Effectiveness and Safety of Cabozantinib Treatment in Patients with Advanced Renal Cell Carcinoma in Spanish and Portuguese Real-world Practice: The SOGUG-SPRWEC Study

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Abstract

Evidence of cabozantinib as a second-line treatment in advanced/metastatic renal cell carcinoma (amRCC) is limited. This observational, ambispective, multicenter study investigated its real-world effectiveness and safety. In the 258 included patients, the median PFS was 7.63 months and median OS 15.36 months, in line with previous trials and real-world series, supporting cabozantinib use as a second or subsequent treatment for amRCC.

Background: The SPRWEC study investigated cabozantinib effectiveness and safety in patients with advanced renal cell carcinoma (RCC) in real-world Spanish and Portuguese settings. **Patients and methods:** Observational, ambispective, multicenter study including adult patients with advanced RCC receiving cabozantinib between October 2016 and May 2020 as second or subsequent treatment line. Primary endpoint was progression-free survival (PFS). **Results:** About 258 patients (mean [SD] age 62.5 [11.0] years, 75.6% male) were included, 55.8% with prior immunotherapy.

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Median follow-up was 34.3 months. Median PFS was 7.63 months (95% CI, 6.64-8.72). Median overall survival (OS) was 15.36 months (95% CI, 11.58-19.11); objective response rate (ORR), 29.5% (95% CI, 24.0-35.4); median time to first response, 3.27 months (95% CI, 3.03-3.68); median duration of response, 9.77 months (95% CI, 7.24-12.63); median time to discontinuation, 6.97 months (95% CI, 5.79-8.42). Prior immunotherapy increased ORR (OR 2.132) and decreased OS (HR 1.529). ECOG 0-1 and dose reductions were associated with increased PFS (HR 0.470 and 0.558); poor and intermediate MSKCC (HR 3.861 and 1.681) and IMDC risks (HR 2.558 and 1.537) with decreased PFS. Most common AEs were diarrhea (41.9%), asthenia (34.9%), and anorexia (18.2%). **Conclusion:** Cabozantinib's effectiveness and safety as second or subsequent treatment line for advanced RCC in real-world settings are similar to those observed in clinical trials. This treatment after prior immunotherapy, the front-line standard of care, resulted in increased ORR and decreased OS, without changes in PFS.

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Introduction

Renal cell carcinoma (RCC) represents about 80% of all kidney cancers, with clear cell RCC (ccRCC) being its most common subtype (75%-85%) and the focus of most clinical trials.[1,2] Median age at diagnosis is around 60 years, with male predominance.[3] Approximately 30% of patients present with metastatic disease at diagnosis, and about one third develop distant metastases and/or local recurrences after curative treatment for their primary tumor.[4,5] Patients diagnosed with advanced disease have a poor survival rate, being around 59% in advanced RCC at 5 years and 42% in metastatic RCC (mRCC) at 6 years[6,7]

Until 2018, mainstay treatments for patients with locally advanced RCC and mRCC (amRCC) were vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) and, in selected patients, mammalian target of rapamycin (mTOR) inhibitors.[2] However, the addition of immunotherapy treatments with immune checkpoint inhibitors (CPIs) to the armamentarium of RCC treatments has shifted the treatment landscape, and the current standard of care is based on CPIs.[8] Clinical guidelines recommend dual immunotherapy targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) inhibitor (eg, nivolumab plus ipilimumab), or combination regimens based on CPIs and targeted therapy with a VEGFR TKI (ie, axitinib, lenvatinib, and cabozantinib) as first-line treatment for amRCC, irrespective of the risk group.[9-11]

Cabozantinib is an oral multi-kinase inhibitor that targets VEGFR2, MET (hepatocyte growth factor receptor), AXL, RET, FLT3, and c-KIT[12] that was approved for patients with RCC previously treated with antiangiogenic therapy based on the results from the phase 3 METEOR study. In this clinical trial, cabozantinib resulted in increased progression-free survival (PFS) and overall survival (OS) compared to the mTOR inhibitor everolimus, demonstrating a clinical benefit for patients with amRCC.[13] Furthermore, in the first-line setting, the phase 2 randomized CABOSUN trial comparing cabozantinib versus sunitinib showed the superiority of cabozantinib, with a median PFS of 8.2 versus 5.6 months, respectively, in intermediate- and poor-risk patients with amRCC.[14-16] Therefore, cabozantinib is a preferred second-line option.[9,11]

The choice of a second-line treatment largely depends on the first-line treatment received.[2] However, robust evidence in the second-line setting is missing, particularly after front-line CPIs.[9,10] Moreover, data regarding cabozantinib's effectiveness in the real-world setting are needed to understand its benefit-risk profile as an established therapy and to guide treatment decisions. The SPRWEC study aimed to assess the effectiveness and safety of single agent cabozantinib treatment in a nonselected real-world RCC population including patients who received the treatment in the second line or beyond.

Patients and Methods

Study Design and Population

This was an observational, ambispective (retrospective and prospective), multicenter, postauthorization study including adult patients (aged ≥ 18 years) diagnosed with amRCC who received at least 1 dose of cabozantinib between October 2016 and May 2020. Patients were treated in 32 Spanish and Portuguese participating centers and received cabozantinib according to routine clinical practice as the second or subsequent treatment line. Patients who declined to sign the informed consent form and those whose hospital medical records were unavailable for review were excluded. Retrospective data were collected from electronic medical records starting in October 2019 and patients were prospectively followed-up until the last contact or death or the end of the study (December 2021).

This study followed local personal data protection regulations and the ethical principles from the Declaration of Helsinki. Patients provided written informed consent. The *Comité de Ética de la Investigación con medicamentos de Galicia (CEIm-G)* (Committee on the ethics of research with medicines in Galicia) approved the study protocol.

Objectives and Variables

The primary endpoint was progression-free survival (PFS), defined as the time (months) from the start of cabozantinib treatment to the date of the first documented evidence of disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[17] or death from any cause, and was calculated as the median and rate (6 and 12 months). Secondary endpoints were overall survival (OS), calculated as the median and rate, best response, objective response rate (ORR), median time to first response, median and duration of response.

To evaluate the safety of cabozantinib, the incidence of adverse events (AEs) were calculated according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and dose reductions and temporary interruptions or discontinuations were collected.

Additional secondary effectiveness outcomes were to assess the positioning of cabozantinib in the treatment pathway and describe the baseline characteristics of patients treated with cabozantinib. To assess the positioning of cabozantinib in the treatment pathway, variables related to treatment were evaluated, including time to treatment initiation (months) from first RCC diagnosis and amRCC diagnosis, duration of treatment (months), relative dose intensity, dose reduction, and prior and subsequent therapies. The relative dose intensity was calculated by dividing the total dose received—sum of the daily doses administered during treatment—by the total number of days in the treatment period, considering any dose reductions and treatment interruptions, and was expressed as a percentage.

Baseline characteristics of patients treated with cabozantinib included demographic characteristics (age and gender), clinical characteristics (ie, family history, and comorbidities), and baseline prognostic factors, including RCC characteristics (RCC grading and TNM Stage), Eastern Cooperative Oncology Group (ECOG) performance status (PS), modified Charlson comorbidity index, risk groups based on the Memorial Sloan-Kettering Cancer Center (MSKCC) and International Metastatic RCC Database Consortium (IMDC), and metastatic sites.[18,19]

Statistical Analysis

Effectiveness and safety were analyzed in the Full Analysis Set (FAS), including all patients receiving at least 1 drug exposure in the second or subsequent treatment lines.

Quantitative variables were described as the mean and standard deviation (SD) or as median and interquartile range (IQR: Q1, Q3). Categorical variables were described as frequencies and percentages. Survival was estimated with the Kaplan-Meier method for time-to-event endpoints (PFS, OS since treatment initiation, OS since RCC diagnosis, time to first response, duration of response, and time to discontinuation). Median PFS was calculated with the corresponding 95% confidence interval (CI). Categorical outcomes (ORR and best response) were described with frequencies and percentages, and the 95% CI was estimated using the Clopper-Pearson exact method.

PFS and OS were analyzed in patient subgroups according to the number of prior lines of RCC treatment (< 2 and ≥ 2), ECOG (0-1 and ≥ 2), ccRCC (yes and no), renal insufficiency (yes and no), dose reduction (yes and no), modified Charlson index (< 3 and ≥ 3), risk category based on MSKCC (favorable, intermediate, and poor), risk category based on IMDC (favorable, intermediate, and poor), prior CPI treatment (yes and no), bone, brain and liver metastases (yes and no), and age (≥ 65 and < 65 years). ORR, time to first response, and duration of response were reported for key prognostic categories (prior treatment with CPIs, IMDC and MSKCC risks, metastasis locations, modified Charlson index, and prior treatment lines (< 2 and ≥ 2). Patients were classified into subgroups according to available data.

The relationships between prognostic factors and time-to-event primary (PFS) and secondary effectiveness outcomes (OS, time to first response, and duration of response) were investigated using the Cox regression model adjusted by potential prognostic subgroups. Covariate estimates, hazard ratios, corresponding 95% CI, and *P*-values were presented. The Efron method for tie handling in survival analysis was used. *P*-values were based on the likelihood ratio. The 95% CI for the hazard ratio (HR) was based on the profile-likelihood method. The assumption of proportional hazards was assessed by plotting survival over time by prognostic factor. To investigate the relationship between prognosis factors and ORR, a logistic regression analysis was used.

Sample size was based on the log-rank test power analysis. A sample size of 122 events (progressions) from 130 patients was needed to attain a 90% power at a nominal level of one-sided alpha of 0.025 estimating the PFS. In the case of an 80% power, then only 91 events from 97 patients were enough. As observed in previous studies, a median PFS of 7.5 months was assumed for subjects on cabozantinib.[13] Patients were followed up for a minimum of 32 months, as per routine practice in every participating site, usually every 3 months. Therefore, based on the methods described by Jung et al. to calculate the number of required events for the estimation of PFS,[20] the final analysis was performed on a minimum of 190 patients with 184 progression events.

Statistical significance was set at a 2-sided $\alpha < 0.05$. Statistical analyses were conducted using the SAS® software for Windows, version 9.3 or later.

Results

Baseline and Treatment Characteristics of Study Patients

Twenty-seven of 285 recruited patients failed to meet the inclusion criteria, resulting in a study population of 258 patients (Supplemental Figure 1). Median follow-up was 34.3 months (95% CI, 28.9-43.8). Mean (SD) age of study patients was 62.5 (11.0) years and most (75.6%) were male. More than half of patients were staged at T3 and T4, 63.4% did not have lymph node involvement (N0), and all had metastatic disease. Most patients had favorable and intermediate risk based on MSKCC and IMDC criteria and had an ECOG 0-1. Regarding prior therapies, 95.6% of patients received VEGF/VEGFR inhibitors, and 55.8% received CPIs. Other clinical characteristics are described in Table 1 .

The characteristics of cabozantinib treatment are summarized in Supplemental Table 1. Mean (SD) time since first diagnosis of RCC and advanced RCC to cabozantinib initiation were 56.2 (50.8) and 35.1 (29.2) months, respectively. The initial dose of cabozantinib was 60 mg for 74.7% of patients, 40 mg for 24.1%, and 20 mg for 1.2%, with a median minimum daily dose of 40 mg (IQR: 40.0, 60.0). Median (range) duration of cabozantinib treatment was 6.15 (0.03-46.78) months. VEGF/VEGFR inhibitors and CPIs were also the most frequent subsequent therapies (41.5% and 54.7% of patients, respectively).

Effectiveness Outcomes in Overall Population

Median PFS was 7.63 months (95% CI, 6.64-8.72) with a PFS rate of 32.9% (95% CI, 27.1-38.8) at 12 months and 20.5% (95% CI, 15.7-25.8) at 18 months (Figure 1). Of the 258 patients, 228 (88.8%) experienced a progression event during median overall follow-up of 34.3 months.

Table 1 Baseline Demographic, Clinical, and Treatment Characteristics of Study Patients, n (%) $n = 258$[a]

Demographic Characteristics	
Age, years	
< 50	30 (11.6)
50-59	66 (25.6)
60-69	92 (35.7)
70-79	65 (25.2)
≥ 80	5 (1.9)
Sex	
Male	195 (75.6)
Female	63 (24.4)
Clinical characteristics	
Comorbidities	
Obesity, $n = 251$	16 (6.4)
Hypertension, $n = 258$	134 (51.9)
Diabetes, $n = 258$	45 (17.4)
Polycystic kidney disease, $n = 256$	1 (0.4)
Renal insufficiency, $n = 256$	23 (9.0)
Family history of renal cancer or dysfunction, $n = 200$	
Renal cancer	7 (3.5)
Renal dysfunction	1 (0.5)
Clinical characteristics (Prognosis factors)	
ECOG PS, $n = 198$	
0	56 (28.3)
1	110 (55.6)
2	30 (15.2)
3	2 (1.0)
RCC histology, $n = 243$	
Clear cell	204 (84.0)
Papillary	28 (11.5)
Chromophobe	11 (4.5)
RCC stage (TNM)	
T staging, $n = 198$	
1	31 (15.7)
2	43 (21.7)
3	101 (51.0)
4	23 (11.6)
N staging, $n = 131$	
0	83 (63.4)
1	29 (22.1)
2	19 (14.5)
M, $n = 252$	
1	252 (100.0)
Modified Charlson comorbidity index without solid tumor score, categorized	
< 3	137 (53.1)
≥ 3	121 (46.9)
MSKCC risk, $n = 252$	
Favorable	69 (27.4)
Intermediate	159 (63.1)
Poor	24 (9.5)

(*continued on next page*)

Table 1 (*continued*)

Demographic Characteristics	
IMDC risk, $n = 255$	
Favorable	77 (30.2)
Intermediate	141 (55.3)
Poor	37 (14.5)
Metastatic sites	
Lungs	145 (56.2)
Bone	72 (27.9)
Liver	57 (22.1)
Kidneys	18 (7.0)
Brain	18 (7.0)
Previous therapies, n (%) $n = 251$	
VEGF/VEGFR	240 (95.6)
Immunotherapy	140 (55.8)
Radiotherapy	21 (8.4)
Chemotherapy	3 (1.2)
mTOR inhibitor	37 (14.7)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; IMDC = International Metastatic RCC Database Consortium; MSKCC = Memorial Sloan-Kettering Cancer Center; OS = overall survival; RCC = renal cell carcinoma.
[a] Unless otherwise stated.

Secondary effectiveness outcomes are shown in Figure 2. Median OS was 15.36 months (95% CI, 11.58-19.11) with an OS rate of 55.0% (95% CI, 48.6-60.9) at 12 months and 45.9% (95% CI, 39.6-51.9) at 18 months. Of the 258 patients, 185 (71.7%) had died. Almost one third (29.5%) of patients (95% CI, 24.0-35.4) had an objective response with a median time to first response of 3.27 months (95% CI, 3.03-3.68) and a median duration response of 9.77 months (95% CI, 7.24-12.63). Median time to discontinuation was 6.97 months (95% CI, 5.79-8.42).

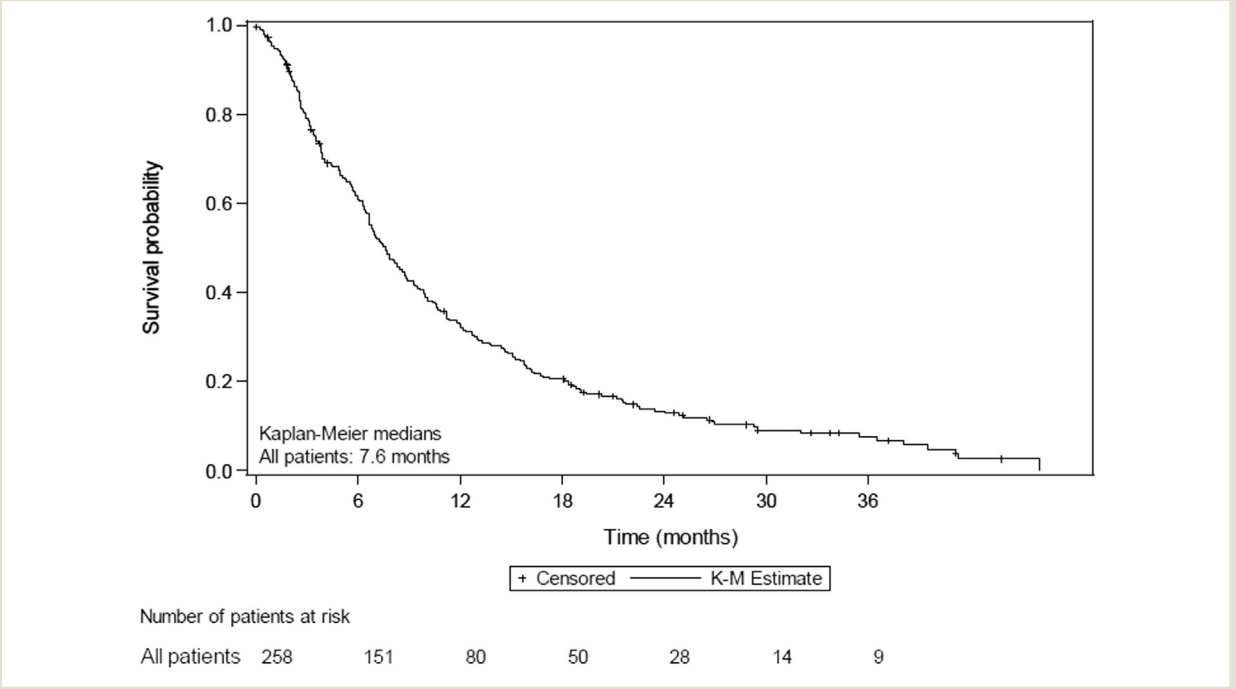
Regarding treatment response, of 231 evaluable patients, 2 (0.9%) showed a complete response, 74 (32.0%) a partial response, 104 (45.0%) a stable disease, and 47 (20.3%), a progressive disease. Four (1.7%) patients showed no complete response/no progressive disease.

Effectiveness Outcomes in Prior Immunotherapy Treatment Subgroup

Of the 140 patients with prior CPI treatment, median PFS was 7.66 months (95% CI, 6.48-8.72) with a PFS rate of 28.7% (95% CI, 21.4-36.5) at 12 months and 16.2% (95% CI, 10.6-22.9) at 18 months. Of the 140 patients with prior CPI treatment, 125 (89.3%) experienced a progression event. Median OS since treatment initiation was 11.97 months (95% CI, 9.51-15.56) with an OS rate of 49.6% (95% CI, 40.9-57.6) at 12 months and 36.7% (95% CI, 28.7-44.8) at 18 months.

Regarding response, 36.4% of patients (95% CI, 28.5-45.0) had an objective response with a median time to first response of 3.06 months (95% CI, 2.80-3.52) and a median duration response of 8.52 months (95% CI, 5.79-13.13). Of the 112 evaluable patients with prior immunotherapy, no patients showed a complete response, 51 (41.8%) showed a partial response, 42 (34.4%) a stable disease, and 29 (23.8%) a progressive disease.

Figure 1 Kaplan–Meier curve estimating progression-free survival.



Prognostic Factors for PFS (Primary Outcome)

Univariate subgroup analyses of PFS showed that only ECOG, dose reductions, and progression risk based on MSKCC and IMDC influenced PFS (Figure 3). Patients with ECOG 0-1 versus ≥ 2 and those with dose reductions vs. those without dose reductions showed increased median PFS and a significantly decreased risk of progression (HR 0.470; 95% CI, 0.319−0.715; $P < .001$ and HR 0.558; 95% CI, 0.428-0.725 $P < .001$), respectively. In contrast, median PFS decreased in patients with poor and intermediate MSKCC and IMDC risk compared to those with favorable risk group. Accordingly, the risk of progression significantly increased in patients with poor and intermediate MSKCC risk (HR 3.861; 95% CI, 2.290-6.324 $P < .001$ and HR 1.681; 95% CI, 1.231-2.331 $P = .001$) and in those with poor and intermediate IMDC risk (HR 2.558; 95% CI, 1.669-3.864 $P < .001$ and HR 1.537; 95% CI, 1.134-2.107 $P < .001$) (Figure 3). The 39 patients with non-ccRCC showed no differences in median PFS compared to those with ccRCC ($P = .795$).

Prognostic Factors for Secondary Effectiveness Outcomes

Univariate subgroup analyses of OS showed that ECOG, dose reductions, progression risk based on MSKCC and IMDC, brain metastasis, and prior CPIs influenced OS (Figure 4). Patients with ECOG 0-1 versus ≥ 2 and those with dose reductions versus without dose reductions showed longer estimated median OS and significantly reduced risk of death (HR 0.376; 95% CI, 0.251-0.579 $P < .001$ and HR 0.544; 95% CI, 0.406-0.727; $P < .001$), respectively. In contrast, patients with poor and intermediate risks based on MSKCC and IMDC and those with prior CPIs and brain metastasis had significantly increased risk of death (Figure 4). Patients with non-ccRCC showed no difference in median OS compared to those with ccRCC ($P = .836$).

Objective response, median time to first response, and median duration of response showed no significant differences according to hepatic or bone metastasis and Modified Charlson index (< 3 vs. > 3). In contrast, patients with prior CPIs had a significantly increased objective response rate (Odds ratio 2.132; 95% CI, 1.218-3.731; $P = .008$), with no significant differences in the median time to first response and the median duration of response. Patients with brain metastasis had a shorter median time to first response than those without (HR 2.997; 95% CI, 1.029-6.970, $P = .045$), with no significant differences in other outcomes (Supplemental Tables 2 to 4).

Safety

More than 75% of patients experienced AEs related to cabozantinib, most being G1-G2 (Table 2). One patient experienced a G5 AE, recorded as general health status deterioration, which the investigator attributed to cabozantinib treatment. The most common AEs were diarrhea (41.9%), asthenia (34.9%), and anorexia (18.2%) (Supplemental Table 5). Regarding treatment changes due to AEs ($n = 201$ patients with AEs), 70 (34.8%) patients required dose reductions, 79 (39.3%) required a treatment interruption, and 42 (20.9%) discontinued treatment. Moreover, 110 (54.7%) patients required additional medication due to an AE.

Discussion

This multicenter, observational, ambispective study evaluated the effectiveness and safety of cabozantinib use in a nonselected RCC

Figure 2 Kaplan–Meier curves estimating. (A) overall survival since treatment initiation, (B) time to first response, (C) duration of response, and (D) time to discontinuation.

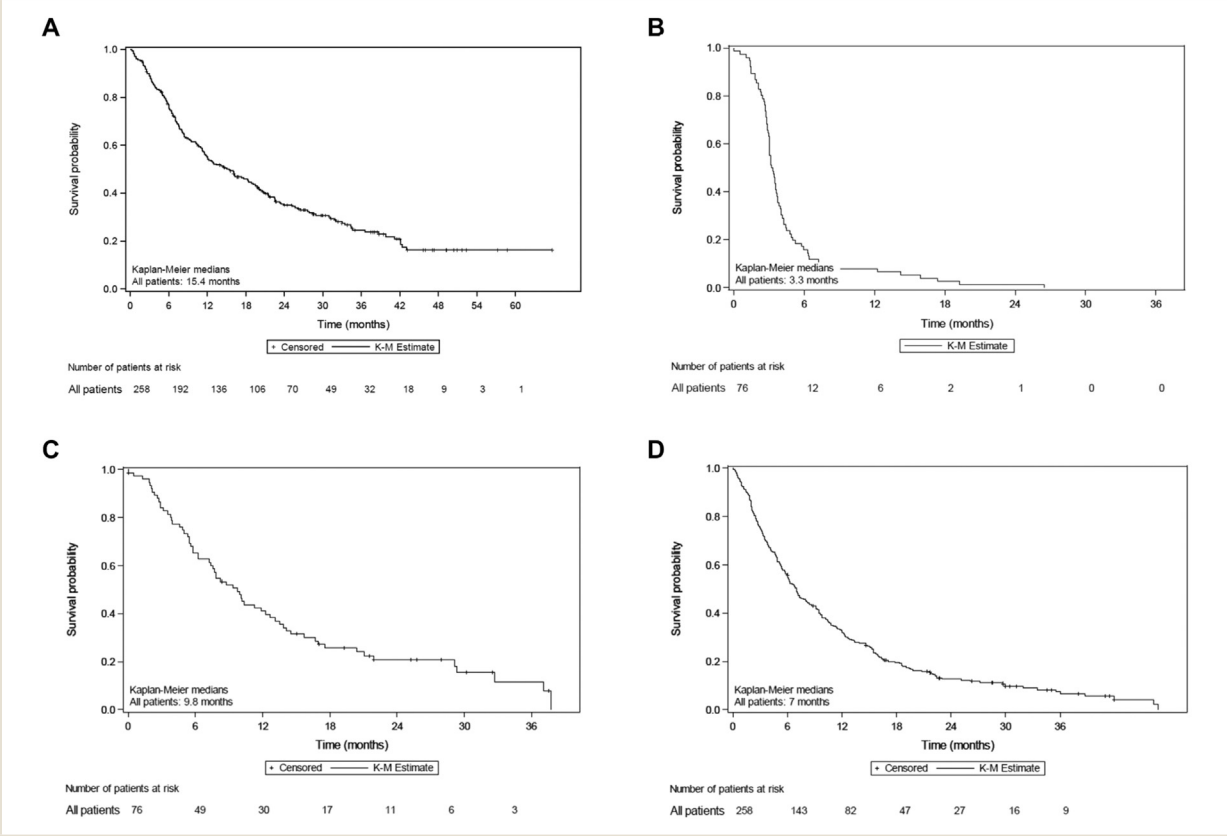


Table 2 Summary of Adverse Events, n (%) Patients/n Events, $n = 258$

	Patients ($n = 258$)
Patients with adverse events related to cabozantinib	201 (77.9)/954
Maximum severity grade	
1	42 (16.3)/449
2	78 (30.2)/293
3	68 (26.4)/102
4	4 (1.6)/4
5 (death)[a]	1 (0.4)/1
Unknown	8 (3.1)/105
Serious adverse event	22 (8.5)/34

[a] Recorded as general health status deterioration and attributed to cabozantinib treatment by the investigator.

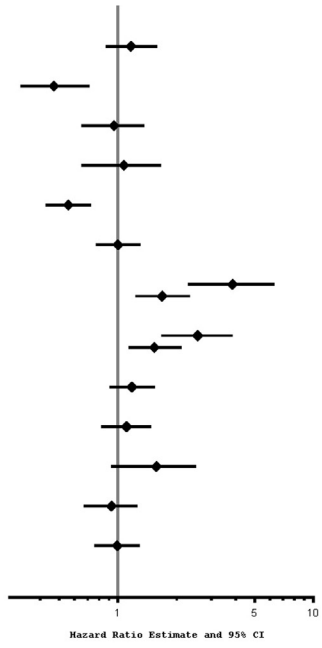
real-world population. In our cohort, median PFS was 7.63 months (95% CI, 6.64-8.72), median OS was 15.36 months (95% CI, 11.58-19.11), and ORR was 29.5%. In the subgroup of patients with prior CPIs, a median PFS of 7.66 months (95% CI, 6.48-8.72), a median OS of 11.97 months (95% CI, 9.51-15.56), and an ORR of 36.4% were found. Univariate subgroup analyses showed that ECOG 0-1 and dose reductions were associated with increased median PFS and OS, whereas poor and intermediate MSKCC and IMDC risk were associated with decreased median PFS and OS compared to favorable risk. Brain metastases were associated with decreased median OS but not PFS. Prior CPI treatment was associated with increased ORR and with decreased median OS. Regarding safety, more than 75% of patients presented with AEs, most of them of G1-G2, and .

In our study, cabozantinib use was similar to other real-world studies (RWS) regarding treatment initiation at the prescribed dose of 60 mg, with 70.9% of patients in the CABOREAL and 84.0% in the study by Venugopal et al. (73.5% in this study).[21,22] Moreover, median daily doses were similar among RWS: 40 mg (min-max: 23.9-60) in the CABOREAL and 45.5 mg (19.6-59.8) in Venugopal et al. (40.0 mg [IQR: 40.0, 60.0] in this study); these doses were similar to the 43 mg (IQR: 36, 56) in the METEOR study, despite all patients initiating treatment at 60 mg/day in the trial setting.[13,21,22] Median treatment duration in our study (6.2 months) was shorter than the median of 7.6 months in the METEOR and CABOREAL studies,[13,22] but similar to the median of 6 months in the Venugopal et al. study.[21]

The median PFS obtained with cabozantinib in the overall population of this study (7.63 months) was similar to other RWS,

Figure 3 Forest plot for stratified analyses of progression free survival. 95% CI = 95% confidence interval; NE = not estimable; CBZ = cabozantinib.
(A) The reference category is favorable risk. (B) Kaplan-Meier estimation. (C) Hazard ratios with respect to the reference category estimated using the Cox regression model. The Efron method is used for tie handling. The 95% CI for hazard ratio is based on the profile-likelihood method. *P*-values are based on the likelihood ratio.

Subgroup parameters	Number of patients	Events, n (%)	Median time in months (95% CI) [B]	Hazard ratio [C]	95% CI [C]	p-value [C]
Overall PFS time	258	229 (88.8%)	7.632 (6.645, 8.717)			
0 to 2 lines of RCC previous to CBZ (vs >= 3)						
Yes	193	169 (87.6%)	6.941 (6.283, 8.092)	1.166	0.870, 1.586	0.309
No	63	58 (92.1%)	10.559 (6.776,13.059)			
ECOG performance status < 2 (vs >= 2)						
Yes	166	149 (89.8%)	7.862 (6.645, 9.507)	0.470	0.319, 0.715	<.001
No	32	30 (93.8%)	3.914 (2.007, 5.296)			
Non-clear cell carcinoma						
Yes	39	34 (87.2%)	7.862 (5.592,12.697)	0.953	0.649, 1.356	0.795
No	204	180 (88.2%)	7.730 (6.645, 9.276)			
Renal insuficiency						
Yes	23	20 (87.0%)	7.237 (2.961,15.559)	1.069	0.654, 1.651	0.778
No	233	207 (88.8%)	7.632 (6.645, 8.816)			
Dose reduction						
Yes	129	110 (85.3%)	9.934 (7.862,11.349)	0.558	0.428, 0.725	<.001
No	129	119 (92.2%)	5.757 (3.816, 7.072)			
Modified Charlson index < 3 (vs >= 3)						
Yes	137	122 (89.1%)	7.434 (6.414, 8.816)	1.001	0.770, 1.301	0.996
No	121	107 (88.4%)	7.730 (5.987, 9.934)			
Risk factor based on MSKCC [A]						
Poor	24	23 (95.8%)	3.849 (2.105, 5.526)	3.861	2.290, 6.324	<.001
Intermediate	159	149 (93.7%)	7.467 (6.480, 8.717)	1.681	1.231, 2.331	<.001
Favorable	69	52 (75.4%)	10.855 (6.776,15.954)			
Risk factor based on IMDC [A]						
Poor	37	36 (97.3%)	3.882 (2.566, 6.250)	2.558	1.669, 3.864	<.001
Intermediate	141	129 (91.5%)	7.862 (6.678, 9.507)	1.537	1.134, 2.107	<.001
Favorable	77	61 (79.2%)	9.638 (6.842,14.572)			
Previous immunotherapy						
Yes	140	125 (89.3%)	7.664 (6.480, 8.717)	1.179	0.906, 1.538	0.221
No	118	104 (88.1%)	7.467 (5.822,10.855)			
Bone Metastasis						
Yes	72	63 (87.5%)	6.283 (4.474, 7.862)	1.105	0.821, 1.470	0.503
No	186	166 (89.2%)	8.289 (6.776, 9.507)			
Brain Metastasis						
Yes	18	17 (94.4%)	5.411 (1.908, 8.816)	1.570	0.921, 2.499	0.094
No	240	212 (88.3%)	7.730 (6.678, 9.276)			
Liver Metastasis						
Yes	57	52 (91.2%)	7.286 (4.474, 9.507)	0.926	0.670, 1.257	0.629
No	201	177 (88.1%)	7.664 (6.678, 9.276)			
Age >= 65 years (vs < 65 years)						
Yes	114	100 (87.7%)	7.862 (6.414, 9.638)	0.991	0.760, 1.288	0.945
No	144	129 (89.6%)	7.007 (6.086, 8.816)			

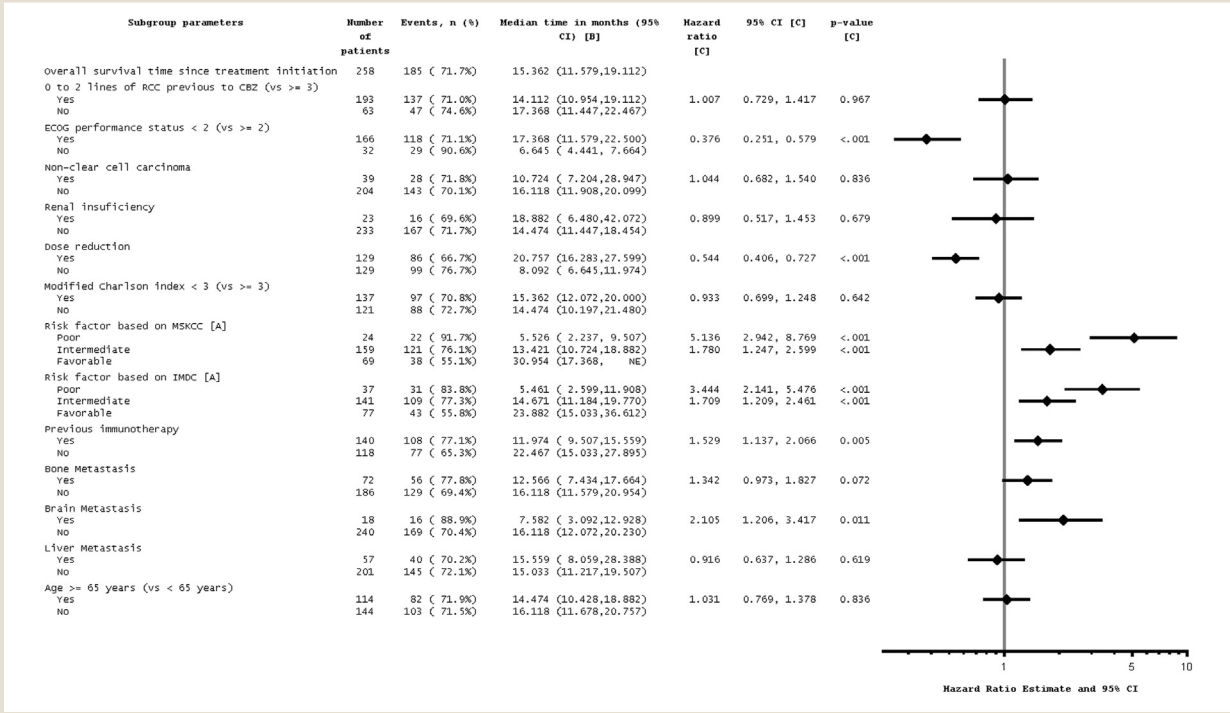


with a median PFS of 7.76 months (95% CI, 6.51-10.88) and 8.0 months (range: 0.5-10.8)[23,24] but shorter than a recently published patient series, reporting a median PFS of 10.8 months (95% CI, 5.5-16.2).[25] These results are consistent with previous efficacy data obtained in the clinical trial setting, such as the METEOR study, with a median PFS of 7.4 months (95% CI, 6.6-9.1).[13] However, median OS (15.36 months) was found to be lower than in the pivotal phase III METEOR study (21.4 months 95% CI, 18.7-not estimable).[13] Other RWS also showed lower OS than that obtained in pivotal clinical trials, which could be partly explained by the differences between randomized trials and real-life studies regarding patient characteristics and criteria to reduce the dose or discontinue the treatment.

Data from the CaboPoint study, an ongoing phase 2 multicenter, open-label study of cabozantinib in adults with unresectable, locally advanced, or metastatic ccRCC who have progressed after first-line CPI-based therapy, were recently presented.[26] Although not directly comparable due to differences in study design and follow-up times (3 months for now in CaboPoint and 34.3 months in our study), results in the population of patients with prior CPIs were similar between studies, with a similar ORR (29.5% in CaboPoint and 36.4% in our study), complete response (1.2% and 0%), partial response (30.5% and 36.4%), and progressive disease rates (17.1% and 20.7%). However, in the CaboPoint study, a higher percentage of patients had stable disease (51.2% in CaboPoint and 30.0% in our study). In the METEOR study, 18 (22%) patients who had received prior CPIs (anti-PD-1 or PD-L1) showed an objective response rate (95% CI, 6%-48%), lower than in our study, and did not reach PFS (not reached [NR]; 95% CI, 3.8-NR) and OS endpoints (NR, 95% CI, 12.4-NR). Similar to our study, no patients showed a complete response, although other response outcomes differed from our study, with 22% showing partial response, 50%, stable disease, and 11%, progressive disease.[27] In our study with prolonged follow-up, patients with prior CPIs had a shorter median OS compared to those without this therapy. These results may be explained by subsequent immunotherapy treatments, which may have contributed to prolonged survival after cabozantinib treatment in patients with no prior CPIs. Conversely, cabozantinib treatment after prior CPI resulted in increased ORR compared to patients with no prior CPI (36.4% vs. 21.2%; Odds ratio: 2.132). The absence of any CPI-based treatment regimen may explain these results. Nevertheless, in the context of the current standard of care, consisting of a front-line CPI-based regimen, our study results showing median PFS of 7.66 months, median OS of 11.97 months, and 36.4% objective response provide valuable real-world data.

Notably, our study included 39 patients with non-ccRCC, 28 with papillary RCC, and 11 with chromophobe RCC, who showed

Figure 4 Forest plot for stratified analyses of overall survival since treatment initiation. 95% CI = 95% confidence interval; NE = not estimable; CBZ = cabozantinib.
(A) The reference category is favorable risk. (B) Kaplan-Meier estimation. (C) Hazard ratios with respect to the reference category estimated using the Cox regression model. The Efron method is used for tie handling. The 95% CI for hazard ratio is based on the profile-likelihood method. *P*-values are based on the likelihood ratio.



Subgroup parameters	Number of patients	Events, n (%)	Median time in months (95% CI) [B]	Hazard ratio [C]	95% CI [C]	p-value [C]
Overall survival time since treatment initiation	258	185 (71.7%)	15.362 (11.579,19.112)			
0 to 2 lines of RCC previous to CBZ (vs >= 3)						
Yes	193	137 (71.0%)	14.112 (10.954,19.112)	1.007	0.729, 1.417	0.967
No	63	47 (74.6%)	17.368 (11.447,22.467)			
ECOG performance status < 2 (vs >= 2)						
Yes	166	118 (71.1%)	17.368 (11.579,22.500)	0.376	0.251, 0.579	<.001
No	32	29 (90.6%)	6.645 (4.441, 7.664)			
Non-clear cell carcinoma						
Yes	39	28 (71.8%)	10.724 (7.204,28.947)	1.044	0.682, 1.540	0.836
No	204	143 (70.1%)	16.118 (11.908,20.099)			
Renal insuficiency						
Yes	23	16 (69.6%)	18.882 (6.480,42.072)	0.899	0.517, 1.453	0.679
No	233	167 (71.7%)	14.474 (11.447,18.454)			
Dose reduction						
Yes	129	86 (66.7%)	20.757 (16.283,27.599)	0.544	0.406, 0.727	<.001
No	129	99 (76.7%)	8.092 (6.645,11.974)			
Modified Charlson index < 3 (vs >= 3)						
Yes	137	97 (70.8%)	15.362 (12.072,20.000)	0.933	0.699, 1.248	0.642
No	121	88 (72.7%)	14.474 (10.197,21.480)			
Risk factor based on MSKCC [A]						
Poor	24	22 (91.7%)	5.526 (2.237, 9.507)	5.136	2.942, 8.769	<.001
Intermediate	159	121 (76.1%)	13.421 (10.724,18.882)	1.780	1.247, 2.599	<.001
Favorable	69	38 (55.1%)	30.954 (17.368, NE)			
Risk factor based on IMDC [A]						
Poor	37	31 (83.8%)	5.461 (2.599,11.908)	3.444	2.141, 5.476	<.001
Intermediate	141	109 (77.3%)	14.671 (11.184,19.770)	1.709	1.209, 2.461	<.001
Favorable	77	43 (55.8%)	23.882 (15.033,36.612)			
Previous immunotherapy						
Yes	140	108 (77.1%)	11.974 (9.507,15.559)	1.529	1.137, 2.066	0.005
No	118	77 (65.3%)	22.467 (15.033,27.895)			
Bone Metastasis						
Yes	72	56 (77.8%)	12.566 (7.434,17.664)	1.342	0.973, 1.827	0.072
No	186	129 (69.4%)	16.118 (11.579,20.954)			
Brain Metastasis						
Yes	18	16 (88.9%)	7.582 (3.092,12.928)	2.105	1.206, 3.417	0.011
No	240	169 (70.4%)	16.118 (12.072,20.230)			
Liver Metastasis						
Yes	57	40 (70.2%)	15.559 (8.059,28.388)	0.916	0.637, 1.286	0.619
No	201	145 (72.1%)	15.033 (11.217,19.507)			
Age >= 65 years (vs < 65 years)						
Yes	114	82 (71.9%)	14.474 (10.428,18.882)	1.031	0.769, 1.378	0.836
No	144	103 (71.5%)	16.118 (11.678,20.757)			

no differences in PFS and OS compared to those with ccRCC after cabozantinib treatment. The median PFS in this subpopulation (7.86 months) was similar to the median 7 months reported in the PAPMET trial, which assessed cabozantinib in patients with papillary RCC in the first-line setting.[28] However, median OS was shorter in our study (10.73 months) compared to the median 21.5 months in this previous trial.[28] In this regard, OS was highly variable in our study subpopulation (95% CI, 7.204-28.947 months), likely reflecting patients' heterogeneity due to different non-ccRCC types.

In our study, some of the main prognostic factors for PFS and OS evaluated in other real-life studies were analyzed, including ECOG, IMDC and MSKCC risk groups, prior treatment lines, age, histology (clear cell vs. nonclear cell), dose reduction, and site of metastasis (bone, liver, and brain). Univariate subgroup analyses in our study showed that ECOG 0-1 and dose reductions were associated with increased median PFS and OS, whereas poor and intermediate MSKCC and IMDC risks, with decreased median PFS and OS compared to favorable risk groups. Brain metastasis and prior CPIs were associated with decreased median OS but not PFS. Previous studies had reported a relationship between cabozantinib dose reduction and improved PFS in patients with mRCC.[29] The improved outcomes in patients with dose reductions may be explained by variable pharmacokinetics among individuals, resulting in variable drug exposures, as reported for cabozantinib and other TKIs.[30–32] Thus, AEs leading to dose reductions may reflect increased drug exposures (ie, higher area-under-the-curve concentrations), resulting in improved outcomes.[32,33] Other real-world studies found that fewer lines of treatment (≤ 3 vs. > 3), ECOG ≥ 1, time to first progression after diagnosis > 1 year, hemoglobin level $\leq$ upper limit of normal, and bone metastases were predictive of poor PFS and OS.[23,24,34] Bodnar et al. also found that liver metastases and Hb level $\leq$ upper limit of normal were associated with shorter PFS but not OS.[34] The CABOREAL study reported that BMI ≥ 25 kg/m^2, prior nephrectomy, and favorable/intermediate IMDC groups were significant indicators of longer OS. In contrast, shorter OS was associated with not starting at the full daily dose of cabozantinib (40 mg/20 mg vs. 60 mg).[22] These results not only show that real-life studies are heterogeneous in terms of the type of predictors evaluated, but also suggest that RCC is an heterogenous disease, which limits comparisons between studies.

Regarding safety, cabozantinib showed a similar safety profile compared to the results obtained in the clinical trial and real-world setting. Thus, the incidence of AEs overall (77.9%) and of grade 3-4 (28.0%) in our study was similar to other real-world studies reporting lower overall rates of AEs (68%) than those observed in the METEOR study (100%).[13,24] These observations are not surprising given the differences between trial and real-world settings in the comprehensive collection of AEs. In our study, a significant

proportion of patients initiated cabozantinib at lower doses than the prescribed 60 mg (24.1% at 40-mg and 1.2% at 20-mg doses). The proportion of patients requiring dose reductions due to AEs in our study (34.8%) was lower than in the METEOR study and other RWS, with percentages varying between 42% and 69%.[13,21,22,24,34] The proportion of patients requiring a permanent suspension of treatment in our study (20.9%) was also within the ranges reported in RWS (4%−22.1%) but higher than in the METEOR study (9%).[21,22,24,34] This could be explained by differences between real-life studies and randomized trials in which criteria for dose reductions or treatment interruption are usually established at physician's discretion, according to the routine practice.

Limitations of this study are attributed to the observational nature of its design, such as the risk of reporting bias. General limitations of observational designs include the uneven sample size across variables due to missing data; however, despite the large sample size of our study, few data were missing. Furthermore, the real-world nature of this study limited the number of variables analyzed to those captured in the routine practice, precluding additional analyses of other prognostic factors, such as specific biomarkers. Despite these limitations, the results of this study, in which the effectiveness and safety of cabozantinib and its use in the real-world setting were assessed, provide the first feedback on the experience with this treatment in Spanish and Portuguese patients. This study also adds evidence that contributes to a better understanding of how to best manage patients with amRCC in routine clinical practice, which could guide policy decisions and contribute to updated treatment guidelines.

Conclusions

The effectiveness and safety profile of cabozantinib as second and subsequent treatment lines in a nonselected RCC real-world population was similar to that observed in clinical trials. ECOG, dose reductions, and MSKCC and IMDC risk groups based were identified as prognostic factors for PFS and OS.

Clinical Practice Points

Cabozantinib is an oral multi-kinase inhibitor and is the preferred second-line option in patients with advanced/metastatic renal cell carcinoma (RCC) after front-line antiangiogenic treatment. However, robust evidence in the second-line setting is still limited, particularly after immune checkpoint inhibitors and more data are needed in the real-world setting to understand its benefit-risk profile. This observational, ambispective, multicenter study assessed the effectiveness and safety of cabozantinib treatment in a nonselected real-world RCC population from Spain and Portugal. We found that cabozantinib use regarding initial dose was similar to previous clinical trials and other real-world studies. PFS and OS outcomes were similar to these real-world studies, although OS was shorter than in clinical trials. ECOG 0-1 and dose reductions were associated with increased PFS and OS, whereas poor and intermediate MSKCC and IMDC risk were associated with decreased PFS and OS. Brain metastases were associated with decreased OS but not PFS. Prior treatment with immune checkpoint inhibitors was associated with increased ORR and decreased OS. Most adverse events were mild and moderate, and no new safety signals were detected. Our results provide the first feedback on the experience with cabozantinib treatment in Spanish and Portuguese patients, supporting its use as a second or subsequent treatment line for advanced/metastatic RCC. This study adds evidence that contributes to a better understanding of how to best manage patients with advanced/metastatic RCC in routine clinical practice, which could guide policy decisions and update treatment guidelines.

Disclosure

CS reports a consultant or advisory role for BMS, Pfizer, Ipsen, MSD, EUSA Pharma, and Eisai, received research funding from Ipsen, BMS, Pfizer, and MSD, honoraria as a speaker for Ipsen, Eisai, Astellas, and MSD, and travel and accommodation expenses from Ipsen, Merck, and Bayer. ORT reports receiving honoraria from BMS, Ipsen, and Pfizer, a consulting or advisor role for Eisai, participating in speakers' bureau for Bayer, BMS, Ipsen, Janssen-Cilag, Pfizer, and Sanofi, and receiving funding for travel and accommodation expenses from Ipsen. RMB reports advisory roles for MSD, Pfizer, Merck, Janssen, and Astellas Pharma, and receiving honoraria or travel expenses from Roche, Sanofi Aventis, Astellas, Janssen, MSD, Bayer, Merck, and Pfizer. GAP received honoraria as consultant or advisory board member from Merck, grants for attending meetings/conferences from Ipsen, Merck, BMS, MSD, and Janssen, and participated in sponsored speakers bureau for Ipsen, BMS, Merck, Astellas, and Janssen. AMBM received honoraria as consultant/speaker from Amgen, Astellas, AstraZeneca, Bayer, B. Braun, BMS, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, OMPharma, Pfizer, Pierre Fabre, Roche, and Servier. NFN reports an advisory/consultant role for Pfizer, receiving honoraria as a speaker from Pfizer, Ipsen, Roche, BMS, and Bayer, and travel and accommodation expenses from Pfizer, Ipsen, Roche, BMS, Bayer, AstraZeneca, MSD, and Lilly. MJMV received travel grants from Astellas, BMS, Roche, Pfizer, Merck, and Ipsen and honoraria for speaker engagements, advisory boards, and continuous medical education from Astellas, Sanofi, Bayer, Roche, Ipsen, BMS, MSD, Pfizer, EUSA Pharma, Eisai, Novartis, AAA, and AstraZeneca. IGC received honoraria as a speaker from Ipsen, and honoraria for travel and accommodation expenses from Ipsen. OFC reports a consultant or advisory role for Astellas Pharma, Pfizer, BMS, Ipsen, Merck, and Eisai and received honoraria as a speaker for Novartis, BMS, Ipsen, Roche, Astellas Pharma, and Bayer, and travel and accommodation expenses from BMS, Ipsen, and Astellas. RGS reported advisory roles for BMS, Roche, AstraZeneca, Pfizer, Ipsen, MSD, Merck, Novocure, and Novartis, and received honoraria for travel, accommodation, and conference expenses from BMS, Roche, Pfizer, AstraZeneca, Janssen, Astellas, MSD, Merck, Ipsen, and Bayer. GCH received honoraria as consultant or advisory board member from BMS, and grants for attending meetings/conferences from Ipsen, BMS, and MSD, and participated in sponsored speakers bureau or educational activities for Ipsen, BMS, and MSD. JAA reports consultant/speaking/advisory roles for AstraZeneca, Pfizer, BMS, MSD, Roche, Ipsen, Sanofi, and Novartis, received grant or travel support from MSD, Pfizer, Sanofi, BMS, Takeda, and Roche, and participated as researcher in clinical trials from Pfizer, AstraZeneca, Janssen, BMS, Roche, Ipsen, and Astellas. MJJF reports advisory roles and participation in medical

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CRediT authorship contribution statement

Cristina Suárez: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Òscar Reig Torras:** Writing – review & editing, Data curation. **Rafael Morales Barrera:** Writing – review & editing, Data curation. **Ángel Rodríguez Sánchez:** Writing – review & editing, Data curation. **Georgia Anguera Palacios:** Writing – review & editing, Data curation. **André Miguel Branco Manshino:** Writing – review & editing, Data curation. **Natalia Fernández Núñez:** Writing – review & editing, Data curation. **María José Méndez Vidal:** Writing – review & editing, Data curation. **Icíar García Carbonero:** Writing – review & editing, Data curation. **Ovidio Fernández Calvo:** Writing – review & editing, Data curation. **Regina Gironés Sarrió:** Writing – review & editing, Data curation. **Guillermo Crespo Herrero:** Writing – review & editing, Data curation. **Javier Afonso Afonso:** Writing – review & editing, Data curation. **María José Juan Fita:** Writing – review & editing, Data curation. **Josep Gumà Padró:** Writing – review & editing, Data curation. **Martín Lázaro Quintela:** Writing – review & editing, Data curation. **Alejo Rodriguez-Vida:** Writing – review & editing, Data curation. **Carolina Hernández Pérez:** Writing – review & editing, Data curation. **Ana Medina Colmenero:** Writing – review & editing, Data curation. **Ricardo Collado Martín:** Writing – review & editing, Data curation. **Carmen Garcías de España:** Writing – review & editing, Data curation. **Carmen Molins Palau:** Writing – review & editing, Data curation. **Esther Martínez Ortega:** Writing – review & editing, Data curation. **Enrique Gallardo:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Ethics Approval and Consent to Participate

The Sponsor and investigators of the study ensured that patient data procedures followed the General Data Protection Regulation (EU) 2016/679 (GDPR) and personal data protection regulations applicable in both countries, such as Law 58/2019, of 8th August in Portugal and LOPD 3/2018, of 5th December in Spain. This study was performed after obtaining approval by the *Comité de Ética de la Investigación con medicamentos de Galicia* (CEIm-G) (Committee on the ethics of research with medicines in Galicia). Furthermore, it was developed following the ethical principles originating from the latest version of the Declaration of Helsinki accepted by local authorities, which are in line with Good Clinical Practice (GCP) and the requirements of current Spanish and Portuguese regulations. Patients provided informed consent before study inclusion.

Consent for Publication

Patients provided consent for the use of study data in publications.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary information file for the submission "Effectiveness and Safety of Cabozantinib Treatment in Patients with Advanced Renal Cell Carcinoma in Spanish and Portuguese Real-world Practice: The SOGUG-SPRWEC Study" by Suárez et al

This file accompanying the main manuscript includes additional data not considered sufficiently relevant to be included in the main document: A detailed description of cabozantinib treatment characteristics (Table S1), stratified analyses of secondary outcomes (Table S2-S4), description of adverse events (Table S5), and the study patient flow chart (Figure S1).

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Table S1 Characteristics of cabozantinib treatment, n=258.

Time since first diagnosis of RCC to treatment initiation, mean (SD) (months) n=258	56.2 (50.8)
Time since diagnosis of advanced RCC to treatment initiation, mean (SD) (months) n=254	35.1 (29.2)
Duration of treatment, median (min–max) (months) n=254	6.15 (0.03–46.78)
Relative dose intensity, mean (SD) (%) n=253	83.0 (22.1)
Prescribed daily dose, n (%) (mg) n= 257	
60	192 (74.7)
40	62 (24.1)
20	3 (1.2)
Line of treatment, n (%) n=258	
Second line	92 (35.7)
Third line	101 (39.1)
Fourth line	39 (15.1)
Later	26 (10.1)
Subsequent therapies, n (%) n=106	
VEGF/VEGFR inhibitors	44 (41.5)
Immunotherapy	58 (54.7)
Radiotherapy	9 (8.5)
Chemotherapy	1 (0.9)
mTOR inhibitor	31 (29.2)
Dose reduction, n (%) n=258	
Yes	129 (50.0)
No	129 (50.0)

SD, standard deviation; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth; mTOR, mammalian target of rapamycin.

Table S2 Objective response to cabozantinib, n=258.

	n	n (%)	95% CI[1]	Logistic univariate analysis[2] *p*-value	Odds ratio	95% CI
All patients	258	76 (29.5)	24.0–35.4			
Liver metastasis						
Yes	57	14 (24.6)	14.1–37.8	0.360	0.730	0.372–1.431
No	201	62 (30.8)	24.5, 37.7			
Bone metastasis						
Yes	72	20 (27.8)	17.9–39.6	0.713	0.893	0.488–1.632
No	186	56 (30.1)	23.6–37.2			
Brain metastasis						
Yes	18	5 (27.8)	9.7–53.5	0.871	0.915	0.315–2.664
No	240	71 (29.6)	23.9–35.8			
Mod. Charlson index						
<3	137	44 (32.1)	24.4–40.6	0.319	1.316	0.767–2.258
>3	121	32 (26.4)	18.8–35.2			
Prior immunotherapy						
Yes	140	51 (36.4)	28.5–45.0	0.008	2.132	1.218–3.731
No	118	25 (21.2)	14.2–29.7			

95% CI, 95% confidence interval.
[1] The 95% CI for proportions based on Clopper Pearson method.
[2] Comparisons between metastasis subgroups and previous immunotherapy based on a logistic regression model, with "No" being the reference. The 95% CI and *p*-values were calculated using the Wald method. The comparison between modified Charlson index categories is based on the Cox regression model, with >3 being the reference. The Efron method was used for tie handling. The 95% CI for hazard ratio was calculated using the profile-likelihood method and *p*-values using the likelihood ratio.

Table S3 Time to first response to cabozantinib, n (%) n=258.

	n	Median duration (months)[1]	95% CI[2]	Cox univariate analysis[3] *p*-value	Hazard ratio	95% CI
All patients	258	3.273	3.026–3.684			
Liver metastasis						
Yes	57	3.618	2.105–4.770	0.904	1.037	0.553–1.816
No	201	3.191	2.895–3.684			
Bone metastasis						
Yes	72	3.586	2.862–4.441	0.729	0.914	0.534–1.502
No	186	3.109	2.895–3.586			
Brain metastasis						
Yes	18	2.730	0.526–3.520	0.045	2.997	1.029–6.970
No	240	3.388	3.026–3.717			
Mod. Charlson index						
<3	137	3.059	2.796–3.651	0.306	1.271	0.804–2.033
>3	121	3.586	3.026–4.441			
Prior immunotherapy						
Yes	140	3.059	2.796–3.520	0.096	1.506	0.932–2.496
No	118	3.717	3.026–5.954			

95% CI, 95% confidence interval; NE, not estimable.
[1] The estimation is based on the Kaplan-Meier method.
[2] The 95% CI for proportions was calculated using the Clopper Pearson method.
[3] Comparisons between metastasis subgroups and previous immunotherapy based on a logistic regression model, with "No" being the reference. The 95% CI and *p*-values were calculated using the Wald method. The comparison between modified Charlson index categories is based on the Cox regression model, with >3 being the reference. The Efron method was used for tie handling. The 95% CI for hazard ratio was calculated using the profile-likelihood method and *p* -values using the likelihood ratio.

Table S4 Duration of response to cabozantinib, n=258.

		Median duration (months)[1]	95% CI[2]	Cox univariate analysis[3] *p*-value	Hazard ratio	95% CI
All patients	76	9.77	7.24–12.63			
Liver metastasis						
Yes	14	10.51	3.13–29.31	0.599	0.841	0.414–1.560
No	62	9.77	6.25–12.63			
Bone metastasis						
Yes	20	10.05	2.73–20.43	0.782	1.084	0.595–1.877
No	56	9.77	7.24–12.63			
Brain metastasis						
Yes	5	5.79	0.03–10.13	0.055	2.854	0.976–6.683
No	71	9.93	7.60–13.55			
Mod. Charlson index						
<3	44	9.77	5.79–12.24	0.670	1.119	0.670–1.895
>3	32	10.31	5.46–16.97			
Prior immunotherapy						
Yes	51	8.52	5.79–13.13	0.606	1.149	0.682–1.990
No	25	11.25	5.30–21.09			

95% CI, 95% confidence interval.
[1] The estimation is based on Kaplan-Meier method.
[2] The 95% CI for proportions based on Clopper Pearson method.
[3] Comparisons between metastasis subgroups and previous immunotherapy based on a logistic regression model, with "No" being the reference. The 95% CI and *p*-values were calculated using the Wald method. The comparison between modified Charlson index categories is based on the Cox regression model, with >3 being the reference. The Efron method was used for tie handling. The 95% CI for hazard ratio was calculated using the profile-likelihood method and *p* -values using the likelihood ratio.

Table S5 Adverse events of any grade, n (%) n=258.

System Organ Class and Preferred Term classification	Total (n=258)
Blood and Lymphatic System Disorders	
Anemia	10 (3.9)
Endocrine Disorders	
Hypothyroidism	36 (14.0)
Gastrointestinal Disorders	
Diarrhea	108 (41.9)
Vomiting	25 (9.7)
Stomatitis	22 (8.5)
Nausea	21 (8.1)
Abdominal pain upper	15 (5.8)
General Disorders and Administration Site Condition	
Asthenia	90 (34.9)
Mucosal inflammation	19 (7.4)
Fatigue	15 (5.8)
Malaise	12 (4.7)
Metabolism and Nutrition Disorders	
Anorexia/decreased appetite	47 (18.2)
Nervous System Disorders	
Dysgeusia	12 (4.7)
Respiratory, Thoracic, and Mediastinal Disorders	
Dysphonia	15 (5.8)
Skin and Subcutaneous Tissue Disorders	
Palmar-plantar erythrodysesthesia	42 (16.3)
Vascular Disorders	
Hypertension	31 (12.0)

Figure S1 Disposition of study patients.