A new scenario in metastatic renal cell carcinoma: a SOG-GU consensus

S. Vázquez Estévez[1]; U. Anido[2]; M. Lázaro[3]; O. Fernández[4]; N. Fernández Núñez[1]; N. de Dios Álvarez[3]; V. Varela[2]; B. Campos Balea[1]; S. Agraso[3]; M. C. Areses[4]; L. Iglesias[4]; M. Blanco[2]; S. Maciá[5]; L. M. Anton Aparicio[6]

[1] Medical Oncology Department, Hospital Universitario Lucus Augusti (Lugo), Dr. Ulises Romero, s/n, 27003 Lugo, Spain
[2] Medical Oncology Department, Complejo Hospitalario Universitario Santiago de Compostela, Trav. da Choupana, s/n, 15702 Santiago de Compostela, Spain
[3] Medical Oncology Department, Hospital Álvaro Cunqueiro, Camiño dos Cañotais 44, 36312 Vigo, Spain
[4] Medical Oncology Department, Complexo Hospitalario Universitario de Ourense, Ramón Puga Noguerol, 54, 32005 Ourense, Spain
[5] Oncology Medical Department, Pivotal, Calle Gobelas, no 19, 28023 Madrid, Spain
[6] Medical Oncology Department, Complejo Hospitalario Universitario A Coruña, As Xubias, 84, 15006 A Coruña, Spain

Abstract

Background

This article describes and compares approved targeted therapies and the newer immunotherapy agents.

Materials and methods

This article especially performs an in-depth review of currently available data for tivozanib, explaining its mechanism of action, its safety profle and its role as an efcacy drug in the management of renal cancer.

Results

Despite the fact that the treatment of advanced RCC has been dramatically modifed in recent years, durable remissions are scarce and it remains a lethal disease. For frst- and second-line therapy, there is now growing evidence to guide the selection of the appropriate treatment.

Conclusions

Several TKIs are standard of care at diferent settings. Among those approved TKIs, tivozanib has similar efcacy than others with a better safety profle. The use of prognostic factors is critical to the selection of optimal therapy.

Introduction

Renal cancer is one of the most common malignancies worldwide, being 2–3% of all adult tumors [1]. Approximately 90% of all renal tumors are renal cell carcinomas (RCC) [2].

Over the last 2 decades the incidence of RCC increased approximately 2% worldwide [1]. However, there has been a parallel improvement in survival, with the advent of antiangiogenic drugs, tyrosine kinase inhibitors (TKI), other targeted therapies and immunotherapy [3]. Consequently, cytokine-based treatments, such as interferon-α and interleukin-2 (IL-2), which were formerly standard-of-care treatment, were quickly abandoned or restricted to very selected situations. Several agents targeting the vascular endothelial growth factor (VEGF) pathway (sunitinib, bevacizumab, pazopanib, axitinib) or the mammalian target of rapamycin (mTOR) pathway (temsirolimus, everolimus) were approved since then progressively approved for first-line or later-line use in the treatment of patients with metastatic RCC (mRCC) and became the new standard of care [4,5,6,7,8,9]. As a result, the survival of patients with mRCC has significantly improved [3]. During last years, the treatment of mRCC has experienced a second revolution with the advent of immune checkpoint inhibitors, especially agents targeting the programmed cell death-1 (PD-1) receptor as well as with the advent of new-generation TKIs.

This article describes and compares currently approved targeted therapies and the newer immunotherapy agents, taking into account that the current approach is focused on selecting the most appropriate therapy, based not only in efficacy but also on its safety profile, providing a better quality of life for the patients. This article especially performs an in-depth review of one of the most recently approved tyrosine kinase inhibitors (TKIs), tivozanib, explaining its mechanism of action, its safety profile and its role in the management of mRCC.

Materials and methods

A panel of experts convened to review currently available data for tivozanib and its comparison versus other approved agents. Evidence acquisition is based on the most recent publications of comparative randomized and non-randomized studies as a basis, on moved from there by adding ESMO guidelines update from 2018 [10].

Full electronic searches were performed in the PubMed biomedical literature database using medical subject headings (MeSH), a controlled vocabulary thesaurus. The search phrase was ((("Carcinoma, Renal Cell"[Mesh]) AND tivozanib)) AND ((second-line) OR first line OR (second line)E). Additional searches were carried out in the EMBASE database using the search terms: "tivozanib AND AND renal AND cell AND carcinoma". Conference abstracts published in the annual meeting of the American Society of Clinical Oncology (ASCO) and that of the European Society for Medical Oncology (ESMO) are included in the EMBASE database. The date of the last search was 22 March 2019.

TIVOZANIB: mechanism of action

VEGF-targeted therapies with TKIs were developed as a result of improved understanding of von Hippel–Lindau (VHL) gene mutations leading to the induction of angiogenic protein. VEGF-TKIs currently approved for mRCC include sunitinib, sorafenib, pazopanib, axitinib, cabozantinib and tivozanib [11, 12].

Tivozanib (Fotivda®, EUSA Pharma, Netherlands) is a new oral multi-targeted TKI that potently and selectively blocks all three vascular endothelial growth factor receptors (VEGFR) and has been shown to block various VEGF-induced biochemical and biologic responses in vitro, including VEGF ligand-induced phosphorylation of all three VEGFR 1, 2 and 3, and proliferation of human endothelial cells. The specificity to the VEGFR targets differentiates tivozanib hydrochloride from other available TKIs used in mRCC. Among the three VEGFR, VEGFR-2 at endothelial cells seem to be the key target [13]. VEGF develops its function mainly by binding to endothelial cells and activating VEGFR-2 (also known as KDR) and VEGFR-3 (known as FLT4), with a different join affinity for each of these receptors [14]. Hence, the binding of each VEGFR-TKI activates a different posterior pathway with various results, which lead to tumor proliferation by inducing changes within the tumor vasculature and promoting angiogenesis.

The VEGF pathway is a dominant mediator of tumor angiogenesis, which is essential for tumor development and growth [15]. By blocking the activation of VEGFR, tivozanib inhibits angiogenesis and vascular permeability in tumor tissues, leading to the inhibition of tumor growth. VEGFR2 is a major angiogenic receptor which plays a key role in blood vessels homeostasis, being involved in cancer progression and metastasis, and is the subtype that is strongly linked to inflammatory processes.

A comparison of the potency of VEGFR inhibition for each of the approved TKIs and tivozanib, using the maximum inhibitory concentration values reported (IC50) for each VEGFR, demonstrated that tivozanib is more potent than sunitinib, pazopanib and sorafenib, with a similar potency than axitinib (Fig. 1) [16].

Non-clinical studies confirmed the anti-tumor activity of tivozanib. These in vivo studies, performed on a wide panel of models, including the tumor xenograft models of human RCC, demonstrated anti-tumor effects of tivozanib ranging from significant inhibition of the tumor to complete regression of the tumor [16].

VEGFR inhibition by tivozanib is approximately eight times more potent than c-kit inhibition, the second most potentially inhibited TKI [17].

The pharmacokinetics (PK) of tivozanib is similar in subjects with solid tumors compared to healthy volunteers. Dosing with food was shown not to have a significant impact on the exposure [area under the curve (AUC)] of tivozanib compared to the fasted state [although a reduction in maximum concentration (Cmax) was observed], indicating that tivozanib can be administered in both the fed and fasted states [18].

Following a single-dose administration of tivozanib, absorption is rapid with peak plasma concentrations occurring at approximately 3 h after administration. However, the absorption process is highly variable, probably due to enterohepatic recirculation. Tivozanib is highly bound to albumin (>99%) with no concentration dependence over the range 0.1–5 μM and widely distributed throughout the body with a volume of distribution (Vz/F) about 100 L. Its half-life determined in healthy volunteers is 4.5–5.1 days (108–123 h), longer than sunitinib (40–60 h), pazopanib (30.9 h) sorafenib (48 h) and axitinib (2.5–6.1 h) [18]. This long t1/2 allows to administer a daily dose reaching serum levels well above the inhibitory concentrations of VEGFR. Clearance is similar between acute and chronic dosing indicating no time-dependent changes in PK.
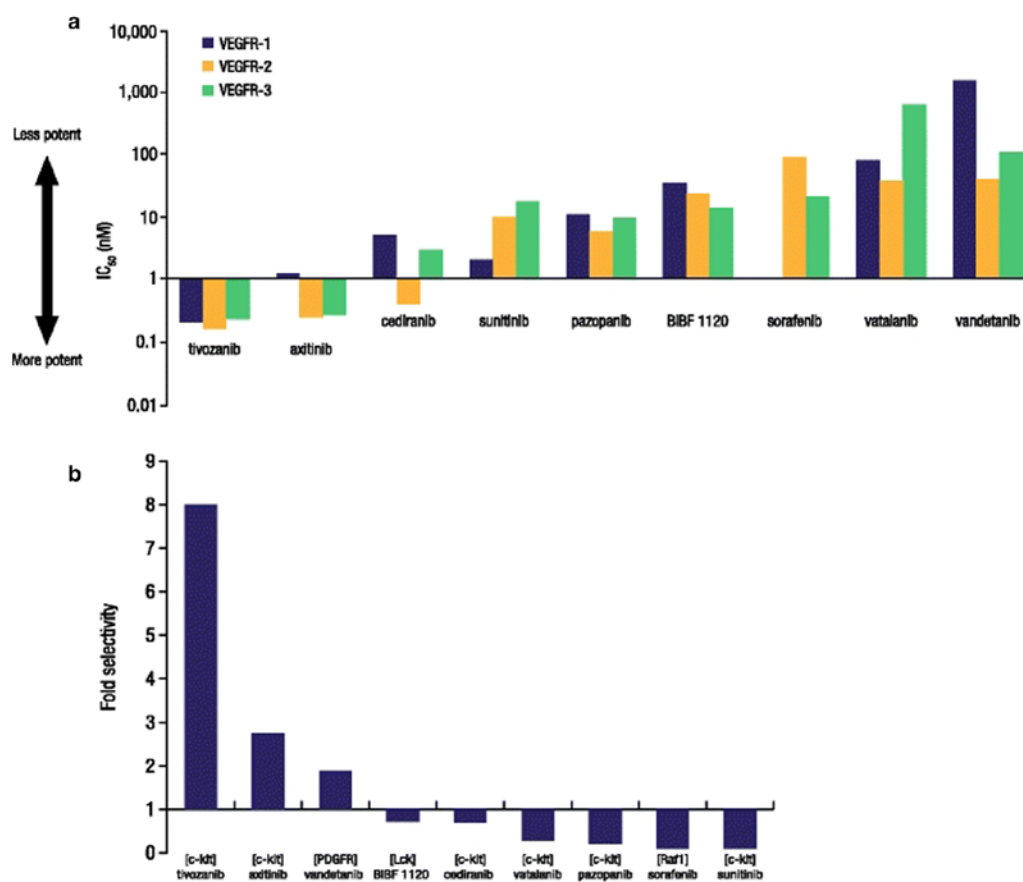
Fig. 1. Relative VEGFR potencies (a) and selectivities (b) for TKIs. Extracted from Pankaj Bhargava and Murray O. Robinson's manuscript "Development of Second-Generation VEGFR Tyrosine Kinase Inhibitors: Current Status"

Safety and tolerability studies in subjects with hepatic impairment show that tivozanib was eliminated more slowly in subjects with moderate (Child–Pugh Class B) or severe (Child–Pugh Class C) hepatic impairment. Tivozanib exposure was increased in patients with severe hepatic impairment and in patients with moderate hepatic impairment. No significant increase in exposure was observed in patients with mild (Child–Pugh Class A) hepatic impairment. Therefore, no dose adjustment is required when administering tivozanib to patients with mild hepatic impairment.

Tivozanib, as opposite to other targeted therapies for mRCC, does not undergo renal excretion, hence, it does not require dose adjustment based on creatinine clearance [18].

Clinical studies with tivozanib were conducted in RCC patients with serum creatinine concentration ≤ 2 times the upper limit of normal, including those who may have had a prior nephrectomy. Although the impact of further impairment of renal function on the overall disposition of tivozanib is unknown, a clinical study has shown that no unchanged tivozanib is excreted in the urine indicating that tivozanib does not undergo renal excretion. According to the population pharmacokinetic analysis of tivozanib exposure, no dose adjustment is required in patients with mild or moderate renal impairment [18]. Clinical experience is limited in patients with severe renal impairment.

Tivozanib can be dosed concomitantly with CYP3A4 inhibitors, unlike other approved TKIs.

Results

Efficacy of first-line treatment for mRCC

First-line treatment in mRCC has been marked by the use of TKIs. Sunitinib, bevacizumab plus interferon and pazopanib showed a benefit in progression-free survival (PFS) in this context compared to either interferon, in patients with either good or intermediate or poor prognosis. Although the combination bevacizumab plus interferon achieved similar benefits [4, 19], oral TKIs were implanted as the standard treatment.

The first TKI that showed activity against interferon-alpha (IFN-α) was sunitinib, in a phase III study that included 750 patients with mainly favorable or intermediate prognosis (with up to 6% poor prognosis in sunitinib arm versus 7% IFN-α arm) according to Memorial Sloan Katering Cancer Center (MSKCC) criteria, and who were randomized to receive sunitinib or IFN-α [20]. The main objective of the study was PFS, which was 6 months longer for the sunitinib arm, 11 versus 5 months (HR 0.42, 95% CI 0.32–0.54; $p < 0.001$). Secondary objectives included response rate (RR), being favorable to sunitinib (31 versus 6%, $p < 0.001$) and overall survival (OS), which was not initially reached. In a subsequent analysis [21], OS was longer in the sunitinib arm (26.4 versus 21.8 months, HR 0.821, 95% CI 0.673–1.001, $p = 0.051$) although it did not reach statistical significance and RR was 47 versus 12% ($p < 0.001$) favorable to sunitinib.

Pazopanib was compared to sunitinib in a non-inferiority study (COMPARZ), PFS being the main objective in the intention-to-treat population. Primary objective was achieved, PFS being 8.4 months for pazopanib and 9.5 months for sunitinib (HR 1.05, 95% CI 0.90–1.22). Overall survival was not inferior for pazopanib and RR was 33% for the pazopanib arm versus 29% for sunitinib arm ($p = 0.12$).

Tivozanib was compared with sorafenib in the TIVO-1 study, as first- or second-line treatment [22]. The study included 517 patients (260 in the tivozanib arm and 257 in the sorafenib arm); 362 received treatment in the first-line setting. Baseline characteristics were well balanced between groups, although tivozanib group had slightly worse conditions (more than 2 metastases locations 33 versus 25%; MSKCC poor prognosis 7 versus 4%, ECOG 1 55 versus 46%). In each treatment arm, around 99% patients had metastatic disease at screening, and around 30% had received a prior treatment for metastatic disease. Most patients had intermediate International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk (173 patients in tivozanib arm; 160 patients in sorafenib arm).

The study showed a favorable benefit to tivozanib in terms of PFS (11.9 versus 9.1 months, HR 0.797, 95% CI 0.639–0.993, $p = 0.042$), leading to EMA approval as first-line treatment and hence, it was first second-generation TKI approved in this setting. In the subgroup of patients receiving first-line treatment (70%), a prespecified analysis showed median PFS was 12.7 months for tivozanib versus 9.1 months for sorafenib with a HR of 0.756 (95% CI 0.580–0.985, $p = 0.037$) [23].

Response rate (RR) was 33.1% for tivozanib (95% CI 27.4–39.2%) versus 23.3% (95% CI 18.3–29.0%) for sorafenib ($p = 0.014$). Median duration of response by independent radiology review (IRR) was 15.0 months for tivozanib compared to 12.9 months for sorafenib [23].

Overall survival (OS) showed a favorable trend to sorafenib, although it was not statistically significant (29.3 versus 28.8 months, HR 1245, 95% CI 0.954–1.624, $p = 0.105$). In this study, 63% of the patients in the sorafenib arm received tivozanib at the time of progression, while only 13% in the tivozanib arm received a next-line targeted therapy. A formal treatment cross-over was not built into the study design; however, patients randomized to sorafenib were given the option of crossing over to tivozanib in extension study AV-951-09-902 upon progressive disease (PD). This

cross-over was potential for confounding and it was concluded that no clear difference in OS has been observed between the two treatment groups [23].

Looking at demographics, there were important differences in terms of geographical regions. Post hoc analysis of PFS and OS data was performed on the 186 patients enrolled in North America and the European Union (US, Canada, Italy, France, UK, Bulgaria, Czech Republic, Romania, Poland, Hungary) to evaluate data by geographical stratification and retain the EU as a single region. This analysis revealed a median PFS in the EU/North America region of 12.9 months versus 7.6 months for sorafenib (p = 0.008) with a HR of 0.597. Additionally, a trend towards longer OS in the tivozanib arm (HR 0.503; 95% CI 0.174–1.451; p = 0.195) was observed in the group of patients from North America/Western Europe (n = 40) [23].

Study 902 was a second-line single-arm study designed as an extension study for TIVO-1 included patients. Patients who developed PD while on prior TKI were crossed over to tivozanib. This study reinforced the high efficacy of tivozanib in terms of anti-tumor activity [24].

Including both studies (TIVO-1 and 902), median PFS by investigator assessment was 14.7 months for tivozanib compared to 9.7 months for sorafenib patients, p = 0.006, HR 0.755 (95% CI 0.617–0.922). For the 161 patients who crossed over to tivozanib, ORR was 18.0% (95% CI 12.4%, 24.8%). Median OS from the start of the first dose was 21.6 months (95% CI 17.0–27.6 months). For patients who remained on initial randomized tivozanib or sorafenib, the ORR was 55.7% (95% CI 44.7%, 66.3%) and 57.1% (95% CI 37.2%, 75.5%) respectively [18].

Cabozantinib was compared to sunitinib in a randomized phase II study (CABOSUN study) with 157 included patients of poor (19%) or intermediate risk (81%) according to IMDC criteria [25, 26]. Up to 36% patients had bone metastasis. Primary objective was met with an improvement in PFS (8.2 versus 5.6 months). The RR was 46% in the cabozantinib arm (95% CI 34–57) versus 18% (95% CI 10–28) in the sunitinib arm. Median OS was better for cabozantinib although it was not statistically significant [26.6 versus 21.2 months for cabozantinib and sunitinib, respectively (HR 0.80, 95% CI 0.53–1.21)] [26].

A retrospective assessment performed by an independent review committee (IRC). This analysis resulted in fewer events compared with the previous investigator analysis. Response rate with cabozantinib was higher when assessed by the investigator, however, the disease control rate with cabozantinib was similar by both assessments.

Cross-study comparisons are confounded by uncontrolled variables in patient characteristics and physician practice. The CABOSUN study included a relatively high incidence of patients with poor prognostic features not explicitly included in the IMDC criteria, such as the presence of bone metastases, greater number of metastatic sites, and worse ECOG PS.

This phase 2 study was designed having a primary endpoint of PFS, and the secondary endpoint of OS was not powered to reach survival differences. The observed improvement in PFS with cabozantinib compared with sunitinib could be secondary to inhibition of MET and AXL by cabozantinib in addition to VEGF receptors. Focusing on the MET status data, 41% were positive in cabozantinib arm versus 38% in sunitinib arm. Subgroup analyses of PFS based on MET expression level favored cabozantinib over sunitinib regardless of MET status. Although the HR more strongly favored cabozantinib for MET-positive versus MET-negative patients, the subgroup size was small and analyses were descriptive.

The new immunotherapeutic drugs have also been compared to sunitinib. The CheckMate 214 study compared the combination of nivolumab (an anti-PD-1 agent) with ipilimumab (anti CTLA-4) versus sunitinib [27]. A total of 1096 patients were included in this study, in which the co-primary objectives comprised OS, RR and PFS in patients included with poor or intermediate prognosis according to IMDC risk groups and stratified by IMDC 0 versus 1–2 versus 3–6, and

geographical region. The survival rate at 18 months was 75% in the arm under study compared to 60% with sunitinib, with a median OS not reached in the combination versus 26.0 months with sunitinib (HR 0.63, p < 0.001). The RR was 42% versus 27% favorable to the combination of nivolumab and ipilimumab (complete responses 9 versus 1%). The median PFS also favored the combination: 11.6 versus 8.4 months (HR 0.82; p = 0.03, not significant by the prespecified 0.009 threshold). In an update presented in ASCO-GU 2019 [28], the complete RR reached 11%. On the other hand, focusing on those patients who had to suspend treatment by protocol [29], it was observed that the treatment-free survival was longer in the arm of nivolumab/ipilimumab, with survival at 3 years of around 20% in this subgroup.

Several combinations of immunotherapy with TKI have also been compared. Among them, results of the KEYNOTE-426 study were recently presented [30], analyzing the combination of axitinib–pembrolizumab versus sunitinib, in patients that were stratified by IMDC risk group and geographic region; its co-primary objectives included OS and PFS in the ITT population. The percentage of patients who were alive at 18 months was 89.9% in the pembrolizumab–axitinib group versus 78.3% in the sunitinib group (HR 0.53, 95% CI 0.38–0.74, p < 0.0001). The median PFS was 15.1 versus 11.1 months in favor of the axitinib/pembrolizumab arm (HR 0.69, 95% CI 0.57–0.84, p < 0.001). The RR also favored the combination: 59.3% versus 35.7% (p < 0.001). In addition, the benefit was observed in all risk groups of the IMDC.

Other combinations of immunotherapy and anti-VEGF have also been studied (atezolizumab–bevacizumab in IMMotion-151, axitinib–avelumab in Javelin Renal 101), although results still await further follow-up [31, 32]. IMMotion-151 study showed longer PFS for atezolizumab plus bevacizumab versus sunitinib in PD-L1-positive patients with a HR of 0.74 (95% CI 0.57, 0.96), with a safety profile consistent with the expected for each of these agents. JAVELIN 101 study also showed a PFS benefit in patients harboring PD-L1 expression, with a HR of 0.63 (95% CI 0.49, 0.81), also assessing other molecular features, such as tumor. There was no relation between PFS and TMB. High-angio GES was associated with significantly improved PFS in the sunitinib arm but did not lead to benefit in PFS.

TiNivo study assessed tivozanib combined with nivolumab in patients who had not been exposed to any of them. This was a phase Ib–II study, including up to 28 patients (6 in dose escalation; 22 in dose expansion) [33]. Results are explained in detailed in the following sections.

First-line treatment for mRCC: intermediate risk criteria group analysis

There are two prognostic models that are used to predict OS in mRCC in the first-line setting: Memorial Sloan Kettering Cancer Center (MSKCC) [34], developed for patients treated with cytokines, but validated for targeted therapies [35], and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [36] for those treated with anti-VEGF.

The MSKCC model [34] uses five clinical and analytical pre-treatment factors (interval between diagnosis and treatment, Karnofsky index, hemoglobin levels, calcium and LDH) to classify patients as good prognosis (0 risk factors), intermediate (1–2 risk factors) and bad (≥ 3 risk factors). The IMDC model [36] uses six pre-treatment clinical and analytical factors (those of the MSKCC except LDH plus platelet and neutrophil levels).

Two recent studies with sunitinib as control arm and focused on the population of intermediate and poor prognosis have shown benefit for their primary objective, OS, and PFS respectively: a phase III study, CheckMate-214 [28], for the combination of nivolumab plus ipilimumab, and a randomized phase II study, CABOSUN [26] for cabozantinib. However, in an exploratory analysis of the CheckMate-214 study, the sunitinib arm obtained better efficacy results than the combination arm in the good prognosis population.

Approximately half of patients diagnosed with mRCC met intermediate prognosis group criteria. The discordant results between the population of good and intermediate prognosis in the CheckMate-214 study lead us to think, taking into account the heterogeneity of the prognostic factors in both classifications, that intermediate risk population could be stratified to better predict the efficacy of the available first-line treatments.

At least four retrospective studies have demonstrated differences in OS between patients with one and two risk factors [37,38,39,40]. A retrospective analysis of the phase III pivotal study of sunitinib versus IFN-α was carried out in the first line of mRCC. Significant differences were found for OS among patients with intermediate prognosis with one or two risk factors independently of the prognostic model (MSKCC: 23.1 versus 16.7 months and IMDC: 28.2 versus 16.3 months) [40].

In the subanalysis of 363 intermediate risk patients of the prospective observational study of real-life pazopanib PRINCIPAL [41], it was found that patients could be stratified by number of prognostic factors (1 versus 2) to predict with a better security the efficacy results in this subpopulation; hence, the heterogeneity of this risk subgroup risk was observed. Median PFS data were obtained (13.8 versus 7.4 months and 13.1 versus 8.1 months for MSKCC and IMDC, respectively) and OS (NA versus 15.2 and 33.9 versus 19.4 months, respectively) in patients with one versus two risk factors. Similar results were obtained when analyzing the population with PS (ECOG) < 2 versus ≥ 2, with a PFS of 11.2 versus 5.6 months and 11.8 versus 2.3 months for MSKCC and IMDC, respectively and OS of 33.9 versus 9.5 and 5 months, respectively.

This stratification of the intermediate prognostic group may have lost importance after recently published results with combinations of axitinib plus pembrolizumab [30] and axitinib plus avelumab [32] versus sunitinib in all risk groups, although it allows us to define more accurately the prognosis of patients diagnosed with mRCC and make decisions on the first line in those patients who are not subsidiary or in whom we do not consider using combinations of anti-VEGF and immunotherapy.

Clinical trials design and included populations

Five pivotal first-line trials design will be analyzed in this section: fase 3 comparing sunitinib versus interferon [5], TIVO-1 which compared tivozanib versus sorafenib [23], CheckMate024 [28], which compared nivolumab plus ipilimumab versus sunitinib, COMPARZ [22], comparing pazopanib versus sunitinib, and CABOSUN [26], comparing cabozantinib versus sunitinib.

At the pivotal study of sunitinib [5], 375 patients were recruited in each arm, stratifying the patients by the value of serum lactate dehydrogenase (LDH), PS-ECOG and prior nephrectomy. The randomization was 1:1. The main objective was PFS and patients had clear cell mRCC. In TIVO-1 [23], 517 patients were recruited and stratified by region, number of previous treatments and number of metastatic locations. In the CheckMate 024 [28], 1096 patients randomized 1:1 to nivolumab–ipilimumab or sunitinib stratified by region and prognostic classification IMDC were included, but both in this study and in the CABOSUN [25], phase 2 study with 157 patients who were of intermediate or poor prognosis and randomized to cabozantinib or sunitinib, while in the other studies all prognostic groups were included. The COMPARZ [22] study randomized 1100 patients, who were stratified by Karnofsky index, LDH and PS-ECOG, but this phase 3 study had a non-inferiority objective. Four of those studies included only naive patients, while in TIVO-1 up to 30% of patients in each arm had received at least one previous treatment (interferon, IL2, chemotherapy, hormone therapy, chemotherapy or clinical trial). In TIVO-1 and CABOSUN studies, patients with stable brain metastases ≥ 3 months were allowed to be included; COMPARZ also allowed it, provided they were stable for at least 6 months (see Table 1).

Table 1 Descriptive comparison among studies ᵃPhase 2 study

	CheckMate214		TIVO-1		COMPARZ		*SUNITINIB*		CABOSUN[a]		JAVELIN 101		KEYNOTE-426	
Treatment	Nivolumab–ipilimumab	Sunitinib	Tivozanib	Sorafenib	Pazopanib	Sunitinib	Sunitinib	*Interferon-alfa*	*Cabozantinib*	Sunitinib	Avelumab+axitinib	Sunitinib	Pembrolizumab + axitinib	Sunitinib
n	*N* = 550	*N* = 546	*N* = 260	*N* = 257	*N* = 557	*N* = 553	*N* = 375	*N* = 375	*N* = 79	*N* = 78	*N* = 442	*N* = 444	*N* = 432	*N* = 429
IMDC	IMDC		IMDC		IMDC		Motzer		IMDC		MSKCC and IMDC: no restriction		IMDC	
Good prognosis	0 (125 ITT)	0 (124 ITT)	70 (27%)	87 (34%)	142 (25%)	137 (225%)	143 (38%)	121 (34%)	–	–	94 (21.3%)	96 (21.6%)	138 (31.9%)	131 (30.5%)
Intermediate prognosis	334	333 (336 ITT)	173 (67%)	160 (62%)	299 (54%)	308 (56%)	209 (56%)	212 (59%)	64 (81%)	63 (80.8%)	271 (61.3%)	276 (62.2%)	238 (55.1%)	246 (57.3%)
Poor prognosis	91	89	17 (7%)	10 (4%)	106 (19%)	94 (17%)	23 (6%)	25 (7%)	15 (19%)	15 (19.2%)	72 (16.3%)	71 (16%)	56 (13%)	52 (12.1%)
Unknown	–	–	–	–	10 (2%)	14 (3%)	–	–	–	–	5 (1.1%)	1 (0.2%)	–	–
Nephrectomy	80% (82% ITT)	76% (80% ITT)	100%	100%	82%	84%	340 (91%)	335 (89%)	57 (72.2%)	60 (76.9%)	352 (79.6%)	355 (80%)	357 (82.6%)	358 (83.4%)

Previous treatment (1)	0	0	78 (30%)	76 (30%)	0	0f	0	0	0	0	0	0	0	0
Primary objective	PFS (*p* < 0.009), OS (*p* < 0.04), ORR (*p* < 0.001)		PFS (*p* < 0.05)		Non-inferiority. PFS. Analysis ITT		PFS by ITT		PFS, also designed to check differences according to MET +		PFS (blinded central review) and OS		OS and PFS (blinded central review)	
Population	First line. Intermediate or poor prognosis		First line. Some patients second line (IFN-α, IL2, chemotherapy, clinical trial)		mRCC clear cell first line		mRCC clear cell first line		mRCC clear cell first line, intermediate or poor prognosis		First line. All prognostic risk groups		mRCC clear cell first line	
	No brain metastases		Brain metastases allowed stable 3 months		Brain metastases allowed stable 6 months		No brain metastases		Brain metastases allowed stable 3 months		Brain metastases allowed stable 3 months		Excluded symptomatic brain metastases	
	IK ≥ 70%		PS0-1		IK ≥ 70%		PS0-1		PS0-2		PS0-1		IK ≥ 70%	
Bone metastases	112 (20%)	119 (22%)	61 (23%)	52 (20%)	110 (20%)	85 (15%)	112 (30%)	112 (30%)	29 (36.7%)	28 (35.9%)	–	–	–	–
Liver metastases	88 (21%)	89 (21%)	67 (26%)	49 (19%)	86 (15%)	110 (20%)	99 (26%)	90 (24%)	–	–	–	–	–	–
PFS	11.6 months	8.4 months	11.9 months	9.1 months	8.4 months	9.5 months	11 months	5 months	8.2 months	5.6 months	13.8 months	8.4 months	15.1 months	11.1

	12.7 months 1L								MET + 13.8 months MET − 6.9 months	MET + 3 months MET − 6.1 months	PD-L1 +: 7.2 months		The benefits of pembrolizumab plus axitinib with respect to overall survival and progression-free survival were observed in all subgroups examined	
	HR 0.82, IC95% (0.64–1.05) $p = 0.03$ mild-poor risk		HR 0.797 95% CI (0.64–0.99), $p = 0.042$		HR 1.05 95% CI (0.90–1.22)		HR 0.42 95% CI (0.32–0.54), $p < 0.001$		HR 0.66 95% CI (0.46–0.95), $p = 0.012$		HR 0.69; 95% CI, 0.56 to 0.84; $p < 0.001$		HR 0.69 (95% CI, 0.57 to 0.84; $p < 0.001$)	
OS	Not reached	26 months	29.3 months	28.8 months	28.4 months 95% CI (26.2–35.6)	29.3 months 95% CI (25.3–32.5)	26.4 months	21.8 months	30.3 months 95% CI (14.6–35.0)	21.8 months 95% CI (16.3–27.0)	–	–	–	–
	HR 0.63 99.8% CI (0.44—0.89), $p < 0.001$ mild risk group		HR 1.245 95% CI (0.95–1.62), $p = 0.105$ 63% (156/162) cross-over 13% patients on tivozanib received further treatment lines		HR 0.91 95% CI (0.76–1.08), $p = 0.28$ log rank stratified		HR 0.821 95% CI (0.673–1.001), $p = 0.051$		HR 0.80 95% CI (0.50–1.26)		–		–	
ORR	42% (RCR 9%)	27% (CR1%)	33.1% (CR 1.2%)	23.3% (CR 0.8%)	31% (CR < 1%)	24.5% (CR < 1%)	47% (CR 3%)	12% (CR 1%)	33% (RC1.3%)	12% (RC 0)	51.4% PD-L1+: 55.2% (CR 4.4%)	25.7% 25.5% (CR 2.1%)	59.3%	35.7 %
	$p < 0.0001$, mild and poor risk groups		$p = 0.014$		$p = 0.03$		$p < 0.001$		–		–		$p < 0.001$	

In all these studies, the percentage of nephrectomized patients was high, ranging from 72% in CABOSUN to 100% in TIVO-1. Primary objective was PFS for all of them except for the CheckMate 024, which had three co-primary objectives: OS ($p < 0.04$), PFS ($p < 0.009$) and RR ($p < 0.001$). In the CABOSUN study, a PS-ECOG of 0–2 was allowed, while in the others PS-ECOG had to be 0–1 for sunitinib versus interferon-alfa and TIVO-1) or Karnofsky index > 70% (CheckMate 024 and COMPARZ).

Regarding the statistical design, all had superiority design except for the COMPARZ study, that was designed to demonstrate non-inferiority for pazopanib compared to sunitinib and the limit for the positive study was the upper limit of the 95% confidence interval.

The characteristics of the patients besides the prognostic classification were similar in most of the studies, although with some exceptions, as listed in Table 1. Focusing on liver metastases, all studies were well balanced, but TIVO-1 had a higher percentage of patients with liver metastases globally; the study with the highest percentage of patients with bone metastases was CABOSUN, with 36.7% in the cabozantinib arm and 35.9% in the sunitinib arm, with around 20% in the other studies.

The distribution of patients by the prognostic classification of Heng is described in Table 1. In all the phase 3 studies, a quality of life analysis was carried out. Figure 2 shows the forest plot for PFS and OS data for each of these studies. Figure 3 shows response rate for each agent.
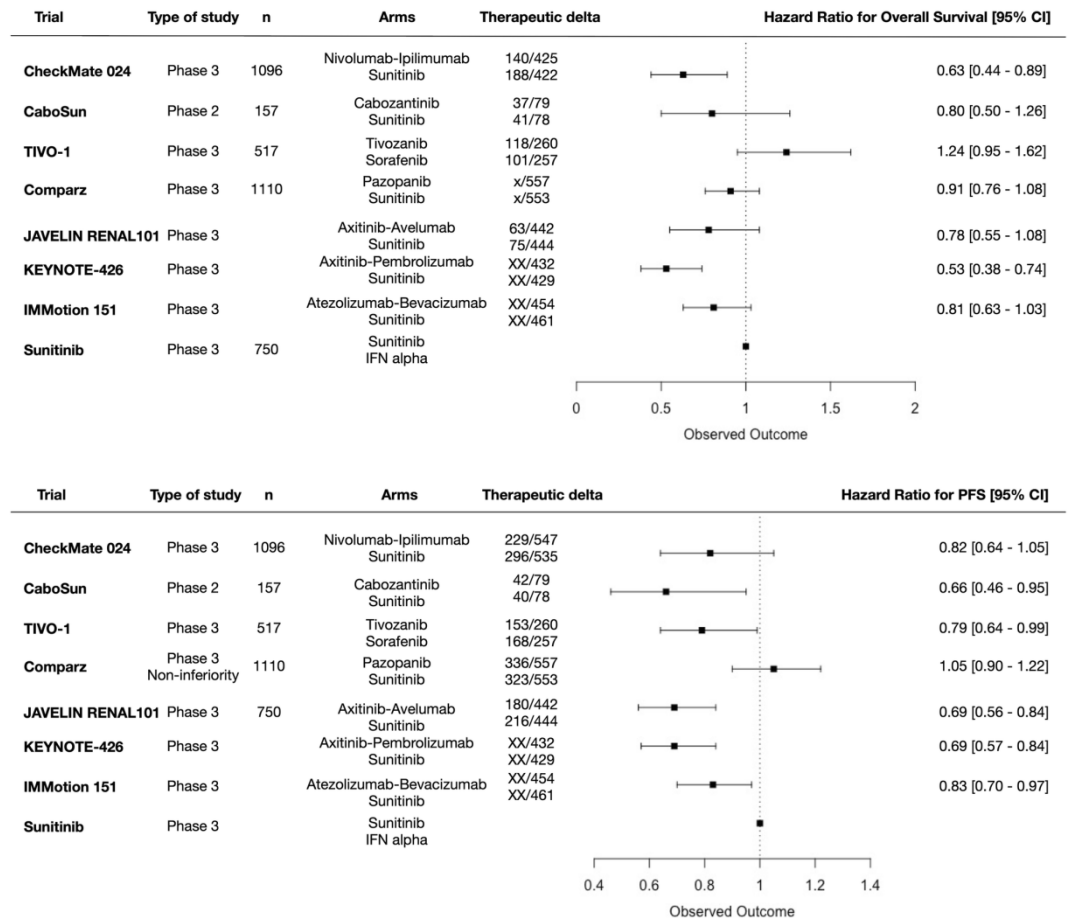

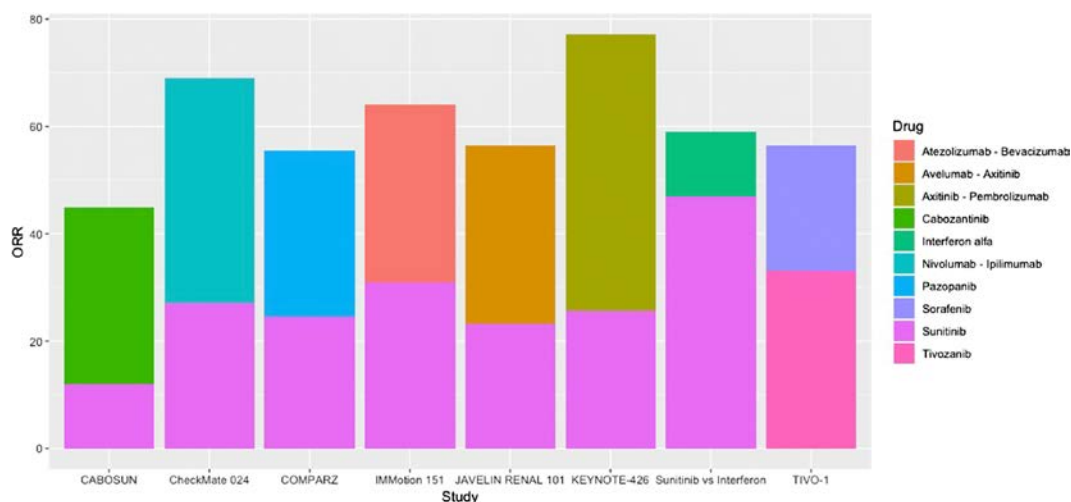**Fig. 2** Forest plot for OS and PFS analysis

Fig. 3 RR for each arm in each of these studies

Tivozanib safety profile

The toxicity profile of tivozanib differs, due to its mechanism of action, to other VEFG inhibitors, with a lower percentage of toxicities as shown in Table 2.

In the TIVO-1 study, adverse events (AEs) were more frequent for sorafenib arm, mainly due to an excess of hand-foot syndrome cases. Additionally, more patients in the sorafenib arm underwent either a dose reduction or interruption due to AEs (37.4% versus 11.6%).

However, in the phase III pivotal trial, AEs were more commonly reported for tivozanib (10.8 versus 5.8%); these AEs were mainly related to progressive disease. Most frequently reported AEs in the tivozanib arm included arterial hypertension (44%), diarrhea (23%), dysphonia (21%) and fatigue (19%); the most frequent analytical alterations being proteinuria (72%) and ALT (28%), AST (37%), amylase (40%) and lipase elevation (46%), anemia (41%), neutropenia (11%), thrombocytopenia (18%). The most frequent grade 3–4 AEs were high blood pressure, fatigue and elevated lipase.

Hypertension in tivozanib-treated patients was managed with anti-hypertensive medications as directed in the study protocols and infrequently led to dose modification; therefore, it was considered a manageable risk.

Data show a slightly more favorable safety profile for tivozanib compared with sorafenib in terms of lower requirements of dose interruptions. The reduced incidence of hand-foot syndrome and diarrhea is an advantage for tivozanib, although counteracted by an increased incidence of dysphonia and hypertension.

Another differential aspect of tivozanib lies in the dose intensity as well as in the percentages of reductions, interruptions and treatment discontinuations.

The relative dose intensity of tivozanib and sorafenib was 94% and 80%, respectively.

Table 2. Most prominent adverse events (appearing in at least 5%) with VEGFR inhibitors

Agent	All grade adverse events
Sunitinib	Diarrhea 61% Fatigue 54% Nausea 52% Dysgeusia 31% Vomiting 31% Hypotension 30% Stomatitis 30% Hand-foot syndrome 9% Asthenia 8% Anemia 79% Leukopenia 78% Neutropenia 77% Creatinine increase 70% Thrombocytopenia 68% AST increase 56% ALT increase 51%
Sorafenib	Diarrhea 48% Skin toxicity 41% Hand-foot syndrome 33%
Pazopanib	Diarrhea 52% Hypertension 40% Hair color changes 38% ALT and AST increase 53% Hyperglycemia 41% Bilirubin increase 36% Thrombocytopenia 32%
Tivozanib	Hypertension 44% Diarrhea 23% Stomatitis 8% Nausea 5% Vomiting 2% Dysphonia 21% Dyspnea 5% Hand-foot syndrome 10% Fatigue 19% Asthenia 8% Proteinuria 72% ALT increase 28% AST increase 37% Amylase increase 40% Lipase elevation 46% Anemia 41% Neutropenia 11% Thrombocytopenia 18%
Cabozantinib	Diarrhea 73% AST increased 59% Fatigue 64% ALT increased 54% Dysgeusia 41% Hypertension 57% Thrombocytopenia 39% Anemia 33% Stomatitis 37% Creatinine increased 25% Weight decreased 32% Vomiting 23% Dizziness 22% Dysphonia 22% Hyperglycemia 21%

Data extracted from Pivotal trials and summary of product characteristics

Second-line treatment for mRCC

For the second-line treatment of mRCC, there are several targeted agents available, like TKI or mTOR inhibitors. To the already approved second-line options of everolimus, axitinib and sorafenib, now we can include the anti-PD-1 inhibitor nivolumab, the VEGFR/cMet inhibitor cabozantinib and the VEGFR/FGFR inhibitor lenvatinib combined with the mTOR inhibitor everolimus.

Cabozantinib was compared with everolimus in a phase III study (METEOR trial), in patients with advanced RCC that had progressed after VEGFR-targeted therapy [42], PFS being the primary endpoint. The median PFS was 7.4 months with cabozantinib and 3.8 months with everolimus (HR 0.58, 95% CI 0.45–0.75, p < 0.001). The benefit in PFS with cabozantinib was observed in all prespecified subgroups regardless of the number of prior VEGFR inhibitors and MSKCC prognostic risk category. Importantly, the final mature OS results published 1 year later showed an improvement in OS for the first time with a VEGFR inhibitor in advanced RCC [43]. The median OS was 21.4 months (95% CI 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI 14.7–18.8) with everolimus (HR 0.66, 95% CI 0.53–0.83, p = 0.00026).

Regarding the VEGFR/FGFR inhibitor lenvatinib combined with the mTOR inhibitor everolimus, recently, the first study to ever show a PFS benefit combining these two drugs was published [44]. It was a randomized phase II trial comparing lenvatinib plus everolimus versus single-agent lenvatinib or single-agent everolimus as second-line therapy. Lenvatinib is a multi-TKI of VEGFR-1–3, with inhibitory activity against fibroblast growth factor receptors (FGFR1-4), PDGFRα, RET and KIT. Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone (14.6 versus 5.5 months, HR 0.40, 95% CI 0.24–0.68, p = 0.0005). Single-agent lenvatinib also significantly prolonged PFS compared with everolimus alone (HR 0.61, 95% CI 0.38–0.98; p = 0.048). At the primary data cutoff, OS did not differ significantly between treatment arms (median OS of 25.5 months with lenvatinib plus everolimus, versus 17.5 months with single-agent everolimus). However, in the post hoc updated analysis, the combination resulted in extended OS compared with everolimus alone (25.5 versus 15.4 months, HR 0.51, 95% CI 0.30–0.88; p = 0.024). Despite the small sample size of the study and the tolerability issues, the FDA approved the combination of lenvatinib plus everolimus in May 2016 for the treatment of advanced RCC following one prior antiangiogenic therapy. EMA subsequently granted approval in Europe.

Nivolumab is the first new immunotherapy agent to get regulatory approval for the treatment of advanced clear cell RCC. Motzer et al conducted a phase III randomized trial (CheckMate 025 trial) of nivolumab versus everolimus in advanced clear cell RCC [45]. The primary endpoint was OS. The median OS was 25.0 months (95% CI 21.8 to not estimable) with nivolumab and 19.6 months (95% CI 17.6–23.1) with everolimus (HR 0.73, 98.5% CI 0.57–0.93, p = 0.002). The OS benefit was observed irrespective of the MSKCC group and number of prior antiangiogenic therapies. Similarly, the benefit with nivolumab over everolimus was seen regardless of PD-L1 tumor immunohistochemistry expression. The ORR was also significantly greater with nivolumab than with everolimus (25% versus 5%; OR 5.98, 95% CI 3.68–9.72, p < 0.001). The median PFS, however, was similar in both arms: 4.6 months (95% CI 3.7–5.4) with nivolumab and 4.4 months (95% CI 3.7–5.5) with everolimus (HR 0.88, 95% CI 0.75–1.03, p = 0.11). Nivolumab was better tolerated than everolimus, grade 3 or 4 treatment-related AEs occurring in 19% of the patients receiving nivolumab as compared with 37% with everolimus. Consequently, in November 2015, the FDA approved the use of nivolumab to treat patients with metastatic RCC who have previously progressed to one or two regimens of antiangiogenic therapy, becoming a new standard-of-care treatment option in that setting. Nivolumab was subsequently EMA-approved for RCC in February 2016.

Moreover, for the first time in the second-line setting, these three agents were approved based on an improvement in OS compared with an active and valid comparator drug such as everolimus. Importantly, OS is generally considered as the most relevant surrogate factor of meaningful clinical benefit with a given drug. This has led to the most influential international oncology guidelines such as the NCCN guidelines [46] and the ESMO guidelines [10] to recommend both nivolumab and cabozantinib as the new preferred standard-of-care, second-line options in advanced RCC.

Supporting tivozanib use in the second-line setting, extension study (902), provides strong evidence of tivozanib in this setting. This study was set up as an open-label extension protocol for the pivotal study (AV-951-09-301) and included those patients who received second-line tivozanib upon progression to sorafenib control arm. Exclusion criteria included progression of CNS metastases, hematological or serum chemistry abnormalities, uncontrolled hypertension and treatment with another anti-cancer therapy.

A total of 277 patients were enrolled. Of these, 161 who were initially randomized to sorafenib received at least one dose of tivozanib in the extension study. This includes 14 patients who started the extension study on sorafenib, 6 of whom had documented PD in the pivotal study. Eighty-eight patients who were initially randomized to tivozanib received at least one dose of tivozanib in this study. Twenty-eight patients who were initially randomized to sorafenib received at least one dose of sorafenib in this study (but did not cross-over to tivozanib).

Median PFS by investigator assessment, including data from the pivotal and extension study for the ITT population, was 14.7 months for tivozanib patients compared to 9.7 months for sorafenib patients (p = 0.006), HR 0.755 (95% CI 0.617, 0.922).

For the 161 patients who crossed over to tivozanib, ORR was 18.0% (95% CI 12.4%, 24.8%), all PR. Median duration of PR was 15.2 months. One hundred and eight patients (67.1%) had PD or died during the study; median PFS was 11.0 months (95% CI 7.3–12.7 months). Seventy-eight patients (48.4%) died during the study; median OS from the start of the first dose in this study was 21.6 months (95% CI 17.0–27.6 months).

For patients who remained on initial randomized tivozanib or sorafenib, the ORR was 55.7% (95% CI 44.7%, 66.3%) and 57.1% (95% CI 37.2%, 75.5%), respectively. Thirty-five (39.8%) patients on tivozanib treatment and one (3.6%) patient on sorafenib treatment had PD or died during this study [18].

Beyond second line

As for the third and subsequent treatment line, patients should ideally be assessed whenever possible for inclusion in clinical trials. If no clinical trial is available, and due to the absence of randomized clinical trials comparing one sequential therapy with another, several possible treatment sequences may exist depending on the drugs administered in the first and second line.

Clinical trials in the third-line setting are limited to the GOLD and the RECORD-1 studies. Sorafenib can be recommended after a sequence of TKI–mTOR inhibitor, based on the data of the GOLD study [47]. Treatment with the mTOR inhibitor everolimus can be given after the sequence TKI–TKI, this recommendation being based on a subgroup analysis of the RECORD-1 study [48].

Most of the targeted therapies have been established in phase III trials that were conducted within the same timeframe, so very few were done with comparisons to another agent [49].

Regarding tivozanib in the third-line setting, TIVO-3 was a phase 3 randomized study very recently presented at ASCO-GU [50]. It included patients who already failed two or three prior systemic regimens, one of which included a VEGFR TKI other than sorafenib or tivozanib; patients were stratified based on IMDC risk factors and prior treatment, and then received tivozanib or sorafenib. Primary objective was PFS by IRR. Up to 350 patients were enrolled. The study was designed with a power of 88% to detect a difference of an increase in 2 months of PFS. Both arms were well balanced in terms of baseline characteristics. Up to 40% patients had received three prior lines; 60% had two prior lines of therapy. Median PFS was longer in the tivozanib arm: 5.6 (95% CI 7.3–5.3) versus 3.9 months (95% CI 5.6–3.7; HR 0.73; p = 0.02). PFS rate at 2 years was 18% for tivozanib versus 5% for sorafenib. Patients treated with a prior checkpoint inhibitor had a statistically significant benefit with tivozanib (HR 0.55). PFS favored tivozanib over sorafenib in most patient subgroups, including either IMDC favorable or intermediate, two prior VEGFR-TKIs, prior checkpoint inhibitors and VEGFR-TKI, third and fourth line, and regardless of age group [51]. At a median duration on study of 32.5 months, 20 patients remained progression free on the tivozanib arm compared with 2 patients on the sorafenib arm. Median OS was 16.4 months for tivozanib (95% CI 13.4–22.2) and 19.7 months (95% CI 15.0–24.2) for sorafenib (HR 0.99; 95% CI 0.76–1.29; p = 0.95), according to findings from the second prespecified analysis.

Future treatment options

As the combination of immunotherapy agents plus targeted therapy is highly interesting, TiNivo trial studied the combination of tivozanib plus nivolumab, testing a dose escalation of tivozanib with standard doses of nivolumab of 240 mg every 14 days. The combination was found safe with a manageable toxicity profile. Patients had an ORR of 56% with a disease control rate of 96%. Eighteen patients (72%) had tumor shrinkage of at least 25% and one patient had a complete response, showing a promising anti-tumor efficacy and a manageable toxicity profile. Up to 15 patients (60%) experienced at least one grade 3–4 AE, but excluding uncomplicated hypertension, treatment-related AE was 44% [33].

Discussion

The field of kidney cancer has surprisingly thrived on targeted therapy. Although new advances have improved response rates, OS, and treatment-related toxicities, the treatment paradigm continues to evolve [52].

As the landscape for RCC treatment has been successfully evolving, widely acceptable criteria for treatment selection has become needed. Treatment choice should be based not only on treatment line and sequence, but also on some molecular histology features including angiogenic profile and immunogenic characteristics. Additionally, patients' profiles including comorbidities (making them suitable for immunotherapy) age and risk factor score are key.

The evidence is still somehow limited regarding which the best treatment and sequential therapy could be for each group of patients. Sequentiality is not clear at all yet.

The success of future next-generation agents will depend on our ability to select patients most likely to respond to treatment. Further studies are needed to inform on the prognostic factors, which are critical for the selection of optimal therapy and will be crucial to try to identify those patients most likely to get benefit, avoiding unnecessary toxicities in those patients who are unlikely to benefit.

Several TKIs are standard of care at different settings. As targeted therapies became a revolution which positively impacted on survival, now quality of life is a key objective. TKIs monotherapy improve survival with very well-manageable AEs, hence, every effort should be directed to identify which patients may have more benefit by receiving TKIs in the first line. Probably good prognostic patients or those patients with only one risk factor may get the strongest benefit with this treatment sequencing, rather than receiving upfront immunotherapy followed by TKIs. TKI followed by PD-1 inhibitor drugs is an approach that could be considered only after assessing thoroughly the patient's profile and risk factors.

Among those approved TKIs, tivozanib has similar efficacy with a better safety profile and a more comfortable posology, being administered for 3 weeks every 4 weeks, which decreases indirect costs. Renal function should be taken into account, as tivozanib does not have urinary excretion and may be administered in patients with mildly limited creatinine clearance.

Toxicities appear usually during first cycles with TKIs and, once managed, they usually do not reappear and do not usually lead to a dose reduction or interruption. Toxicities also impact on global cost of treatment, which is dramatically different among treatments (especially for new emerging drugs and combinations); this also supports the importance of a carefully performed, based on patients' profiles, regimen selection.

There is a group of patients, without any risk factor, who get the most important benefit from TKIs and can be considered as "long survivors", reaching median overall survival over 40 months [52]. This encourages us to look for robust predictive prognosis criteria to identify this population.

Biomarkers studies are needed to improve the knowledge about those which are related to angiogenesis and their PD-L1 expression. Probably PD-L1 expression plus prognostic score index will be studied to be validated to predict which patients may get better benefit. There was a recent study correlating the IMDC prognostic score at start of systemic therapy with RNA expression of genes involved in angiogenesis and in the immunosuppressive microenvironment. The majority of IMDC good-risk RCC patients had clear cell RCC (CCRCC)-2 tumors (classical subtype according to molecular characteristics), displaying a higher expression of the VEGF-dependent proangiogenic pathway. Molecular subtypes range from 1–4, depending mainly on transcriptome and methylome profiles. These molecular profiles may be supportive to predict response, PFS and OS in patients treated with TKIs [11]. This actually may explain the increased benefit of sunitinib versus ipilimumab–nivolumab in good risk patients in CheckMate214 [53]. Therefore, with combined ipilimumab–nivolumab, some patients may be overtreated.

As a predictive and prognostic factor, immune microenvironment in mRCC is key to understand its response to targeted treatments. T-cell exhaustion/inhibition plays an important role in mRCC pathogenesis. It has been described that the density of PD-1 + cells and the tumor expression of PD-L1 are associated with a poor clinical outcome in patients treated with anti-PD-1/anti-PD-L1 therapy [54].

Tumors with high inflammatory immune infiltrate have a high expression of PD-1 and its ligands, and correlate with the worst prognosis. Indeed, this inflammatory/proangiogenic profile may contribute to local immunosuppression process.

Immune profiles should guide the selection of suitable patients to receive immunotherapies and need to be further validated in larger and independent cohorts.

There is a sound rationale for biomarkers to be incorporated into clinical research to improve the current knowledge. Additionally, data in real-life patients are also essential to improve the knowledge regarding efficacy and toxicity of tivozanib, in combination with tumor microenviroment data.

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