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Updated recommendations from the Spanish Oncology Genitourinary Group on the treatment of advanced renal cell carcinoma

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Abstract The speed at which targeted therapies are being developed and incorporated into the treatment of advanced renal cell carcinoma (RCC) is surprising. After decades in which the only systemic treatment options available for advanced disease were interleukin-2 and interferon-α, in the last decade, six new targeted therapies have emerged showing meaningful clinical benefits to patients with advanced RCC through phase III trials. Recently, the Spanish Oncology Genitourinary Group issued its first public statement of recommendations for the optimal management of advanced RCC. However, most pivotal phase III trials on which these recommendations were based have been updated and/or fully reported. Moreover, a new multikinase inhibitor, pazopanib, has emerged with good quality clinical data. In this report, we review in depth the latest phase III data of targeted therapies for advanced RCC and update our recommendations. Furthermore, we hypothesize about the best environment for patients with advanced RCC to receive cancer therapy.

Keywords Renal cell carcinoma · Spanish Oncology Genitourinary Group · Cancer treatment

1 Introduction

It is estimated that every year, there are almost 58,000 new cases of renal cell carcinoma (RCC) and 13,000 deaths due to the disease in the USA [1]. Approximately 30% of patients with a new diagnosis present with advanced disease. Until recently, treatment of advanced RCC was limited to cytokine therapies, such as interleukin-2 (IL-2)

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and interferon-α (IFN-α), which produce modest objective response rates (ORR) and substantial toxicities.

Due to better understanding of the molecular pathways involved in the development of RCC, six new targeted therapies have emerged in the last decade. Sunitinib, sorafenib, and pazopanib produce their anticancer effect by blocking the intracellular domain of vascular endothelial growth factor (VEGF) receptor, while bevacizumab binds to circulating VEGF protein, preventing interaction with its receptors, without affecting it directly. Lastly, both temsirolimus and everolimus are analogues of rapamycin, which inhibit mammalian target of rapamycin (mTOR), a tyrosine kinase involved in the intracellular signalling pathways of cellular growth, proliferation, and hypoxic stress response.

Recently, the Spanish Oncology Genitourinary Group (SOGUG) issued its first public statement of recommendations for the optimal management of advanced RCC [2]. However, at the time the paper was published, most pivotal phase III trials on which these recommendations were based have been updated and/or fully reported. Moreover, a new multikinase inhibitor, pazopanib, has emerged with new good quality clinical data. Because of this, an update of our previous recommendations is now reported.

In this report, we have analyzed in depth the latest phase III data of targeted therapies for advanced RCC, specifically in the elderly and/or frail patient populations, in patients with severe concomitant diseases (renal, hepatic, or cardiac dysfunction), and in patients without prior nephrectomy or with non-clear RCC. Lastly, we hypothesize about the best environment for patients with advanced RCC to receive cancer therapy. The objective of this review is to issue new updated recommendations from SOGUG for the optimal management of patients with advanced RCC based on phase III data.

2 Update on prognostic and predictive markers for advanced RCC

Information about prognostic and predictive factors is crucial to improve outcomes in patients with RCC receiving novel treatment strategies. Reasons that support this view include the modest to nonexistent response of RCC to standard cytotoxic, endocrine, and cytokine therapy [3]; the aggressiveness that characterizes these tumors [4]; and the specific mechanism of action of new targeted therapies that render them inefficient when certain markers are not expressed.

There are multiple studies that have allowed the identification of prognostic factors for metastatic RCC [5–7]. These factors may be classified into biological, clinical, and histological prognostic factors. Biological factors include laboratory abnormalities, such as anemia, hypercalcemia, liver dysfunction, neutrophilia, thrombocytosis, and elevation of proinflammatory markers (*i.e.*, erythrocyte sedimentation rate, C-reactive protein, ferritin, and α1-antitrypsin levels) [5]. Clinical prognostic factors include Eastern Cooperative Oncology Group performance status (ECOG PS), localization and number of metastases, time to diagnosis, disease-free interval, metastasis-free interval, tumor burden, prior nephrectomy, and prior therapy [2, 5]. Finally, histological factors include nuclear grade, size or shape, histological subtypes (clear cell, papillary, chromophobe, oncocytoma, or collecting duct tumors), and the presence of sarcomatoid features [5]. Outcome models integrating these prognostic factors have been considered in depth by SOGUG [2], and thus will not be further discussed here.

Additionally, there are a number of molecular biomarkers that are being investigated in RCC (Table 1), including VEGF levels; expression of hypoxia inducible factor (HIF); expression of B7-H1, B7-H4, and B7x; phosphatase and tensin homologue deleted from chromosome 10 (PTEN); and carbonic anhydrase IX (CAIX), a von Hippel–Lindau-mediated enzyme expressed in most cases of RCC [8]. Many of these biomarkers are associated with pathological changes, and because of this, they may also constitute therapeutic targets [9].

The last 5 years have seen an increase in the number of clinical trials aimed at developing prognostic nomograms based on clinical and molecular biomarkers rather than on clinical markers alone. A recent report by Escudier *et al*. [10] demonstrated that VEGF levels correlate with ECOG PS and with the Memorial Sloan–Kettering Cancer Center (MSKCC) score. In another study, Heng *et al*. [11] validated the use of the MSKCC nomogram to predict overall survival (OS) in patients with RCC treated with VEGF-targeted therapy. In addition, they demonstrated that neutrophil and platelet counts were also independent predictive factors of shortened survival, and thus should be incorporated into clinical trials which evaluate these agents.

One of the most prolific areas of research in the last few years is the search for genetic patterns or imprints that allow the identification of tumors with poor prognosis, even before they develop adverse clinical manifestations, to be used as prognostic factors in clinical practice (Table 1). In a recent study, tumors of 282 patients who underwent nephrectomy for RCC were cytogenetically analyzed and correlated with pathological factors and disease-free survival [12]. After data analysis, Klatte *et al*. [12] found that tumors with loss of 3p presented at lower TNM stages, whereas loss of 4p, 9p, and 14q were associated with higher TNM stage, higher grade, and greater tumor size; lastly, loss of chromosome Y led to improved progression-free survival (PFS) in patients with metastatic disease. In the

Table 1 Prognostic and predictive biomarkers in renal cell carcinoma

Biomarkers	Expression level	Prognosis	Predictive
Prognostic molecular			
Akt [47]	High cytoplasmic levels	Poor survival	
B7x [48]	High	Advanced tumor stage	
CAIX [49, 50]	Low	Poor survival	
COX-2 [51]	Low	No response; poor survival	
Hepatocyte growth factor [52]	High	Poor survival	
HIF [53]	High	Poor survival	
Ki67 [54]	High	Poor survival	
p21 [55]	High	Poor survival	
p53 [56, 57]	High	Higher recurrence rate	
PTEN [47, 56]	Low	Poor survival	
VEGF [58]	High serum levels	Shorter PFS	
Predictive molecular			
CAIX [56]	High		Good response to immunotherapy
COX-2 [56]	High		Good response to immunotherapy
HIF-1α/HIF-2α [59]	High		Good response to sunitinib
Predictive genetic			
Loss of chromosomes 4, 9, or 17p [60]	NA		No response to IL-2
Various nsSNPs [61]	NA		Significant toxicity with sunitinib
VHL loss of function mutation [62]	NA		Good response to VEGF therapy

CAIX carbonic anhydrase IX, *COX-2* cyclooxygenase-2, *HIF* hypoxia inducible factor, *IL-2* interleukin-2, *nsSNPs* non-synonymous single nucleotide polymorphisms, *PFS* progression-free survival, *PTEN* phosphatase and tensin homologue deleted from chromosome 10, *VEGF* vascular endothelial growth factor, *VHL* von Hippel–Lindau

multivariate analysis, only loss of chromosome 9p was shown to be an independent prognostic factor.

3 Updated results of targeted therapies for patients with advanced RCC

In a previous report issued by the SOGUG, the main results from randomized phase II and phase III trials of systemic therapies for advanced RCC, including immunotherapy, multikinase inhibitors, anti-VEGF therapies, and mTOR inhibitors, were thoroughly analyzed [2]. The present report is focused on relevant data reported since then.

3.1 Multikinase inhibitors

Tyrosine kinase inhibitors (TKIs) such as sunitinib, sorafenib, and pazopanib produce their anticancer effects by blocking the intracellular domain of VEGF receptors.

3.1.1 Sunitinib

Sunitinib (Sutent®, Pfizer) is an oral multitargeted tyrosine kinase that inhibits multiple receptors such as VEGF-1, VEGF-2, and VEGF-3 as well as platelet-derived growth factor receptor (PDGFR)-α and PDGFR-β, stem cell factor (KIT), and Fms-like tyrosine kinase-3 (FLT-3) receptors. In the last years, sunitinib has been demonstrated to yield high ORR in patients with cytokine-refractory advanced RCC in two phase II trials [13, 14].

Sunitinib has also been shown to be superior to IFN-α as first-line treatment of patients with RCC [15, 16]. Very recently, final results of a pivotal phase III trial including 750 treatment-naïve patients with advanced RCC have been reported [17] (Table 2). Patients treated with sunitinib (50 mg once a day for 4 weeks followed by a 2-week rest) achieved a median PFS, which was the primary end point of the study, of 11.0 months, whereas patients who received IFN-α (9 MIU three times a week) achieved a median PFS of 5.0 months (HR, 0.539; 95% CI, 0.451–0.643; $p<0.001$). Compared with IFN-α, secondary end points were significantly better in the sunitinib arm, as in the case of the ORR (47% *vs* 12%, respectively; $p<0.001$), or showed a strong trend towards significance, as in the case of median OS (26.4 *vs* 21.8 months, respectively; HR, 0.821; 95% CI, 0.673–1.001; $p=0.051$). Importantly, 33% of patients in the IFN-α arm received sunitinib after progression, and another 32% of them received other VEGF inhibitors. Thus, when the survival analysis was performed only in those patients from both arms who did not receive any post-study cancer

Table 2 Main efficacy data from phase III trials with targeted therapies for advanced or metastatic renal cell carcinoma

	Phase	Treatment	Patients	Setting	ORR (%)	PFS (months)	OS (months)
Multikinase inhibitors							
Sunitinib							
Motzer *et al.* [16, 17]	III	Sunitinib	750	First-line	47	11.0	26.4
		IFN-α			12; $p<0.001$	5.0; $p<0.001$	21.8; $p=0.051$
Sorafenib							
Escudier *et al.* [10]	III	Sorafenib	903	Second-line (after cytokines)	10	5.5	17.8
		Placebo			2; $p<0.001$	2.8; $p<0.01$	15.2; NS
Pazopanib							
Sternberg *et al.* [29]	III	Pazopanib	435	First and second-line (after cytokines)	30	9.2	Not reached
		Placebo			3; NR	4.2; $p<0.001$	14.7; NS
Anti-VEGF antibodies							
Bevacizumab							
Escudier *et al.* [35]	III	Bevacizumab+IFN-α	649	First-line	31	10.4	22.9
		IFN-α			12; $p<0.0001$	5.5; $p<0.0001$	20.6; NS
Rini *et al.* [34, 36]	III	Bevacizumab+IFN-α	732	First-line	26	8.4	18.3
		IFN-α			13; $p<0.0001$	4.9; $p<0.0001$	17.4; $p=0.097$
mTOR inhibitors							
Temsirolimus							
Hudes *et al.* [39]	III	IFN-α	626	First-line	5	3.1	7.3
		Temsirolimus		Poor prognosis	9; NS	5.5; $p<0.001$	10.9; $p=0.008$
		Temsirolimus+IFN-α			8; NS	4.7; NS	8.4; $p=0.70$
Everolimus							
Motzer *et al.* [43]	III	Everolimus	362	Second-line (after TKIs)	3	4.0	Not reached
		Placebo			0	1.9; $p<0.0001$	8.8; $p=0.233$

IFN-α interferon-alpha, *NR* not reported, *NS* non-significant, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *RCC* renal cell carcinoma, *TKIs* tyrosine kinase inhibitors

treatment, median OS with sunitinib was twice that of IFN-α (28.1 *vs* 14.1 months, respectively; HR, 0.647; 95% CI, 0.483–0.870; $p<0.003$).

Within the same phase III trial, Cella *et al.* [18] analyzed and compared health-related quality of life (HRQoL) results obtained in patients who received sunitinib with those obtained in patients treated with IFN-α. It was concluded that in addition to providing significantly superior efficacy to IFN-α therapy, sunitinib offered a better HRQoL according to different scales and subscales such as the Functional Assessment of Cancer Therapy (FACT) and FACT-Kidney Symptom Index, among others. Moreover, results from an expanded-access trial which included 4,564 patients with previously treated and untreated metastatic RCC confirmed that the safety profile of sunitinib was manageable, even in populations who usually are under-represented in clinical trials such as elderly or patients with poor performance status [19, 20].

Sunitinib has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of advanced or metastatic RCC [21, 22]. The recommended dose is 50 mg once daily, administered for four consecutive weeks, followed by a 2-week rest period, to complete a 6-week cycle. Dose adjustments should be made in 12.5 mg steps, and the minimum dose should not be below 25 mg. Treatment with sunitinib requires close monitoring to detect early signs of congestive heart failure, prolonged QT interval, arterial hypertension, and hemorrhagic events. Thyroid dysfunction may also occur in patients treated with sunitinib.

3.1.2 Sorafenib

Sorafenib (Nexavar®, Bayer Pharmaceuticals) is an orally active multikinase inhibitor that blocks VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, as well as FLT-3 and KIT receptors. As second-line treatment of advanced RCC after cytokines failure, sorafenib has had its activity and safety demonstrated in a previous phase II study [23]. Based on these findings, a randomized, double-blind, phase III trial comparing sorafenib (400 mg twice a day) with placebo as second-line treatment was performed in 903 patients with cytokine-refractory advanced RCC [24]. The primary endpoint of this study was OS, and secondary endpoints included PFS and ORR.

Based upon results of the first planned interim analysis, in which sorafenib provided a clear benefit to patients in terms of PFS, patients on the placebo arm were allowed to crossover and receive sorafenib after progression. As a consequence, 48% of patients initially assigned to the placebo arm were treated with sorafenib, which probably confounded the results of the survival analysis. Thus, in the final analysis of survival [10], sorafenib was not superior to placebo (17.8 *vs* 15.2 months, respectively; HR, 0.88; 95% CI, 0.74–1.04; $p=0.104$; Table 2). However, when patients assigned to the placebo arm who received sorafenib after progression were excluded from the analysis, sorafenib was associated with a significantly longer survival in comparison with placebo (17.8 *vs* 14.3 months, respectively; HR, 0.78; 95% CI, 0.62–0.97; $p=0.0287$). Secondary endpoints of the study also were significantly better in the sorafenib arm in comparison with the placebo arm in terms of PFS (5.5 *vs* 2.8 months, respectively; HR, 0.44; 95% CI, 0.35–0.55; $p<0.01$) and ORR (10% *vs* 2%, respectively; $p<0.001$) [10].

As first-line treatment, sorafenib (400 mg twice a day) was compared with IFN-α (9 MIU three times a week) in a randomized phase II trial including 189 patients with advanced RCC [25]. Although several endpoints such as disease control rate, quality of life, and safety were improved in the sorafenib arm with respect to the IFN-α arm, PFS, which was the primary endpoint, was similar in both arms (5.7 *vs* 5.6 months, respectively; HR, 0.88; $p=0.50$).

Based on these results, sorafenib is currently approved by the FDA and by the EMEA for the treatment of patients with advanced RCC who have failed prior IFN-α or IL-2 therapy or are considered unsuitable for those therapies [26, 27]. The recommended dose of sorafenib is 400 mg twice a day, as long as clinical benefit is observed or until unacceptable toxicity. Dose may be reduced to 400 mg once a day or to 400 mg on alternate days. Precautions at the time of administration are similar to those for other TKIs and, therefore, special attention should be paid to the emergence of cardiac events, bleeding, gastrointestinal perforation, or arterial hypertension.

3.1.3 Pazopanib

Pazopanib (Votrient®, GlaxoSmithKline) is an oral multikinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α and -β, fibroblast growth factor receptor (FGFR)-1 and -3, KIT, IL-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase, and transmembrane glycoprotein receptor tyrosine kinase [28].

In a previous international, multicenter, randomized, double-blind, phase III trial (VEG105192), 435 patients with clear cell advanced RCC (233 treatment-naïve and 202 with no more than one previous cytokine-based treatment) were included and treated with 800 mg of pazopanib once daily ($n=290$) or placebo ($n=145$) [29]. Patients were stratified according to performance status, prior nephrectomy, or prior cytokine therapy. The study's primary endpoint was PFS. Secondary endpoints included OS, RR, and safety.

Baseline characteristics of both arms were well balanced. Forty-two percent of patients were ECOG PS 0, and 58%

were ECOG PS 1. Approximately 50% of patients had three or more organs with metastatic disease, mostly in lung, lymph nodes, bone, and liver. In the cytokine-pretreated group, 75% of them received IFN-α. Prior nephrectomy was performed in the majority of patients in both treatment arms (pazopanib, 89%; placebo, 88%) [29].

PFS was significantly prolonged in patients who received pazopanib (9.2 months) compared with those who received placebo (4.2 months; HR, 0.46; 95% CI, 0.34–0.62; $p<0.001$; Table 2). This effect was observed in both treatment-naïve (11.1 *vs* 2.8 months; $p<0.001$) and cytokine-pretreated patients (7.4 *vs* 4.2 months; $p<0.001$). The prespecified subgroup analysis showed that pazopanib improved PFS in comparison with placebo regardless of risk category, sex, age, or ECOG PS ($p<0.001$ by log-rank test for all).

ORR was also superior in the pazopanib arm (30%) in comparison with placebo (3%). Similar ORRs were observed in both subgroups included in the pazopanib arm, *i.e.*, the treatment-naïve (32%) and cytokine-pretreated (29%) populations. At the time of the report, survival results were still immature. The most common (≥20% of patients) severe adverse events observed in the pazopanib arm, compared with those observed in the placebo arm, were diarrhea (52% *vs* 4%), arterial hypertension (40% *vs* 4%), change in hair color (38% *vs* <1%), nausea (26% *vs* <1%), anorexia (22% *vs* 2%), and vomiting (21% *vs* 2%). Additionally, pazopanib severely increased serum transaminases in 55% of patients [29].

Patients included in the VEG105192 trial who showed disease progression on placebo were offered pazopanib through an extension study (VEG107769) [30]. Thus, 71 patients (34 treatment-naïve and 37 cytokine-pretreated) received 800 mg of pazopanib once a day until disease progression, death, or unacceptable toxicity. RR was observed in 32% of patients (95% CI, 22–43), and median PFS was 8.3 months (95% CI, 6.1–11.4 months). It was concluded that patients with advanced RCC who progress with placebo may also achieve a clinical benefit from pazopanib.

Based on these results, the FDA has already granted approval of pazopanib for the treatment of patients with advanced RCC as first-line treatment or after progression on cytokines [31]. Although the recommended dosage of pazopanib is 800 mg per day, in case of moderate hepatic impairment, it should be reduced to 200 mg. However, pazopanib should be avoided in patients with severe hepatic dysfunction because hepatotoxicity may be severe or fatal [31]. Accordingly, serum liver tests should be performed prior to treatment initiation and every 4 weeks for at least the first 4 months of treatment. Also, pazopanib should be used with caution in patients with a previous history of QT interval prolongation, hemorrhagic or thrombotic events, or patients scheduled for surgery, because of the risk of inadequate wound healing.

3.2 Anti-VEGF antibodies

VEGF is a potent pro-angiogenic protein that leads to increased vascular permeability and endothelial cell proliferation [32].

3.2.1 Bevacizumab

Bevacizumab (Avastin®, Roche) is a potent monoclonal antibody that binds to circulating VEGF protein preventing interaction with its receptors on the surface of endothelial cells. Unlike TKIs, bevacizumab does not affect VEGF receptors.

Two previously reported phase III trials have demonstrated the activity of bevacizumab in combination with IFN-α in treatment-naïve patients with RCC in terms of PFS and ORR [33, 34]. Since our previous review, results from both AVOREN and Cancer and Leukemia Group B (CALGB) 90206 trials have been updated [34–36] (Table 2). The AVOREN trial was performed in 649 untreated patients with advanced RCC who received bevacizumab (10 mg/kg every 2 weeks) plus IFN-α (9 MIU three times a week) ($n=327$) or placebo plus the same dose of IFN-α ($n=322$). An independent radiological review confirmed the previous evaluation performed by investigators; thus, RR was 31% in the study arm and 12% in the control arm. Additionally, PFS was 10.4 and 5.5 months (HR, 0.57) in the study and control arms, respectively. A trend toward improved OS was observed in the bevacizumab plus IFN-α arm, compared with IFN-α only arm, which did not achieve statistical significance. However, subsequent antineoplastic therapy was administered more frequently to the control arm (63%) than to the study arm (55%), and this fact may have influenced the OS analysis [35].

The CALGB 90206 study was performed in 732 previously untreated patients with advanced RCC who were randomized to receive bevacizumab (10 mg/kg every 2 weeks) plus IFN-α (9 MIU three times a week) or the same dose of IFN-α as monotherapy. Primary objective was OS, whereas secondary objectives included PFS, ORR, and safety. In the last update, the median PFS was 8.4 months for bevacizumab plus IFN-α and 4.9 months for IFN-α alone ($p<0.0001$). Although the median OS seemed to favor the study arm, it did not achieve predefined criteria for significance (18.3 *vs* 17.4 months, respectively; $p=0.097$), either for the overall population or for any of the different MSKCC prognosis groups [36].

In both phase III trials, toxicity was significantly greater in the bevacizumab plus IFN-α arm. The extent to which IFN-α contributed to the efficacy and toxicity profile of this

combination was called into question; additional prospective trials will be needed to answer this point.

Based on efficacy and safety data derived from these two phase III trials, bevacizumab in combination with IFN-α is currently approved by the FDA and by the EMEA for the first-line treatment of patients with advanced RCC [37, 38]. Recommended dose for this disease is 10 mg/kg of body weight given once every 2 weeks until progression or unacceptable toxicity. Dose reductions are not recommended. Patients under bevacizumab treatment are at higher risk of gastrointestinal perforations, fistulae, wound healing complications, and arterial hypertension.

3.3 mTOR inhibitors

The mTOR is a tyrosine kinase involved in the intracellular signaling pathways of cellular growth, proliferation, and hypoxic stress response.

3.3.1 Temsirolimus

Temsirolimus (Torisel®, Wyeth) is an intravenously administered rapamycin analogue that functions as a competitive inhibitor of the mTOR kinase. Inhibition of mTOR activity results in a G1 growth arrest in treated tumor cells.

Temsirolimus has been demonstrated to be efficacious in a phase III trial with 626 patients with previously untreated, poor prognosis RCC disease [39]. Poor prognosis was defined as the presence of at least three prognostic factors of short survival. In this study, patients who received temsirolimus alone (25 mg i.v. weekly) had longer OS (HR, 0.73; 95% CI, 0.58–0.92; p=0.008) and PFS (p< 0.001) than patients who received IFN-α alone (between 3 and 18 MIU three times a week; Table 2). Moreover, temsirolimus was better tolerated than IFN-α. In a quality-adjusted survival analysis performed in this trial, patients who received temsirolimus alone had 23% greater quality-adjusted time without symptoms and toxicity (QTWiST) than those patients receiving IFN-α alone (7.0 *vs* 5.7 months, respectively; p=0.0015). In contrast, there were no significance differences in QTWiST between the combination arm and the IFN-α arm (p=0.3469) [40].

Accordingly, temsirolimus has been approved by both the FDA and the EMEA for the first-line treatment of patients with advanced RCC who have at least three to six prognostic risk factors for a poor outcome [41, 42]. The recommended dose is 25 mg administered as a 30- to 60-min infusion once a week until there is no longer clinical benefit for the patient or unacceptable toxicity occurs. If adverse events are not adequately managed with dose delays, the dose of temsirolimus should be reduced by 5 mg/week decrements. Special precautions should be taken in patients with renal insufficiency or hepatic impairment. In spite of this, temsirolimus is well tolerated and, therefore, it is a candidate for combination schedules with other agents. Future prospective trials should be conducted to clarify its role in RCC patients with favorable prognosis or as part of combination therapies.

3.3.2 Everolimus

Everolimus (Afinitor®, Novartis) is an orally administered selective inhibitor of mTOR kinase activity which reduces cell proliferation, angiogenesis, and glucose uptake in *in vitro* and *in vivo* studies. In addition, everolimus inhibits the expression of HIF-1 and VEGF.

Everolimus has been demonstrated to be efficacious in patients with advanced RCC whose disease had progressed on or after VEGFR-TKIs (sunitinib, sorafenib, or both) in a phase III placebo-controlled trial. Recently, the results of RECORD-1 trial have been fully reported [43] (Table 2). Four hundred and sixteen patients were randomized to receive everolimus (10 mg once a day) or placebo. PFS, which was the study's primary endpoint, was significantly better in the everolimus arm (4.9 months) in comparison with the placebo arm (1.9 months; HR, 0.30; 95% CI, 0.22–0.40; p<0.0001). A predefined subset analysis according to MSKCC score indicated that this benefit was maintained across all subgroups. Although a positive effect of everolimus on survival

Table 3 SOGUG recommendations based on phase III data on advanced or metastatic renal cell carcinoma

Prognostic risk groups	Treatment options		
	First-line	Second-line	
		After cytokines	After TKIs
Favorable risk	Sunitinib [16, 17] Bevacizumab-IFN-α [34–36] Pazopanib [29]	Sorafenib [10] Pazopanib [29]	Everolimus [43]
Intermediate risk	Sunitinib [34, 36] Bevacizumab-IFN-α [34–36] Pazopanib [29]		
Poor risk	Temsirolimus [39]		

IFN-α interferon-alpha, *SOGUG* Spanish Oncology Genitourinary Group, *RCC* renal cell carcinoma, *TKIs* tyrosine kinase inhibitors

was observed, it did not achieve statistical significance (HR= 0.83, 95% CI, 0.50–1.37; p=0.23), probably because crossover effect was not taken into account. Thus, when the survival analysis was corrected for crossover, treatment with everolimus reduced the risk of mortality by 45% (HR, 0.55; 95% CI, 0.31–0.97) [44]. Regarding safety, everolimus was well tolerated, and the side effects were manageable. Mild to moderate stomatitis, hyperlipidemia, and hyperglycemia were observed, and a higher proportion of non-infectious pneumonitis compared to patients receiving placebo. However, in all cases, the proportion of severe events was less than 5%.

Everolimus is currently approved by the FDA and the EMEA for the treatment of patients with advanced RCC whose disease has progressed on or after VEGF-targeted therapy [45, 46]. Recommended dosage is 10 mg once a day, although it may be reduced to 5 mg a day to manage adverse events. Special warnings include monitoring for non-infectious pneumonitis, infections, oral ulcerations, and laboratory test alterations. Similarly, during everolimus administration, application of live vaccines should be avoided because of potential drug-induced lymphopenia.

4 Summary of recommendations from SOGUG for the treatment of advanced RCC

The speed at which targeted therapies are being developed and incorporated into the treatment of advanced RCC is surprising. After decades in which the only systemic treatment options available for advanced disease were IL-2 and IFN-α, to date, six new targeted therapies related to two main biological pathways (VEGF and mTOR) have provided meaningful benefits to patients with advanced or metastatic RCC (Table 2).

Very recently, the SOGUG issued its first public statement of recommendations for the optimal management of this disease [2]. One year later, most pivotal phase III trials on which these recommendations were based have been updated and/or fully reported. Moreover, a new multikinase inhibitor, pazopanib, has been demonstrated though a prospective, randomized, phase III, to provide a longer PFS than placebo in treatment-naïve or cytokine-pretreated patients with advanced RCC and, as a consequence, it has already been approved by the FDA and the EMEA. Because of this, we considered it important to update our recommendations to optimize the management of this disease.

Based on data from phase III trials available to date, we consider it is still important to stratify patients with advanced RCC into their prognostic risk group. At this point, we consider sunitinib, bevacizumab plus IFN-α, or pazopanib are valid options for first-line treatment in patients with favorable or intermediate prognosis (Table 3). The toxicity profile of each drug, along with the specific characteristics of the patient, should help to select the optimal drug and schedule to be administered. On the other hand, we recommend that patients with poor prognosis should be treated with temsirolimus as first-line treatment.

Additionally, second-line treatment should be selected taking into account which drugs were administered at first-line setting. Thus, if the patient was previously treated with cytokines, sorafenib should be administered as second-line treatment. In contrast, if the patient received a tyrosine kinase as first-line treatment, everolimus should be considered as the standard second-line treatment.

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