REVIEW

Reviewing Treatment Options for Advanced Renal Cell Carcinoma: Is There Still a Place for Tyrosine Kinase Inhibitor (TKI) Monotherapy?

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ABSTRACT

Renal cell carcinoma (RCC) comprises a highly heterogeneous group of kidney tumours built upon distinct genetic- and epigenetic-driven mechanisms and molecular pathways. Therefore, responsiveness to treatment is considerably variable across patients, adding an extra layer of complexity to the already challenging therapeutic decision process. The last decade brought an unprecedented shift in the medical approach to advanced or metastatic RCC; in fact, immunotherapy-based combinations have significantly transformed the therapeutic arsenal and clinical outcomes of these patients. These strategies were quickly adopted by international guidelines committees as the new standards of care. However, this enhanced efficacy comes at the expense of tolerability, with a predictable negative impact on patients' quality of life. Moreover, subgroup and post hoc analyses of the major clinical trials have shown that not all patients benefit equally from these innovative approaches. In this context, a group of experts on kidney cancer met and discussed the state of the art in the field, with a special emphasis on the appropriateness of using monotherapy with an anti-angiogenesis tyrosine kinase inhibitor (TKI) to treat specific subgroups of patients with RCC. This article reviews the main topics that were

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considered to be pertinent for that discussion and establishes the profile of patients for whom TKI monotherapy remains a sensible frontline option by avoiding overtreatment and an unnecessary exposure to treatment-related toxicity.

Key Summary Points

The treatment of advanced or metastatic renal cell carcinoma (mRCC) has changed dramatically over the last decades: an initially unspecific immune approach has evolved into a targeted strategy, which more recently incorporated the simultaneous use of two agents (as opposed to the more traditional monotherapy).

These combinations involve either two immune checkpoint inhibitors (ICIs) or an ICI associated with an anti-angiogenesis drug (usually a tyrosine kinase inhibitor [TKI] targeted at the vascular endothelial growth factor) and were shown to significantly extend survival in a wide range of patients with mRCC.

However, one should take into consideration that the use of two drugs—instead of a single agent—often impacts treatment tolerability and patients' quality of life, while possibly limiting the range of therapeutic weapons available for subsequent therapeutic lines.

Additionally, not all patients benefit equally from combination treatments; whereas these strategies have a highly significant effect in patients with an intermediate or poor prognosis, their advantages are limited in patients with a favourable one.

A group of kidney cancer experts met in a series of virtual meetings to review the evidence related to the aforementioned points and to discuss the pertinence of TKI monotherapy in selected patients with mRCC: the evidence considered to be relevant for that discussion is described in this article, as are the main conclusions reached by the panel.

INTRODUCTION

Renal cell carcinoma (RCC) is a heterogeneous group of malignancies that account for 2% of global cancer diagnoses and deaths [1]. Associated with several risk factors that are characteristic of so-called modern societies, RCC incidence has been rapidly increasing in the developed world, being now the seventh most common neoplasm in these regions [1, 2]. Of note, RCC has the highest fatality rate among urological neoplasms; whereas the overall 5-year survival rate is 76%, this value drops dramatically to 12% in patients with stage IV disease [1]. Also, approximately 30% of patients newly diagnosed with RCC have metastatic disease, while 20–50% of patients treated for localised disease will eventually relapse and progress to the metastatic stage [1, 3]. Importantly, adjuvant therapeutic alternatives are yet to be approved for this setting in Europe.

RCC incidence and mortality rates vary widely according to its subtype; in fact, RCC comprises a group of independent histological entities, which are characterised by distinctive genetic and epigenetic alterations and molecular pathways, and as such, they respond to systemic therapy [4, 5]. The most common RCC subtype is clear cell, which accounts for 70–75% of all cases. From a genetic standpoint, this subtype is characterised by the loss of the short arm of chromosome 3, which encodes the tumour suppression gene *VHL* (von Hippel–Lindau) [4, 6, 7]. The other RCC forms are generally grouped under an umbrella term: the non-clear cell subtypes. Among these, the papillary variant has the highest incidence, comprising 15% of all kidney cancers [4, 6, 8].

Chromophobe RCC, which occurs in 5–10% of all cases, has a typically indolent course, although it is particularly hard to treat once it has metastasized [4, 6, 7]. Collecting duct carcinoma and renal medullary carcinoma account for less than 5% of all RCC cases. These rare subtypes are often aggressive, being generally resistant to most systemic therapy options available to date [6, 7]. Finally, about 5% of all RCC cases have sarcomatoid features; sarcomatoid RCC is usually symptomatic and highly aggressive, and its outcomes tend to be worse than those of non-sarcomatoid cases [9, 10].

Even among the clear cell subtype, advanced or metastatic RCC (mRCC) is known to be highly heterogeneous in terms of clinical progression and treatment outcomes. For that reason, a few prognostic risk models have been developed, of which the two most commonly used are the Memorial Sloan Kettering Cancer Center model (MSKCC) and the International mRCC Database Consortium model (IMDC). The MSKCC model was based on the retrospective analysis of 463 patients with mRCC treated with interferon-α, in whom the authors were able to identify five risk factors: low Karnofsky performance status (less than 80%), high serum lactate dehydrogenase (above 1.5 times the upper limit of normal), low haemoglobin (below the lower limit of normal), high corrected serum calcium (above 10 mg/dL) and a short time-period between the initial diagnosis and systemic therapy onset (less than 1 year) [11]. Patients were then stratified into three categories according to the number of risk factors present: those without risk factors were classified as of favourable risk; those with one or two risk factors were classified as of intermediate risk; and those with three or more risk factors were classified as poor risk. Accordingly, the median overall survival (OS) was 30, 14 and 5 months in each of these groups, respectively [11]. IMDC was developed a few years later, being based on a retrospective analysis of 645 patients with mRCC treated with tumour vasculature-targeted therapy. The IMDC authors retained four MSKCC risk factors—low Karnofsky performance status (less than 80%), high corrected serum calcium (above the upper limit of normal), low haemoglobin (below the lower limit of normal) and a short time-period between initial

diagnosis and systemic therapy onset (less than 1 year)—and added high neutrophil and platelet counts (above the upper limit of normal) [12]. After 2 years, 75% of the favourable-risk patients were still alive, as were 53% of the intermediate-risk patients and 7% of the poor-risk patients [12]. Afterwards, several adjustments were made to these models, either to validate them in a salvage setting [13, 14] or to include other significant factors, such as metastasis location [15]. Still, despite a number of acknowledged limitations, the classical version of these prognostic models remains commonly used both in clinical trials and during routine clinical practice.

The management of advanced or mRCC has changed dramatically over the past 30 years. Initially based on a non-specific immune approach (high-dose interleukin-2 [IL-2] and interferon-α), this strategy evolved to target the tumour vasculature, intracellular oncogenic pathways and the immune system signalling cascade. The new agents added to the mRCC therapeutic armamentarium include vascular endothelial growth factor (VEGF)-targeted molecules, inhibitors of the mechanistic target of rapamycin (mTOR), and novel immune checkpoint inhibitors (ICIs) [3, 6]. Recently, international guidelines have suggested a combination of two of these agents (ICI/ICI or ICI/VEGF-targeted agent) as the best strategy to manage clear cell mRCC [16–18]. However, despite the undeniable benefits of these combination strategies—which were demonstrated in a number of clinical trials—they also represent enhanced toxicity when compared with monotherapy, with a predictable negative impact on patients' quality of life (QoL), and likely limit the choice of subsequent therapeutic lines. Although this may be a result of the specific anti-VEGF tyrosine kinase inhibitor (TKI) used (e.g. pazopanib or sunitinib), the possible high grade of toxicity in a metastatic setting should be taken into careful consideration. However, whether combination treatment is always the most sensible option to treat mRCC is a question yet to be answered. Whereas the efficacy of any treatment is a key factor in the therapeutic decision-making process, avoiding overtreatment and unnecessary toxicity should also be carefully considered. In

this context, a group of Portuguese experts participated in a series of virtual meetings held between February and April 2021, which were aimed at reviewing the clinical evidence concerning the frontline treatment of mRCC, as well as the profile of patients for whom TKI monotherapy is still the best available therapy. The topics considered to be relevant to this discussion are reviewed hereafter, as are the main conclusions reached by this panel of experts. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

THE THERAPEUTIC LANDSCAPE OF MRCC

The first agents to be approved for mRCC treatment were interferon-α and high-dose IL-2. However, despite inducing highly durable responses in a limited number of patients, the efficacy of these drugs was considerably low (the reported response rates were 12% for interferon-α and 15% for IL-2), and their toxicity was rather high (particularly that of IL-2) [5, 6, 19]. As such, they were later replaced by targeted approaches directed at either the endothelium of the tumour vasculature (anti-VEGF drugs) or at the tumour's oncogenic pathways (mTOR inhibitors). Anti-VEGF drugs include orally available TKIs targeting circulating VEGF itself or its receptors (axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib and tivozanib), as well as an intravenously administered anti-VEGF antibody (bevacizumab combined with interferon alfa-2a), whereas mTOR inhibitors include temsirolimus and everolimus [6, 19]. All of these agents have shown a progression-free survival (PFS) benefit over existing alternatives and have been extensively reviewed elsewhere [20–22].

Lately, there has been a resurgence of interest in immunotherapy to treat patients with mRCC; contrary to the initial non-specific approach, the most recent immunotherapy-based strategies successfully target certain immune checkpoints involved in peripheral tolerance. Nivolumab, an anti-programmed cell death 1 (PD-1) antibody that selectively blocks the interaction between PD-1 and its ligand (PD-L1), was the first ICI approved in this setting. When compared with everolimus in previously treated patients, nivolumab was shown to significantly extend OS (25.0 vs 19.6 months; hazard ratio [HR] 0.73; 98.5% confidence interval (CI) 0.57–0.93; $p = 0.002$) and to elicit a higher objective response rate (ORR 25% vs 5%; odds ratio [OR] 5.98; 95% CI 3.68–9.72; $p < 0.001$) [23].

Finally, a major paradigm shift took place in the mRCC therapeutic armamentarium as dual-agent combinations were introduced and, in many cases, replaced the TKI monotherapy strategy as the standard of care (SOC). One of these combinations involves the concerted action of two ICIs: nivolumab + ipilimumab (an anti-CTL4 [cytotoxic T-lymphocyte-associated protein 4] antibody) [24–26]. Still, the majority of these double treatments consist of the combination of an ICI with a VEGF-targeted drug: avelumab + axitinib [27], atezolizumab + bevacizumab [28], pembrolizumab + lenvatinib [29], pembrolizumab + axitinib [30, 31] and nivolumab + cabozantinib [32]. The rationale behind this strategy is the simultaneous attack of two pivotal features of the RCC tumour: angiogenesis and immunogenic regulation. Indeed, by activating the immune system and suppressing vasculature signalling in the tumour microenvironment, these combination strategies should, in theory, overcome the limitations of each drug individually, leading to a durable immunotherapy-induced response sustained by an effective modulation of the tumour microenvironment [33, 34].

International Guideline Recommended Treatment Strategies

Facing this rapidly evolving therapeutic landscape, the international guidelines were adapted to consider the new treatment combinations. Some of these combinations are promising, but are not yet recommended as they have failed to demonstrate a significant OS signal (e.g. avelumab + axitinib and

axitinib + atezolizumab). However, other combinations have been already considered as the new SOC in mRCC. In fact, in an eUpdate published in September 2021, the European Society for Medical Oncology (ESMO) recommends the use of pembrolizumab + lenvatinib, pembrolizumab + axitinib or cabozantinib + nivolumab as first-line treatment for all patients with clear cell mRCC, irrespective of their IMDC risk group (all recommendations, level I, A; ESMO-MCBS v1.1, score 4) [16]. In patients with an IMDC favourable-risk prognosis, sunitinib or pazopanib are potential alternatives to PD-1 inhibitor-based combination treatment because of a lack of clear superiority of PD-1 inhibitor-based combinations over sunitinib in these patients, and the similar effectiveness of sunitinib and pazopanib in the COMPARZ study [35] (level I, B) [16].

The combinations of pembrolizumab + axitinib, cabozantinib + nivolumab and pembrolizumab + lenvatinib are also recommended as a preferred first-line approach for all patients with RCC according to the latest update of the National Comprehensive Cancer Network guidelines (with category 1 as the evidence level) [18]. Additionally, nivolumab + ipilimumab is also considered to be a preferential choice to treat poor- or intermediate-risk patients with clear cell mRCC. However, cabozantinib monotherapy is also acknowledged as a preferential treatment for poor-/intermediate-risk patients according to this organisation, with a 2A evidence level [18].

Finally, the 2021 update of the European Association of Urology (EAU) guidelines also gives immune-based combinations a central role in the clear cell mRCC treatment, recommending pembrolizumab + axitinib, nivolumab + cabozantinib or pembrolizumab + lenvatinib as the SOC for all patients with clear cell mRCC, and the nivolumab + ipilimumab combination in the poor-/intermediate-risk patients (all with a 1b evidence level) [17]. As in the ESMO guidelines, TKI monotherapy is relegated to an alternative option for patients who cannot receive or tolerate ICIs.

Currently Recommended Combination Treatments: Efficacy and Safety Profile

In this section, we review the main evidence available to date concerning the use of combinations to treat clear cell mRCC. We focus on nivolumab + ipilimumab, pembrolizumab + axitinib, nivolumab + cabozantinib and pembrolizumab + lenvatinib, which are recommended by the three organisations cited earlier [16–18], and are the ones with the greatest amount of accumulated evidence.

The pivotal study that led to the approval and subsequent recommendation of nivolumab + ipilimumab was CheckMate-214 [24–26]. The authors of this phase 3 clinical trial analysed the outcomes and safety profile of 1096 patients with previously untreated clear cell mRCC, who were randomised to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for four doses, followed by nivolumab 3 mg/kg every 2 weeks, or sunitinib 50 mg once daily in 6-week cycles (4 weeks on, 2 weeks off) [24–26]. The primary endpoints of this trial were OS, ORR and PFS in the IMDC-defined intermediate-/poor-risk patients, which comprised approximately 77% of the intention to treat (ITT) population. The latest data release corresponds to a median follow-up of 55 months and clearly demonstrates the superiority of nivolumab + ipilimumab over sunitinib in the intermediate-/poor-risk population: in fact, the risk of death for patients in the experimental arm was 35% lower than that of patients in the control arm (HR 0.65; 95% CI 0.54–0.78) [26]. Moreover, despite showing a delayed benefit, PFS was also significantly longer in nivolumab + ipilimumab-treated patients, with 4-year probabilities of 32.7% vs 12.3% (HR 0.74; 95% CI 0.62–0.88). Finally, the ORR was higher among patients in the experimental arm (41.9% vs 26.8%, $p < 0.0001$), as was the proportion of patients achieving a complete response (10.4% vs 1.4%), and the duration of response (HR 0.45; 95% CI 0.31–0.65) [26].

The pembrolizumab + axitinib combination was addressed in the KEYNOTE-426 trial, which included 861 treatment-naïve patients with clear cell mRCC [30, 31]. These patients were

randomised to receive pembrolizumab 200 mg once every 3 weeks + axitinib 5 mg twice daily or sunitinib 50 mg once daily in 6-week cycles (4 weeks on, 2 weeks off) [30, 31]. OS and PFS were the primary endpoints, and the outcomes of both supported the superiority of the combination treatment compared with sunitinib. With a median follow-up of 30.6 months, the HR for OS was 0.68 (95% CI 0.55–0.85; $p = 0.0003$), while the HR for PFS was 0.71 (95% CI 0.60–0.84; $p < 0.0001$) [31]. The ORR in pembrolizumab + axitinib-treated patients was significantly higher than that in sunitinib-treated patients (60% vs 40%; $p < 0.0001$), as was the percentage of patients with complete response (9% vs 3%) and the median duration of response (23.5 vs 15.9 months) [31].

CheckMate-9ER was the phase 3 clinical trial that addressed the efficacy and toxicity of the nivolumab + cabozantinib combination [32]. Briefly, 651 patients with previously untreated clear cell mRCC were randomised to receive nivolumab 240 mg every 2 weeks + cabozantinib 40 mg once daily or sunitinib 50 mg once daily in 6-week cycles (4 weeks on, 2 weeks off) [32]. After a median follow-up of 18.1 months, the primary endpoint (PFS) was met, with a median PFS of 16.6 months among patients in the experimental arm versus 8.3 months in the control arm (HR 0.51; 95% CI 0.41–0.64; $p < 0.001$). There was also a significant difference in OS: the risk of death in nivolumab + cabozantinib-treated patients was 40% lower than that of sunitinib-treated patients (HR 0.60; 98.89% CI, 0.40–0.89; $p = 0.001$). Accordingly, the ORR reported for patients in the experimental arm was higher than that of patients in the control arm (55.7% vs 27.1%; $p < 0.001$), as was the complete response rate (8.0% vs 4.6%) and the median duration of response (20.2 vs 11.5 months) [32].

The pembrolizumab + lenvatinib combination was evaluated in the CLEAR trial of 1069 patients with previously untreated clear cell mRCC [29]. Patients were randomised to receive lenvatinib 20 mg once daily + pembrolizumab 200 mg every 3 weeks, lenvatinib 18 mg once daily + everolimus 5 mg once daily, or sunitinib 50 mg once daily in 6-week cycles (4 weeks on, 2 weeks off) [29]. After a median follow-up of 26.6 months, median PFS (primary endpoint) was longer with pembrolizumab + lenvatinib versus sunitinib (23.9 vs 9.2 months; HR 0.39; 95% CI 0.32–0.49; $p < 0.001$). Pembrolizumab + lenvatinib-treated patients had improved OS versus sunitinib-treated patients, with risk of death being 34% lower with pembrolizumab + lenvatinib (HR 0.66; 95% CI 0.49–0.88; $p = 0.005$). Compared with sunitinib, pembrolizumab + lenvatinib was associated with a higher ORR (71.0% vs 36.1%), complete response rate (16.1% vs 4.2%) and median duration of response (25.8 vs 14.6 months) [29].

Although treatment combinations brought an undeniable benefit to many patients with clear cell mRCC, they did so at the cost of increased toxicity compared with single-agent therapy. Even though a greater proportion of the sunitinib-treated CheckMate-214 patients suffered grade 3 or 4 treatment-related adverse events (TRAEs) (64.1% vs 47.9% of the patients treated with nivolumab + ipilimumab), the percentage of TRAEs leading to discontinuation was higher in the experimental arm (22.7% vs 13.1% in the control arm) [26]. As for the KEYNOTE-426 trial, the incidence of serious TRAEs was higher among patients treated with the combination (28% vs 16%) [31]. Moreover, 21%, 20% and 7% of patients in the experimental arm discontinued pembrolizumab, axitinib and both drugs, respectively, because of the presence of TRAEs, whereas this percentage was 12% among sunitinib-treated patients [31]. In CheckMate-9ER, grade 3 or higher TRAEs occurred in 60.6% of the nivolumab + cabozantinib-treated patients and 50.9% of the sunitinib-treated patients [32]. Additionally, the percentage of patients who discontinued the treatment because of AEs was 19.7% in the experimental arm (6.6% of patients discontinued nivolumab only, 7.5% discontinued cabozantinib only and 5.6% discontinued both) and 16.9% in the control arm [32]. Lastly, in CLEAR, the incidence of grade 3 or higher TRAEs was 71.6% with pembrolizumab + lenvatinib and 58.8% with sunitinib, and AEs led to treatment discontinuation in 37.2% and 14.4% of patients, respectively [29].

Two meta-analyses were carried out to address the toxicity of the combination treatments from a global perspective. One of them, by Quhal et al., included six phase 3 trials and 5121 patients, and considered the following combinations: nivolumab + ipilimumab, avelumab + axitinib, pembrolizumab + axitinib, atezolizumab + bevacizumab, nivolumab + cabozantinib and pembrolizumab + lenvatinib (Table 1) [36]. When compared with sunitinib-treated patients, those treated with nivolumab + ipilimumab had a significantly higher likelihood of discontinuing treatment because of TRAEs, and of having hyperthyroidism, adrenal insufficiency, pneumonitis, colitis and elevated alanine transaminase (ALT) and aspartate transaminase (AST) levels. Likewise, pembrolizumab + axitinib-treated patients had a significantly higher likelihood of having hyperthyroidism, adrenal insufficiency, pneumonitis, colitis, diarrhoea, hand–foot syndrome and elevated ALT and AST levels. Nivolumab + cabozantinib-treated patients had a significantly higher likelihood of discontinuing treatment because of TRAEs. Similarly, pembrolizumab + lenvatinib-treated patients had a significantly higher likelihood of treatment discontinuation due to TRAEs, and of having hyperthyroidism, adrenal insufficiency, pneumonitis, diarrhoea and elevated AST levels. Of note, when compared with sunitinib, all combinations were associated with significantly lower rates of haematological adverse events (AEs) (namely neutropenia, anaemia and thrombocytopenia) [36].

The second meta-analysis, by Rizzo et al., focused on the incidence of gastrointestinal AEs and considered 3059 patients from four phase 3 trials, treated with either sunitinib or one of the following combinations: pembrolizumab + axitinib, nivolumab + cabozantinib, avelumab + axitinib and pembrolizumab + lenvatinib (Table 1) [37]. When compared with sunitinib-treated patients, those treated with pembrolizumab + axitinib or pembrolizumab + lenvatinib had a significantly higher likelihood of experiencing all-grade diarrhoea, grades 3–4 diarrhoea and grades 3–4 decreased appetite. Moreover, the likelihood of experiencing all-grade diarrhoea

was also significantly higher in nivolumab + cabozantinib-treated patients. The likelihood of grades 3–4 nausea and all-grade decreased appetite was higher with pembrolizumab + lenvatinib; however, the likelihood of all-grade nausea was lower with pembrolizumab + axitinib [37].

Risk Stratification and its Clinical Implications: Patients with a Favourable Prognosis

Except for nivolumab + ipilimumab, the recommendations made by the international guidelines concerning the utilisation of treatment combinations are independent of the patients' prognostic risk. This is because the primary efficacy population of CheckMate-214 was limited to poor-/intermediate-risk patients, while the primary efficacy population of both KEYNOTE-426 and CheckMate-9ER included patients classified in all IMDC risk categories. However, the benefit demonstrated by favourable-risk patients when treated with combination treatments seems to be smaller than that shown by those in the intermediate- or poor-risk categories, sometimes lacking significance in its comparison with sunitinib-treated patients. This trend is consistent across all recommended combinations, as shown by a post hoc pooled analysis [38] and as is briefly outlined below for each study.

In CheckMate-214, 23% of the patients allocated to each arm were of favourable risk (as defined by the IMDC prognostic model) [24, 25]. Although excluded from the primary efficacy analysis, these patients were nevertheless included in the ITT population and their outcomes were analysed. Subgroup analyses revealed an almost overlapping pattern of the OS and PFS survival curves of both treatment arms among favourable-risk patients: at 48 months, 65.1% of patients were alive in the nivolumab + ipilimumab arm versus 68.9% in the sunitinib arm (HR 0.93; 95% CI 0.62–1.40), and 25.4% versus 31.6%, respectively, had not progressed (HR 1.84; 95% CI 1.29–2.62) [26]. In fact, the OS and PFS outcomes of favourable-risk patients treated with sunitinib were numerically

Table 1 Risk of adverse events with guideline-recommended combinations compared with sunitinib as reported in meta-analyses

	AE odds ratio (95% CI)			
	Pembrolizumab + lenvatinib	Nivolumab + cabozantinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib
Quhal et al. [36]				
Treatment discontinuation due to AEs	3.40 (2.35, 4.91)	1.89 (1.15, 3.09)	2.01 (1.45, 2.79)	1.15 (0.81, 1.64)
Grade ≥ 3 treatment-related AEs	1.84 (1.28, 2.64)	1.24 (0.83, 1.87)	0.54 (0.42, 0.69)	1.22 (0.92, 1.62)
All-grade events				
Hypothyroidism	2.45 (1.77, 3.41)	1.27 (0.90, 1.77)	0.59 (0.44, 0.80)	1.20 (0.90, 1.59)
Hyperthyroidism	2.36 (1.18, 4.73)	NR	4.93 (2.67, 9.09)	3.77 (2.12, 6.69)
Adrenal insufficiency	37.66 (2.26, 627.51)	NR	23.30 (1.37, 396.35)	13.28 (1.73, 101.96)
Pneumonitis	39.82 (2.39, 662.16)	NR	55.22 (3.36, 908.79)	12.23 (1.58, 94.46)
Grade ≥ 3 events				
Stomatitis	1.95 (1.02, 3.70)	1.49 (0.72, 3.07)	0.73 (0.41, 1.31)	2.03 (1.16, 3.54)
Hand–foot syndrome	1.04 (0.48, 2.25)	1.00 (0.57, 1.76)	0.01 (0.00, 0.15)	7.62 (2.26, 25.65)
Diarrhoea	0.82 (0.27, 2.48)	1.00 (0.32, 3.13)	0.03 (0.00, 0.56)	0.33 (0.09, 1.21)
ALT elevation	1.85 (0.77, 4.42)	16.79 (2.21, 127.37)	3.20 (1.50, 6.85)	4.86 (2.62, 9.03)
AST elevation	3.62 (1.00, 13.10)	10.29 (1.31, 80.86)	2.91 (1.22, 6.93)	3.13 (1.51, 6.48)
Rizzo et al. [37]				
Diarrhoea				
All grades	1.63 (1.20, 2.20)	1.74 (1.27, 2.38)	NR	1.47 (1.12, 1.93)
Grades 3–4	1.91 (1.06, 3.46)	1.49 (0.72, 3.07)	NR	1.92 (1.16, 3.19)
Nausea				
All grades	1.12 (0.82, 1.53)	0.79 (0.55, 1.15)	NR	0.73 (0.54, 1.00)
Grades 3–4	4.43 (0.95, 20.67)	5.03 (0.24, 105.22)	NR	0.49 (0.09, 2.71)
Decreased appetite				

Table 1 continued

	AE odds ratio (95% CI)			
	Pembrolizumab + lenvatinib	Nivolumab + cabozantinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib
All grades	1.51 (1.11, 2.07)	1.23 (0.82, 1.84)	NR	0.80 (0.59, 1.09)
Grades 3–4	2.78 (0.99, 7.79)	1.50 (0.25, 9.07)	NR	4.53 (0.97, 21.10)

AE adverse event

superior to those treated with the nivolumab + ipilimumab combination. Moreover, the ORR at 4 years was significantly higher in sunitinib-treated patients (51.6% vs 29.6% in the experimental arm, $p = 0.0005$), although the rates of complete response and duration of response favoured nivolumab + ipilimumab [26]. Additionally, a post hoc analysis of the CheckMate-214 population stratified by IMDC risk factors showed that the ORR among patients with no risk factors was actually lower with nivolumab + ipilimumab than with sunitinib (39% vs 50%) [39]. Furthermore, while the ORR in sunitinib-treated patients decreases progressively as the number of risk factors increases, the ORR with nivolumab + ipilimumab is approximately the same for all patient risk categories, being actually slightly lower for patients in the favourable-risk category (39% vs 40–44% for patients with 1–6 risk factors) [39].

The KEYNOTE-426 population included approximately 31% of patients with a favourable-risk prognosis, as defined by the IMDC criteria [30, 31]. As in CheckMate-214, the OS curves of these patients have an overlapping pattern: at 2 years, 85.3% of the patients treated with the combination were still alive, which was slightly lower than the 87.7% observed among sunitinib-treated patients (HR 1.06; 95% CI 0.60–1.86; $p = 0.58$) [31]. In the prespecified subgroup analysis by IMDC risk category, the OS benefit was only evident in the intermediate-/poor-risk group (HR 0.63; 95% CI 0.50–0.81; $p < 0.001$) [31]. In the PFS analysis by IMDC risk category, PFS benefits with pembrolizumab + axitinib were generally consistent across the risk categories, although the results in the favourable-risk category did not reach statistical significance (HR 0.79; 95% CI 0.57–1.09; $p = 0.078$). However, a post hoc subgroup analysis showed that the ORR benefit with pembrolizumab + axitinib was consistent across all IMDC risk categories [31].

Approximately 22% of the 651 patients included in the CheckMate-9ER had an IMDC-defined favourable prognosis [32]. In the prespecified subgroup analysis by IMDC risk category, patients in the favourable-risk category had a borderline significant PFS benefit with

nivolumab + cabozantinib (HR 0.62; 95% CI 0.38–1.01), although the associated HR was higher than that of the intermediate-risk (HR 0.54; 95% CI 0.40–0.72) and poor-risk (HR 0.37; 95% CI 0.23–0.58) categories. For OS, there was no significant benefit with nivolumab + cabozantinib in the favourable-risk (HR 0.84; 95% CI 0.35–1.97) or intermediate-risk (HR 0.70; 95% CI 0.46–1.07) categories, but a significant OS benefit was observed among patients in the poor-risk category (HR 0.37; 95% CI 0.21–0.66). Of note, and as reported in KEYNOTE-426, the likelihood of having a higher ORR with nivolumab + cabozantinib versus sunitinib was observed consistently in patients in the favourable-risk (OR 25.9; 95% CI 9.8–40.2), intermediate-risk (OR 28.2; 95% CI 18.3–37.3) and poor-risk (OR 30.5; 95% CI 16.0–43.9) categories [32].

In the CLEAR study, approximately 33% of patients were in the favourable IMDC prognostic risk group [29]. In the prespecified subgroup analysis by IMDC risk category, the PFS benefit with pembrolizumab + lenvatinib was observed across all risk categories, although the HR was slightly higher in the favourable-risk subgroup (HR 0.41; 95% CI 0.28–0.62) than in the intermediate-risk (HR 0.39; 95% CI 0.29–0.52) or poor-risk (HR 0.28; 95% CI 0.13–0.60) subgroups. Similar to the CheckMate-9ER, significant OS benefit was observed in the poor-risk subgroup (HR 0.30; 95% CI 0.14–0.64), but not in the favourable-risk (HR 1.15; 95% CI 0.55–2.40) or intermediate-risk (HR 0.72; 95% CI 0.50–1.05) subgroups [29].

Non-Clear Cell RCC

The medical management of patients with non-clear cell RCC remains a particularly challenging issue. As these subtypes are seldom included in phase 3 trials, the treatment strategies employed are often an extrapolation of what has been evaluated and approved in the setting of the clear cell histology. However, the outcomes of patients with non-clear cell RCC treated with the currently approved systemic therapies are limited, and usually are significantly inferior to those of patients with clear cell RCC. Acknowledging this fact, both the National Comprehensive Cancer Network (NCCN) and the EAU guidelines recommend inclusion of patients with non-clear cell RCC in clinical trials whenever appropriate [17, 18]. However, both of these organisations also recommend the use of sunitinib, based on data from three phase 2 trials that reported a tendency for superiority of this anti-VEGF TKI compared with everolimus (the ESPN [40], ASPEN [41] and RECORD-3 [42] trials). The NCCN guidelines also recommend cabozantinib [18].

The ESMO guidelines are more detailed regarding the management of the non-clear cell RCC subtype [43]. While they maintain the recommendation of including these patients in appropriate clinical trials, cabozantinib is the preferred first-line treatment option for patients with papillary mRCC without additional molecular testing (level II, B) [43]. The SWOG PAPMET trial demonstrated a PFS benefit for cabozantinib over sunitinib (9.0 vs 5.6 months; HR 0.60; 95% CI 0.37–0.97; $p = 0.02$) and higher ORR (23% vs 4%) [44]. Alternative options include sunitinib (level II, B) and pembrolizumab (level III, B; based on KeyNote-426 [30, 31]) without further molecular testing, and savolitinib in MET-driven tumours, where available (level III, C; based on SAVOIR trial [45]) [43]. In fact, in the era of precision oncology, results point to a SOC in non-clear cell RCC that will, in future, be tailored to the specific histology within this broad group of tumours. For example, in patients with papillary type RCC, as stated above, the SWOG PAPMET Trial suggested a PFS benefit with cabozantinib over sunitinib [44], while savolitinib showed promising efficacy compared with sunitinib in the SAVOIR study [45], crizotinib showed sustained disease control in CREATE [46] and foretinib demonstrated antitumour activity in a phase 2 study [47]. These data suggest that treatment preferences for this specific subtype of tumour may change in the future.

Concerning combination therapy in patients with non-clear cell RCC, data are still scarce. The only trial specifically focused on non-clear cell RCC was reported by Gupta et al. [48]. In

this study, nivolumab + ipilimumab was used to treat a small population of 18 patients with varying histological subtypes (papillary, chromophobe, unclassified, renal adenocarcinoma, translocation and medullary). The results were positive overall, with an ORR of 33.3%, a median duration of response of 4.3 months, a median PFS of 7.1 months and a 12-month OS of 64.2% [48]. However, these values are numerically similar to those obtained using anti-VEGF TKIs. Moreover, the efficacy of this combination may vary with the specific subtype of non-clear cell RCC. Tachibana et al. recently highlighted this aspect by showing that the effect of nivolumab + ipilimumab in papillary RCC was inferior to that demonstrated in patients with clear cell RCC, with a lower ORR (14.2% vs 52.1%, $p = 0.06$) and a shorter median PFS (2.4 vs 28.1 months, $p = 0.014$) [49]. Additionally, Tykodi et al. recently presented the outcomes with nivolumab + ipilimumab treatment in a population of patients with previously untreated non-clear cell mRCC [50]. Although based on a small sample ($n = 52$), these results were rather promising, showing a median PFS of 3.7 months and a median OS of 21.2 months [50].

For all the other combinations, the scarcity of data prevents recommendations in the non-clear cell RCC setting. Therefore, as it currently stands, considering an approach with anti-VEGF TKI monotherapy may provide non-inferior benefits with less toxicity than an ICI-based combination.

EMERGING BIOMARKERS

As the number of available systemic therapies increases, therapeutic decision-making has become more complex. Although the MSKCC and IMDC models have value as prognostic markers, their predictive ability regarding treatment sensitivity is suboptimal. Therefore, identifying surrogate markers to categorise tumours according to their main genetic features and molecular pathways, aiding in the selection of the most suitable targeted agents, has long been the focus of several researchers in the RCC field. The many biomarker candidates

being explored have been extensively reviewed elsewhere [51–53] and will not be addressed here. However, a brief comment should be made concerning PD-L1. Given its role in the immune checkpoint blockade, PD-L1 is probably one of the most studied potential biomarkers for PD-1/PD-L1-targeted therapy responsiveness. Despite being acknowledged as a negative prognostic factor, its ability to predict outcomes with ICI therapy is still debatable. In fact, the data gathered to date are limited by the utilisation of different assessment methods and by tumour heterogeneity, making them insufficient to validate PD-L1 as a predictive biomarker [51, 53].

Omics-based approaches are now emerging in the RCC setting in an attempt to identify biologically driven patient subgroups. Considering the role of angiogenesis and immune blockade in RCC tumour development, as well as the complex crosstalk between these two processes, the utilisation of genomics or transcriptomics seems like a sensible strategy to capture the multifaceted nature of this disease. Two recent studies have employed such techniques in the context of combination treatments and will be briefly reviewed here.

One of those studies was the phase 2, open-label BIONIKK trial, which compared the efficacy and safety of nivolumab versus nivolumab + ipilimumab versus TKI monotherapy in patients with treatment-naïve clear cell mRCC [54]. In BIONIKK, 202 patients were categorised according to the expression of a previously defined 35-gene signature; the resulting groups (ccRcc1–4) were not correlated with IMDC risk categories. Patients belonging to ccRcc1 (immune-low) and ccRcc4 (immune-high) were randomised to receive nivolumab or nivolumab + ipilimumab, whereas patients belonging to ccRcc2 (angio-high) and ccRcc3 (normal-like) were randomised to receive nivolumab + ipilimumab or a TKI. The ORR (primary endpoint) was comparable across all subgroups for patients receiving nivolumab + ipilimumab, reported as 39%, 48%, 25% and 53% in the ccRcc1, ccRcc2, ccRcc3 and ccRcc4 groups, respectively. Interestingly, in the ccRcc1 group, the ORR with nivolumab monotherapy was almost half of

that with nivolumab + ipilimumab (21% vs 39%), whereas these values were comparable in the ccRcc4 group (50% vs 53%). Moreover, TKI-treated patients had an ORR similar to that of nivolumab + ipilimumab-treated patients in the ccRcc2 group (54% vs 48%), but the ORR was clearly lower in the ccRcc3 group (0% vs 25%) [54].

Another study, IMmotion 150, included 305 patients with previously untreated mRCC who were randomised to receive atezolizumab monotherapy or atezolizumab + bevacizumab vs sunitinib [55]. This prospective trial included an exploratory biomarker analysis based on the differential expression of a previously defined group of genes related to angiogenesis (Angio^{Low}/Angio^{High}), T-effector and interferon-gamma activity (Teff^{Low}/Teff^{High}) and myeloid inflammatory response (Myeloid^{Low}/Myeloid^{High}). Sunitinib outcomes were better in the Angio^{High} compared with Angio^{Low} patients, both in terms of ORR (46% vs 9%) and PFS (HR 0.31; 95% CI 0.18–0.55). Furthermore, in Angio^{Low} patients, PFS was longer with atezolizumab + bevacizumab than with sunitinib (HR 0.59; 95% CI 0.35–0.98). Conversely, Teff^{High} patients treated with atezolizumab + bevacizumab had an improved ORR (49% vs 16%) and PFS (HR 0.50; 95% CI 0.30–0.86) when compared with Teff^{Low} patients treated with the same combination. Accordingly, PFS outcomes in atezolizumab + bevacizumab-treated patients were better than those of sunitinib-treated patients in the Teff^{High} population (HR 0.55; 95% CI 0.32–0.95). Finally, Myeloid^{High} patients had a worse PFS outcome compared with Myeloid^{Low} patients when treated with atezolizumab (HR 2.98; 95% CI 1.68–5.29]) or atezolizumab + bevacizumab (HR 1.71; 95% CI 1.01–2.88), and atezolizumab-treated Myeloid^{High} patients had a shorter PFS than sunitinib-treated Myeloid^{High} patients (HR 2.03; 95% CI 1.21–3.40) [55].

While both the aforementioned outlined studies had several limitations and require further validation, they suggest that gene expression signatures may hold some discriminatory potential in terms of responsiveness to anti-angiogenic and ICI treatments. Therefore, molecular-based selection of patients may, in

the long run, be the key to personalised medicine in this challenging context.

PATIENTS' PREFERENCES AND OTHER FACTORS WITH IMPACT ON THE THERAPEUTIC DECISION PROCESS

The plethora of agents and combinations currently available to treat patients with mRCC makes the therapeutic decision-making process in this setting particularly complex. Along with efficacy and tolerability, patients' health-related QoL and preferences should also be taken into account. Whereas the former is intimately related to tumour burden, disease progression and treatment safety, the latter is based on the individual perceptions of the risks and benefits of treatment. The studies conducted on this issue have highlighted that patients usually attribute a considerable weight to treatment efficacy, even at the expense of moderate toxicity and administration comfort. In an online survey carried out in September 2020 that included 1136 patients with kidney cancer (411 of whom were on systemic therapy), complete response was chosen as the most important outcome for treatment selection by 58.8% of the respondents [56]. Of note, only 5.7% and 3.7% of all patients chose low risk of toxicity and chance of discontinuing therapy, respectively. Moreover, 42.1% of patients preferred oral therapy versus 10.9% who preferred infusion therapy; however, nearly half of the respondents (47%) were indifferent to the route of administration. Additionally, 86.3% and 71.7% of all patients defined treatment success as tumour size reduction and stable disease, respectively; better QoL and symptom control were part of this definition for 47.7% and 35.1% of the respondents, respectively [56]. Similarly, PFS was ranked as the most important feature in a survey of 138 patients with RCC [57], whereas the probability of living for 3 years or more was considered to be the most important outcome of RCC treatment in a questionnaire completed by 201 patients and 142 physicians [58].

Interestingly, Mansfield et al. demonstrated that the level of patient information was correlated with their willingness to accept treatment-related toxicities [59]. In fact, their survey of 378 patients with RCC (of whom 50% had advanced disease and 31% were on systemic therapy) showed that well-informed patients were more prone to accept treatment-related toxicities, and preferred treatments with a higher chance of having a longer PFS even at the expense of tolerability [59].

mRCC Management in the Context of COVID-19 (Coronavirus Disease 2019) Pandemic

By November 2021, the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic had been responsible for over 252 million cases and over 5 million deaths globally [60]. This major public health emergency represents a unique challenge for oncologists for several reasons. Patients with cancer are more likely to be infected by SARS-CoV-2 and to develop severe infections and die as a result of COVID-19. Moreover, the delivery of cancer care has been severely impacted by the limitation and prioritisation of healthcare resources [61, 62]. In this context, physicians have been asked to reassess cancer treatment risks and benefits, while weighing the risks of COVID-19 infection. This reassessment is particularly relevant for immunotherapy-based approaches, given the unique immune disruptive effect attributed to SARS-CoV-2. So far, based on the available evidence, the risk of COVID-19-associated immune dysregulation in patients with solid tumours seems to be similar to that of the general population [63]. Moreover, ICIs do not seem to predispose patients with COVID-19 and cancer to worse outcomes [64]. However, further studies are needed to understand the risk–benefit relationship of immunotherapy during the ongoing SARS-CoV-2 pandemic.

Not surprisingly, many physicians and oncology care centres adapted their treatment algorithms to consider the added risk of COVID-19 infection. In the specific case of RCC, a survey of 41 experts revealed a decrease in the use of combination therapy, favouring the prescription of TKI monotherapy [65]. Indeed, while pembrolizumab + axitinib was the preferred treatment option in favourable-risk patients for 53% of respondents before the pandemic, only 38% maintained this preference during the pandemic. Conversely, only 13% of the experts preferred single-agent sunitinib or pazopanib to treat these patients before the pandemic, increasing to 35% during the pandemic ($p < 0.001$). As for fit and intermediate-/poor-risk patients, nivolumab + ipilimumab and pembrolizumab + axitinib were the preferred treatment options in the opinion of 80% and 18% of respondents, respectively, before the pandemic. Amidst the COVID-19 risk, the proportion who preferred the ICI/ICI combination decreased to 41%, whereas the proportion who preferred the ICI/VEGF TKI combination increased to 30%, and 29% reported a preference for TKI monotherapy (sunitinib, pazopanib, tivozanib or cabozantinib) [65].

In the context of the pandemic, the NCCN has issued a number of suggestions focused on the management of COVID-19 in patients with cancer [66]. These experts highlight the lack of robust data concerning ICI therapies. While suggesting that interruption of ICI therapy may be advisable in patients with cancer who develop COVID-19, they also consider that this decision should be individualised and should consider the specific ICI and the COVID-19 severity [66]. Additionally, ESMO published a consensus statement aimed at guiding cancer care amidst the COVID-19 pandemic [67]. Among their many recommendations, these experts advocated that ICI treatment should be interrupted when a patient tests positive for SARS-CoV-2 and resumed upon complete resolution of the infection [67]. Moreover, TKI therapy can be withheld in patients with a low tumour burden in the presence of a severe COVID-19 infection and when their oncological disease is stable. Furthermore, in a specific set of recommendations issued exclusively for the management of patients with RCC, ESMO experts recommend that ICI/VEGF TKI or ICI/ICI combinations should be maintained as the SOC for patients with IMDC intermediate- or

poor-risk prognosis, an exception made to particularly challenging healthcare environments [68]. Conversely, VEGF-targeted oral therapy is considered to be an appropriate choice for patients with favourable-risk prognosis when the risk of ICIs is considered to be too high during acute phases of the pandemic [68].

EXPERT COMMENT

The advent of ICIs and their utilisation in combination with VEGF-targeted therapy have revolutionised the treatment landscape of patients with mRCC. The benefits in terms of survival and response rates are undeniable and have brought renewed hope for the management of this disease. However, as often occurs in oncology care, one size does not fit all. In the absence of predictive biomarkers in clinical practice, international guidelines support basing the therapeutic decision on the patient's clinical risk. Yet, the tools used to evaluate this risk were developed when the SOC was either a non-specific immune approach (MSKCC) or VEGF-targeted single agents (IMDC). Although these models seem to maintain their prognostic ability, they are less accurate when it comes to differentiating responsiveness to new combination strategies. Therefore, in the era of personalised healthcare, physicians should attempt to frame the major clinical trial results alongside patient comorbidities, concomitant medications, willingness and ability to withstand treatment AEs, preferences in terms of valued outcomes and route of administration, drug accessibility and costs. An ideal therapy should attain maximum efficacy, while avoiding overtreatment and unnecessary toxicity. On the basis of this premise and on the evidence reviewed above, we strongly believe that TKI monotherapy still holds a key role in mRCC management and should be considered as the preferential frontline alternative to treat the following patients:

- *Favourable-risk patients with a low tumour burden and with an indolent disease progression pattern*: In these patients, who have a good prognosis and who are not in an immediate need of response, both the ICI/ICI and ICI/ VEGF TKI combination options may represent overtreatment, the benefits of which do not justify the associated increased toxicity risk. In fact, as seen in the subgroup analyses outlined earlier, the PFS and OS benefits in favourable-risk patients treated with these combinations are consistently inferior or similar to those of the unselected population. In the case of ICI/VEGF TKI therapy, the utilisation of two mechanisms of action may elicit resistance to both treatments, thereby limiting the sequential options for subsequent therapy lines, a setting in which the lack of evidence is particularly worrisome. Of note, this recommendation for the use of TKI monotherapy excludes patients who, despite having favourable risk, have a high tumour burden or are extremely symptomatic. These patients might benefit from the higher ORRs observed with combination treatment. In selected patients with indolent low-volume disease, active surveillance may also be an option.

- *Patients with a clearly defined angiogenic profile*: While angiogenesis and immune blockade are two hallmarks of RCC, studies on potential biomarkers and molecular profiles suggest that their relative relevance varies between patients. Treatment outcomes in patients with mostly angiogenesis-driven tumours are expected to be maximised when a single anti-VEGF agent is used. While the current lack of available data hampers the identification of these patients during routine clinical practice, future developments in this field should allow for the differentiation of angiogenic from immunogenic tumours, thereby guiding the therapeutic decision-making process from a biological perspective.

- *Patients who have non-clear cell RCC*: Given the lack of data concerning this rare subset of patients, we believe that patients with non-clear cell RCC should either be enrolled in clinical trials or be treated with standard TKI monotherapy. As previously advocated for patients with a favourable-risk prognosis, the utilisation of a single mechanism may have the advantage of saving alternative

treatments for later therapy lines, which could otherwise be exhausted by the development of resistance mechanisms.

- *Patients who are ineligible for combination treatment, either because of the presence of significant comorbidities (namely, immunosuppressed transplant recipients or those with severe autoimmune diseases) or potential drug interactions (e.g. high-dosage steroids), or in patients who are unable to tolerate the added toxicity associated with dual-agent treatment (e.g. elderly and unfit patients)*: A single anti-VEGF drug is likely to be a sensible choice for these patients, given its enhanced tolerability when compared with combination regimens.

- *Well-informed and educated patients who prefer to be treated with a VEGF TKI*: VEGF TKIs are orally administered drugs with a generally manageable safety profile that seldom require hospitalisation; this option may be preferred by patients who value being at home and would rather be on oral therapy only (compared with intravenous therapy). Also, as these drugs can be managed through a telehealth approach or from an outpatient clinic, this option may be particularly desirable in the context of limited healthcare resources during the current SARS-CoV-2 pandemic.

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