3K/AKT/mTOR pathway plays an important role in the tumorigenesis of ccRCC. The mTOR complex regulates cell growth, metabolism and angiogenesis; mutations can lead to dysregulation of these functions[21]. Everolimus and Temsirolimus are mTOR inhibitors approved for use in mRCC [Figure 1][22]. Of the two known mTOR signaling pathways, namely mTORC1 and mTORC2, these therapies only block one (mTORC1), leaving the second downstream signaling of mTOR activation unopposed[23,24]. Research has identified that tumor mutations in mTOR, TSC1 or 2 (mTOR regulators) are more common in patients who clinically respond to mTOR inhibitors[25]. However, one study found that a large proportion of responders had no mTOR pathway mutation detected[25], suggesting that these mutations cannot yet be considered as useful biomarkers.

ICIs are commonly used in the treatment of mRCC. The combination of Nivolumab, a Programmed Cell Death (PD-1) inhibitor and Ipilimumab, a Cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA-4) inhibitor, is an approved first-line systemic therapy[26]. In many malignancies, Programmed Death-Ligand 1 (*PD-L1*) expression has been demonstrated as a reliable predictor of therapy response; however, this is not the case in RCC. The CheckMate-025 and -214 trials recorded respectable response rates with immunotherapy regardless of *PD-L1* expression[27-29]. Unfortunately, its use as a potential biomarker is limited because of tumor heterogeneity and the fact that *PD-L1* expression can be modified by prior VEGF-targeted therapies[30]. Nevertheless, research suggests that a high level of *PD-L1* expression is an unfavorable prognostic factor[30,31].

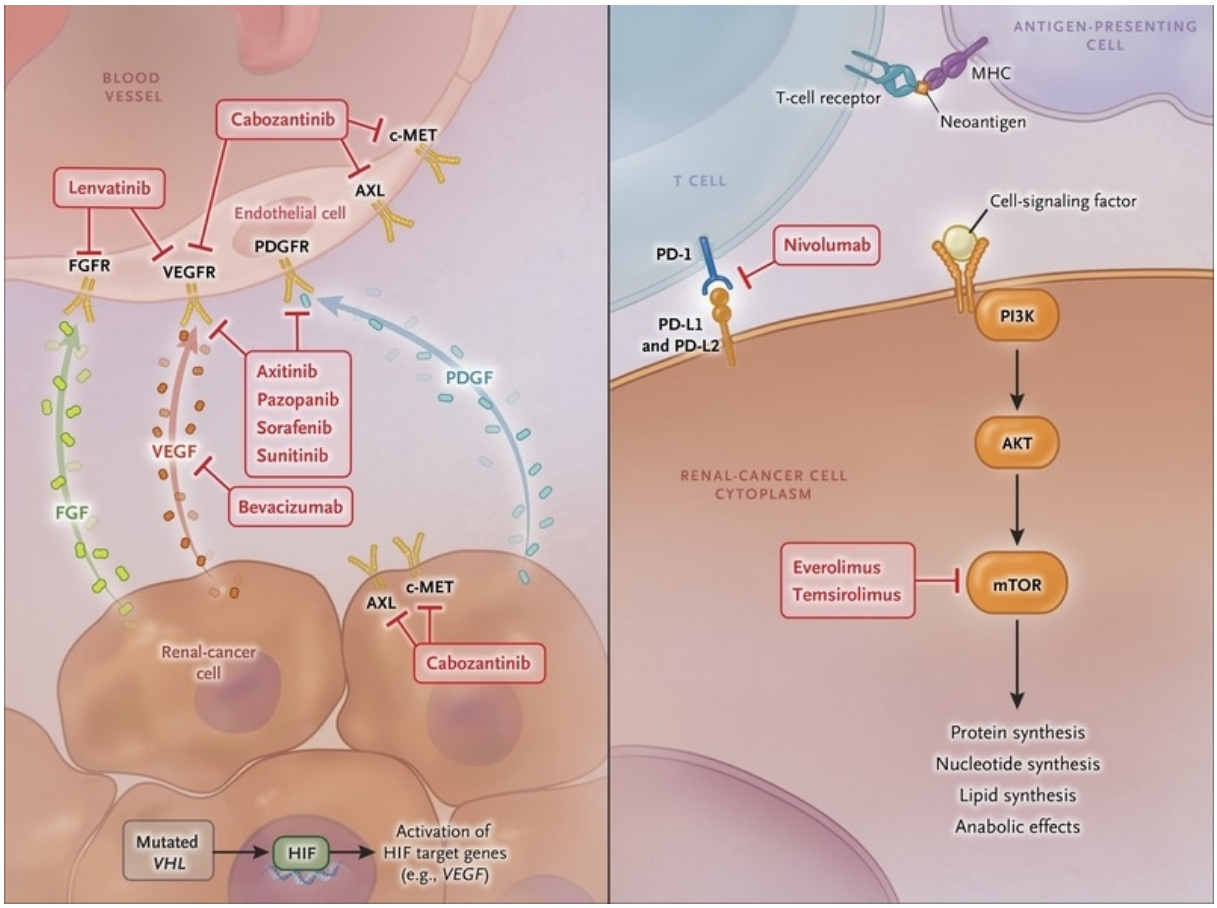

Figure 1. Metabolic pathways and the corresponding drug inhibition in mRCC [Choueiri and Motzer (2017)][46].

Whole exome sequencing of metastatic ccRCC from patients treated with Nivolumab, found that PBRM1 loss was associated with a greater response to immune checkpoint therapy[32]. It has therefore been proposed that the loss of PBRM1 may alter a tumor's responsiveness to immunotherapy[32], although this would need to be validated further before potential clinical use as a predictive biomarker.

The use of gene expression profiling has also been investigated to aid with the prognostication of RCC. Analysis implies that there are two dominant subgroups of ccRCC-type A and type B[33]. Patients with type A tumors have been found to have a significantly improved survival rate[33]. ClearCode-34 is a multigene signature model that can identify these different molecular RCC subtypes; data suggests that, when used in conjunction with the IMDC model, it can improve prognostic accuracy[34].

Non-clear cell renal cell cancer

Approximately 25% of RCC diagnoses are of the non-clear cell subtype[35]. Non-clear cell RCC (nccRCC) consists of several different variants, each with unique histology; the most common of these is papillary RCC (pRCC) in approximately 15% of RCC diagnoses[35]. Like the clear cell, the papillary RCC is also thought to arise from the epithelium of the proximal tubule. Genomic analysis of non-clear cell tumors has identified ten notable gene mutations, including *MET*, *SLC5A3* and *NF2*[35]. The Cancer Genome Atlas Network has established that there are two biologically distinct subtypes of pRCC-type 1 and type 2[36]. Type 1 tumors exhibit a greater number of MET proto-oncogene mutations and type 2 tumors are more heterogeneous in nature; although deletions of the tumor suppressor gene, *CDKN2A*, are associated with

type 2 and a poorer prognosis[36].

Investigating the efficacy of MET-directed therapies in pRCC is an area of ongoing research. A phase II trial demonstrated that the presence of a *MET* mutation in pRCC is highly predictive of a response to the MET inhibitor, Foretinib[37]. Furthermore, Choueiri *et al.*[38] concluded an improved objective response rate (ORR) and progression-free survival (PFS) with MET-driven disease on Savolitinib, another MET inhibitor. Cabozantinib, a TKI, is already approved as a first or second-line therapy in ccRCC[39,40]; the SWOG 1500 trial is currently evaluating its specific use in pRCC due to the prevalence of *MET* mutations in this subtype. The results may alter the nccRCC treatment algorithm and the presence of a *MET* mutation could well be used as a predictive biomarker for nccRCC in the future.

Other less common nccRCC are chromophobe (~5% of cases), oncocytoma (~3%-7% cases) and collecting duct RCC (< 1% of cases), whereas sarcomatoid RCC is no longer considered as a true subtype as sarcomatoid differentiation is associated with all RCC types. Unlike ccRCC and pRCC, these rarer subtypes are thought to arise from the distal nephron, likely the epithelium of collecting tubules. Unlike in ccRCC, *VHL* mutation has not been found in the chromophobe subtype. However, point mutation of *p53* is significantly more common (~25%) as well as upregulation of KIT proto-oncogene, although gene sequencing did not show any activating point mutation[41-44]. Collecting duct RCC meanwhile shows loss of heterozygosity of chromosome 1q, 6p, 13q and 21q[45].

Circulating tumor markers

Circulating tumor DNA (ctDNA) may accelerate biomarker discovery and provide the future solution for a more individualized approach to the management of mRCC.

Analysis has revealed extensive heterogeneity within primary RCC tumors; as such, several genetic mutations may be overlooked by obtaining only a solitary tumor biopsy. Utilizing ctDNA for testing instead provides us with a non-invasive method that could increase the likelihood of detecting genetic alterations[46,47].

A large study by Pal *et al.*[48], which evaluated the use of ctDNA in mRCC, found that genomic alterations were identified peripherally in approximately 79% of patients; this included mutations of *TP53*, *VHL*, *EGFR*, *NF1* and *ARIDIA*. They also noted ctDNA variability during different lines of therapy; there was a substantial increase in mutation frequency observed in patients on subsequent therapy, compared to first-line[47]. This data may help broaden our understanding of therapeutic resistance.

ACTIVE SURVEILLANCE IN METASTATIC RENAL CELL CARCINOMA

The traditional approach of initiating systemic therapy immediately after diagnosing metastatic disease has been challenged in recent years. mRCC is a diverse disease with many different prognostic factors; patients with low-risk or slowly progressive malignancy may instead benefit from an initial period of active surveillance before starting systemic therapy[49]. Several trials and analyses have demonstrated that this approach may be advantageous in certain circumstances.

In 2014, Park *et al.*[49] concluded that, in asymptomatic or minimally symptomatic patients, the response rates and overall survival with deferred systemic treatment were comparable to those without a surveillance period. Given the toxic and non-curative nature of therapy, this regime could positively impact a patient's quality of life.

A similar conclusion was attained from a prospective phase II trial conducted by Rini *et al.*[50]. This study involved 52 asymptomatic, treatment-naïve patients who received regular radiographic follow-up throughout the surveillance period. Results suggested that deferred systemic therapy was favorable for patients with 0-1 IMDC risk factors and < 2 organs with metastatic disease[50].

THE TREATMENT LANDSCAPE OF METASTATIC RENAL CELL CARCINOMA

Cytoreductive nephrectomy

An important element of an mRCC individualized treatment plan is the consideration that whether a cytoreductive nephrectomy (CN) would be of benefit to the patient.

Retrospective analysis of 1658 patients, who all received targeted therapy, demonstrated that, in general, survival outcomes are substantially improved with CN *vs.* without CN[51]. However, patients with a poor prognosis (≥ 4 IMDC factors) may not benefit from CN[46], and offering the procedure to this group could therefore be detrimental. Other factors to consider would be the extent of tumor burden and whether surgery is feasible.

The SURTIME randomized clinical trial investigated whether patient outcomes differed with immediate CN *vs.* deferred CN, after an initial period of Sunitinib before surgery[52]. Bex *et al.*[52] concluded that there was no significant difference between the 28-week progression-free rate; however, there was an improvement in overall survival with the deferred approach.

The CARMENA phase 3 trial comparing CN followed by Sunitinib, with Sunitinib alone in the setting of untreated MSKCC intermediate or poor-risk metastatic ccRCC showed that the median OS was 18.9 months with Sunitinib alone *vs.* 13.9 months with CN followed by Sunitinib (stratified HR for death, 0.89)[53,54]. There were no significant differences in response rate or PFS between both groups. A subsequent analysis, reclassifying patients into IMDC risk groups, demonstrated that in the intermediate-risk group in which 48.1% of patients had only one risk factor, the median OS was 30.5 months *vs.* 25.2 months in those treated with CN followed by Sunitinib *vs.* Sunitinib alone, respectively. For the remaining 51.9% of patients with two risk factors, the median OS was 16.6 months *vs.* 31.2 months with CN followed by Sunitinib *vs.* Sunitinib alone. Thus, the study suggested that those with either 0 or 1 IMDC risk factor should be considered for nephrectomy[53,54].

First-line systemic treatment

In recent years, targeted therapies have supplanted cytokines in the management of mRCC, owing to a better understanding of the biological factors driving cancer growth. A new standard of care was forged in 2007 when the VEGFR-TKI, Sunitinib, outperformed Interferon-alpha in ORR (47% *vs.* 12%) and median PFS (11 months *vs.* 5 months)[55]. Comparison of median disease-specific survival for newly diagnosed mRCC between 1992-2004 (pre-targeted therapy era) and 2005-2009 (targeted therapy era) showed an improvement from 13 months to 16 months[56]. To date, nine targeted drugs have been approved for treating mRCC: Sunitinib, Sorafenib, Pazopanib, Cabozantinib, Tivozanib, Axitinib, Everolimus, Temsirolimus and Bevacizumab (in combination with Interferon-alpha)[22,57].

An improved understanding of the biological immune response to cancer has led to the development of immunotherapy as a new treatment modality for mRCC. PD-1 and CTLA-4 are both expressed on the T cell surface, and their activation leads to a diminishing response of anti-tumor T cells. Enhanced T-cell-mediated toxicity is therefore achieved by the blockade of these pathways with monoclonal antibodies against CTLA-4 (Ipilimumab) and PD-1 (Nivolumab and Pembrolizumab) or their ligand, PDL-1

(Atezolizumab)[58]. The significant efficacy of these new immunotherapy agents in other malignancies, such as melanoma and lung cancer, ignited a burgeoning interest in using immune therapies in mRCC[59,60]. The treatment landscape for mRCC was revolutionized after the FDA approval of Nivolumab and Ipilimumab in April 2018[26]. Since then, three additional combination therapies, Pembrolizumab plus Axitinib, Avelumab plus Axitinib, Nivolumab plus Cabozantinib, have also shown remarkable results, leading to their FDA approvals in April 2019, May 2019, and January 2021 respectively[61-63].

Favorable-risk disease

Sunitinib has been, for many years, the preferred first-line treatment for patients identified as having favorable risk[64]. A large, randomized, phase III trial of treatment-naïve patients demonstrated that the median PFS, ORR and median OS with Sunitinib was 9.5 months, 25% and 29.3 months respectively[64]. A sub-analysis within a network meta-analysis of 15 randomized control trials showed that Sunitinib resulted in a significant PFS benefit compared with Everolimus[22]. This was likely attributable to the difference in the mechanism of action between the TKI and mTOR inhibitors. Sunitinib blocks VEGFR 1, 2 and 3, as well as PDGFR[17]. Whilst the VEGFRs may be the more pertinent targets, PDGF plays a major role in pericyte recruitment on developing tumor vessels[65]. Resistance against antiangiogenic drugs has been associated with the presence of pericyte-covered vessels[65]. As stated above, Everolimus and Temsirolimus only block the mTORC1 activation pathway, leaving mTORC2 signaling unopposed[23,24]. It has been suggested that there may be a potentially synergistic benefit from using combinations of targeted agents that inhibit separate pathways. However, a combination of Temsirolimus plus Bevacizumab, or Bevacizumab plus Interferon-alpha, only provides little survival benefit compared to Sunitinib alone, while the combination of ICI and VEGFR inhibitors as frontline therapy could provide enhanced efficacy in mRCC[22].

In the favorable-risk group, patients treated with Ipilimumab and Nivolumab in CheckMate 214 had ORR and PFS lower than those achieved with Sunitinib {29% *vs.* 52% and 15.3 months *vs.* 25.1 months [Hazard Ratio (HR) = 2.18; $P < 0.001$]}[26]. In ICI and VEGFR studies, a recent meta-analysis showed that Avelumab plus Axitinib is associated with a significant improvement in PFS when compared with Sunitinib[22,62]. However, additional follow-up is required in the JAVELIN Renal 101 trial to prove that this combination of results is a real OS benefit[62]. Another study, CheckMate 9ER, with Nivolumab plus Cabozantinib *vs.* Sunitinib, has shown benefit across all IMDC risk and PD-L1 subgroups at 18.1-month follow-up, although a longer follow-up is required to assess whether the responses are durable[63].

The Favorable-risk disease tends to be associated with increased angiogenesis[66]. PBRM1 is the second most commonly mutated gene in ccRCC, and it plays a role in suppressing hypoxic transcriptional signatures. Its loss in the metastatic setting confers a favorable effect, potentially through the upregulation of VEGF therapy targets, such as HIF[67].

Intermediate/poor risk disease

For patients with IMDC-identified intermediate or poor-risk disease, several different frontline regimes can be considered. The combination of ICIs with VEGFR-TKIs has emerged to be the optimal first-line therapy of choice. In this patient cohort, the CheckMate 214 trial demonstrated the superiority of Ipilimumab plus Nivolumab over Sunitinib [ORR of 42% *vs.* 27% ($P < 0.0001$), PFS of 11.6 months *vs.* 8.4 months (HR = 0.82; 99%CI: 0.64-1.05; $P = 0.03$), median OS not reached *vs.* 26 months][26]. The advantage of using Avelumab plus Axitinib, over Sunitinib, in mRCC patients of all IMDC risk subgroups was demonstrated in the JAVELIN 101 trial, with an ORR of 55.2% *vs.* 25.7% and a median PFS of 13.8 months *vs.* 8.4 months (HR = 0.69; 95%CI: 0.56-0.84; $P = 0.0001$)[62]. The KEYNOTE-426 trial showed an OS benefit in favor of the Pembrolizumab plus Axitinib combination *vs.* Sunitinib at 18 months (82.3% *vs.* 72.1%, $P < 0.0001$)[61]. It also demonstrated an improvement in ORR and median PFS with combination therapy compared with

Sunitinib alone [59.3% *vs.* 35.7% and 15.1 months *vs.* 11.1 months ($P < 0.001$) respectively][61]. A recent Bayesian network meta-analysis suggested that the Pembrolizumab plus Axitinib combination gives optimum OS benefit for mRCC patients with intermediate and poor-risk disease[22].

Another combination treatment study, CheckMate 9ER, with Nivolumab plus Cabozantinib *vs.* Sunitinib, in untreated advanced RCC, showed that at median follow-up of 18.1-month, the median PFS was 16.6 months *vs.* 8.3 months (HR = 0.51; 95%CI: 0.41-0.64; $P < 0.001$) and the median OS was not reached (HR = 0.60; 98.89%CI: 0.40-0.89; $P = 0.001$) with benefit across all IMDC risk and PD-L1 subgroups, and ORR was 55.7% *vs.* 27.1% with the median duration of response of 20.2 months *vs.* 11.5 months, respectively[63].

Recent data from the CLEAR study (study 307)/KEYNOTE-581 with a combination of Pembrolizumab plus Lenvatinib or Lenvatinib plus Everolimus *vs.* Sunitinib in the setting of advanced RCC with no prior systemic therapy showed a significantly better outcome in the combination cohorts compared to Sunitinib alone, with a median PFS of 23.9 months in the Pembrolizumab plus Lenvatinib, 15 months in the Lenvatinib plus Everolimus, and 9.2 months in Sunitinib cohort with benefit seen across all MSKCC or IMDC risk groups. Similarly, the HR for OS in Pembrolizumab plus Lenvatinib *vs.* Sunitinib was 0.66, with benefits seen across all MSKCC and IMDC risk groups, except for IMDC favorable risk. However, in the OS, there was no statistical difference between Lenvatinib plus Everolimus and Sunitinib, pointing to the important role of ICI in the combination strategy. The ORR was 71%, 54%, and 36%, with the complete response rate in these groups being 16%, 10%, and 4%, respectively. These results demonstrated that Pembrolizumab plus Lenvatinib is a meaningful alternative to Ipilimumab plus Nivolumab as a first-line strategy for intermediate or poor-risk patients[68,69].

However, there is a paucity of head-to-head randomized controlled trials directly comparing the effectiveness of all available therapies. Given the variety of regimes available, it is a genuine challenge for clinicians to identify the best treatment option for each patient. Several other first-line clinical trials with combination agents (all in comparison with Sunitinib) are currently pending analyses, including Atezolizumab/Bevacizumab (IMmotion151)[70] [Table 2].

In a patient group for which immunotherapy is contraindicated (e.g., autoimmune disease or patients on > 10 mg baseline Prednisolone), targeted therapies can be considered as first-line. Cabozantinib is a VEGF, MET and AXL inhibitor [Figure 1], and results from the randomized phase II CABOSUN trial demonstrate improved PFS (8.2 months *vs.* 5.6 months) and superior ORR (46% *vs.* 18%) with Cabozantinib *vs.* Sunitinib respectively. In addition, patients with osseous metastatic disease receiving Cabozantinib responded better than those treated with Sunitinib[39].

Agents inhibiting mTOR pathways, such as Temsirolimus, can be used to treat patients with the poor-risk disease. However, they are utilized less commonly than other therapies due to their limited efficacy and laborious administration schedules, which involve weekly infusions[66]. Although they can be considered for patients unable to tolerate oral drugs and those with contraindications to ICIs.

Beyond first-line therapy

A high percentage of patients with mRCC will eventually have disease progression while on first-line therapy, and switching to an alternative agent is recommended; however, the optimal therapy sequence is still an active area of research. Whilst many clinicians choose second-line VEGF-targeted therapy based on response to first-line therapy, a retrospective study of 464 patients receiving both first and second-line VEGF inhibitors demonstrated no correlation between response[71].

Table 2. Selected clinical trials investigating combination therapies in the first-line setting

Study	Treatment *vs.* control	No. of patients	Comparison of median PFS (months *vs.* months)	Comparison of OS (months *vs.* months)
CheckMate 214[26]	Nivolumab/Ipilimumab *vs.* Sunitinib	1096	11.2 *vs.* 8.3	Median OS 48.1 months *vs.* 26.6 months (HR = 0.65; 95%CI: 0.54-0.78)
KEYNOTE-426[61]	Pembrolizumab/Axitinib *vs.* Sunitinib	861	15.1 *vs.* 11.1	12-months OS: 89.9% *vs.* 78.3% (HR = 0.53; $P < 0.0001$)
JAVELIN Renal-101[62]	Avelumab/Axitinib *vs.* Sunitinib	886	13.8 *vs.* 7.0 (in PD-L1 positive population) 13.3 *vs.* 8.0 (in overall population)	OS not yet reported
IMmotion151[69]	Atezolizumab/Bevacizumab *vs.* Sunitinib	915	11.2 *vs.* 7.7 (in PD-L1 positive population)	OS not yet reported
CheckMate 9ER[63]	Nivolumab/Cabozantinib *vs.* Sunitinib	636	16.6 *vs.* 8.3	OS not yet reported
CLEAR (Study 307)/KEYNOTE-581[68,69]	Pembrolizumab/Lenvatinib *vs.* Everolimus/Lenvatinib *vs.* Sunitinib	1069	23.9 *vs.* 14.7 *vs.* 9.2	OS not yet reported

For patients progressing on first-line ICIs, a TKI can be considered. In the phase III METEOR trial, 658 patients, previously treated with a VEGF TKI or ICI, were randomly assigned to receive Cabozantinib or Everolimus. PFS improvement was seen in the Cabozantinib group (7.4 months *vs.* 3.8 months) with a HR of 0.58 (95%CI: 0.45-0.75; $P < 0.001$)[40]. Another phase III study, investigating the use of Tivozanib (a novel EGFR-TKI) *vs.* Sorafenib in the third or fourth-line setting, showed a PFS benefit with Tivozanib across all groups, including approximately 25% of patients previously treated with VEGF-TKI/ICI combination[72].

If a single-agent TKI is used as frontline therapy in mRCC, Nivolumab has recently been approved as a second-line option. The CheckMate 025 trial compared Nivolumab with Everolimus in 821 patients after previous antiangiogenic therapies. The study established that Nivolumab was associated with a significant improvement in OS (25.0 months *vs.* 19.6 months; HR = 0.73) and an increased ORR (25% *vs.* 5%)[27].

The combination of Guadacitabine, a DNA hypomethylating agent, and Durvalumab, a PD-L1 inhibitor, in the setting of advanced ccRCC, has recently been investigated in a single-arm phase Ib/II trial. The first cohort consisted of patients unexposed to ICI and 0 or 1 previous treatments. Recently published data from this cohort of 42 patients, including 36 from phase II with metastatic disease, showed at a median follow-up of 20.1 months, best RECIST 1.1 response was partial response (PR) in 9 patients (22%), stable disease (SD) in 25 patients (61%) and progressive disease in 7 patients (17%), with 1 non-evaluable patient. Sixty-six percent of patients derived clinical benefit, which was defined as PR or SD ≥ 6 months with median OS not reached and median PFS being 17 months[73].

Hypoxia-inducible factor (HIF-2α) is a transcription factor that is a key oncogenic driver in RCC. MK-6482 or Belzutifan, a first-in-class small molecule HIF-2α inhibitor, has been shown to induce tumor regression in mouse xenograft RCC models. The NCT02974738 phase I/II trial investigating Belzutifan in the setting of advanced clear-cell RCC with ≥ 1 prior therapy has shown promising results. In 55 treated patients, with a median number of prior therapies of 3, the ORR was 25%, and the median PFS was 14.5 months. The disease control rates for IMDC favorable risk ($n = 13$) and intermediate or poor risk ($n = 42$) were 92% and 76%, respectively[74].

On-treatment predictive markers

The paucity of predictive biomarkers in mRCC renders it difficult for a clinician to foresee treatment response. In recent years, it has become apparent that on-treatment predictive markers are important in determining response to therapy.

VEGF-targeted therapies e.g., Sunitinib, have common adverse effects which have been identified as potential biomarkers of clinical efficacy. These include hypertension, neutropenia and hypothyroidism[75].

Treatment-related hypertension occurs in approximately one third of patients on Sunitinib[76]. In a large, retrospective study by Rini *et al.*[76], patients with a systolic blood pressure of ≥ 140 mmHg had a significantly improved ORR to Sunitinib, when compared with patients without systolic hypertension. PFS and OS were also longer. Further research suggests that the higher the blood pressure, the greater the systemic VEGF receptor blockade, which in turn, increases the treatment efficacy[77]. However, there is insufficient outcome data to justify changes in ongoing treatment based on these clinical biomarkers only.

Oligometastatic renal cell carcinoma

The most common sites of metastatic disease in RCC are the lung (45%), bone (30%), lymph nodes (22%) and liver (20%)[78].

Sites of metastatic disease can be targeted using local therapies; this can include surgical resection (metastasectomy) and radiotherapy. These local therapies form an important part of an individualized management plan for patients with mRCC. Evidence suggests that a metastatectomy with curative intent is associated with a good long-term survival rate, particularly in younger patients with a long disease-free interval and a solitary site of metastasis[79].

Stereotactic radiation therapy and cryotherapy are two non-invasive local therapies that are increasingly being used for oligometastatic RCC. They are also beneficial when utilized after systemic therapy to suppress residual masses[80]. Aoun *et al.*[81] concluded that cryoablation is a safe and effective procedure in the management of RCC. Additionally, a study by Wang *et al.*[80] reported that 1-year local control rates of extracranial metastatic sites were > 90% post stereotactic radiation therapy.

Emerging data from clinical trials suggests that there may be a direct and abscopal response observed when a combination of immunotherapy and ablative therapy is used to treat mRCC[82]. However, systemic therapy is yet to be proven beneficial following complete resection of metastatic disease; the ongoing ECOG 2810 research study has, thus far, found that treatment with Pazopanib for one year after surgery does not improve chances of survival[83].

CONCLUSION

The development of several novel therapies over recent years has revolutionized the treatment of metastatic RCC. The use of ICIs and TKIs, and their combinations, across multiple lines of therapy, have significantly improved the overall survival of patients. However, it is now becoming increasingly important for us to establish a more individualized treatment plan for mRCC, using both clinical and biological prognostic factors to guide us.

The IMDC, a clinical prognostic tool, is routinely used in practice worldwide; the model stratifies risk into three groups: favorable, intermediate and poor. Nevertheless, there is a distinct paucity of research that demonstrates any reliable predictors to therapy response. Advances in tumor genomic profiling have

revealed potential predictive biomarkers, but further data is required before these can be used to aid clinical decision-making.

Ongoing research trials will likely continue to discover new and improved combination therapies which will further expand our capabilities of treating mRCC successfully. If we can predict who will respond to these therapies, by integrating valid biomarker data into existing prognostic tools, the development of more robust individualized RCC treatment plans will become a real possibility in the future.

DECLARATIONS

Authors' contributions

Made substantial contributions to literature review required for the manuscript as well as writing and editing it: Atmaja B, Wood I

Contributed to writing and editing the manuscript: Suyanto S, Sawhney P, Michael A, Pandha HS

Authors contributed equally.

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Conflicts of interest

Suyanto S is employed by Eisai Ltd., but this review paper does not represent the view of Eisai Ltd. Suyanto S is affiliated with Royal Surrey County Hospital. The remaining authors declared that there are no conflicts of interest

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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