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Real-world evidence of nivolumab monotherapy in advanced renal cell carcinoma from a multicenter retrospective cohort study by the Spanish Genitourinary Oncology Group

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Abstract

Background The efficacy of nivolumab for advanced renal cell carcinoma (aRCC) has been evaluated in real-world evidence (RWE) studies across several European countries, yet data from Spain have been lacking.

Patients and methods We conducted a multicenter, retrospective study of 222 previously treated aRCC patients to assess the efficacy of nivolumab and the influence of pre-treatment factors on clinical outcomes across 13 Spanish centers. Eligible patients had received at least one dose of nivolumab in routine clinical practice. Demographic, clinical, and laboratory data were extracted from electronic records. Efficacy endpoints were overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and overall response rate (ORR). Survival estimates were calculated by the Kaplan–Meier method, and groups were compared with the log-rank test. The Cox proportional hazards regression model was used to evaluate factors independently associated with OS. Factors associated with disease control (DC) and response were tested with logistic regression in univariable and multivariable analyses.

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Comparisons between patient and disease characteristics were carried out using Fisher's exact test. All *P* values were two-sided, and those < 0.05 were considered statistically significant. Results were contextualized with key clinical experiences involving nivolumab monotherapy in aRCC.

Results With a median follow-up of 14.6 months, median overall survival (OS) was 18.1 months (95% confidence interval [CI], 14.2–23.7 months), and median progression-free survival (PFS) was 4.96 months (95% CI, 3.98–7.13). The disease control rate was 51% (95% CI, 45–58%), and the objective response rate was 23% (95% CI, 18–30%). Poor International Metastatic RCC Database Consortium (IMDC) risk score was independently associated with shorter OS, while prior nephrectomy predicted improved OS. Poor IMDC risk and ≥ 3 metastatic sites were independently associated with shorter PFS; ≥ 3 metastatic sites also correlated with reduced disease control.

Conclusion Consistent with previous clinical trials and RWE studies, our findings reinforce the efficacy of nivolumab in routine clinical practice for an unselected cohort of previously treated aRCC patients in Spain.

Keywords Immunotherapy, Kidney cancer, Nivolumab, Real-world evidence, Renal cell carcinoma

Introduction

Over the past few decades, the treatment landscape for advanced renal cell carcinoma (aRCC) has evolved significantly. Initially, cytokine therapies such as interleukin-2 and interferon-alpha were the standard of care, although their high toxicity limited widespread use. In the mid-2000s, targeted therapies emerged, beginning with the tyrosine kinase inhibitors sorafenib and sunitinib, which inhibit angiogenesis by blocking the VEGF pathway. These treatments led to substantial improvements in patient outcomes and became the standard of care for several years. However, most aRCC patients eventually developed resistance to these therapies, resulting in disease progression. Subsequently, mTOR inhibitors such as everolimus were introduced for patients who had progressed on tyrosine kinase inhibitors [1–3].

Fortunately, in November 2015, the U.S. FDA approved nivolumab, an anti-PD-1 antibody, for aRCC patients previously treated with anti-angiogenic agents [4, 5]. A few months later, in April 2016, the European Medicines Agency (EMA) granted its approval as well [6]. This milestone, which marked a major shift in the treatment landscape of aRCC, was based on results from the multicenter, randomized, two-arm, open-label phase 3 CheckMate 025 (CM-025) trial, in which nivolumab demonstrated a significant overall survival (OS) benefit compared to everolimus—yielding a 27% reduction in the risk of death and a remarkable median OS of 25 months [4].

However, because clinical trials are conducted in rigorously controlled patient populations, their results may not fully reflect the real-world efficacy of treatments when applied to unselected populations with more diverse clinical characteristics [7]. Accordingly, we conducted this multicenter retrospective study in a cohort of previously treated aRCC patients to evaluate the efficacy of nivolumab and the impact of various pre-treatment factors on treatment outcomes in routine clinical practice in Spain. Additionally, we placed our findings in the context of the most relevant clinical experiences reported to date in similar settings involving aRCC patients treated with nivolumab monotherapy.

Patients and methods

Study design and patient population

We conducted a multicenter retrospective study involving a cohort of 222 patients with aRCC treated with nivolumab in either the second line of therapy or beyond in the context of routine clinical practice between December 2015 and October 2021 in thirteen Spanish medical centers (Supplementary Table 1). Patients received nivolumab at doses of either 3 mg/kg every 2 weeks, 240 mg every 2 weeks, or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity.

Eligible patients were ≥ 18 years of age with histologically confirmed aRCC, had received at least one dose of nivolumab as part of routine clinical practice, and had no history of active malignancy within the previous 3 years (except for tumors treated with curative intent and with no evidence of recurrence) prior to initiation of nivolumab. Demographic, clinical, analytical, and pathological data, as well as corticosteroid use were extracted from electronic medical records. We considered laboratory parameters and corticosteroid use within a window of 30 days before the start of first nivolumab infusion.

The primary efficacy endpoint was OS. Secondary endpoints were PFS, DCR, and ORR. Tumor responses were assessed according to Response Evaluation Criteria in Solid Tumors guidelines version 1.1 every 10 ± 2 weeks or before if medical reasons were indicated following the local protocols of each center.

This study was approved by the Ethics Committee for Research with medicinal products of Galicia (2020/248), the Ethics Committee for Research with medicinal products of Euskadi (EPA2020065), the Ethics Committee for Research with medicinal products of Cantabria, the Ethics Committee for Research with medicinal products of

Hospital Universitario La Paz (PI-4313), the Ethics Committee for Research with medicinal products of Córdoba (1584-N-20), and the Ethics Committee for Research at Hospital Universitario Elche-Vinalopó. The study was conducted in accordance with the guidelines of Good Clinical Practice and the Declaration of Helsinki. All living patients provided written informed consent before enrollment. Informed consent was waived for deceased patients before study initiation.

Statistical analysis

OS was calculated from the date of nivolumab initiation until death from any cause or the last known follow-up for living patients. PFS was calculated from the date of nivolumab initiation until disease progression, death from any cause, or the last known follow-up for patients without documented disease progression. DCR was defined as the proportion of patients who achieved a complete or partial response and stable disease, and ORR as the proportion of patients who achieved a complete or partial response. Patients who died before radiologic assessment were considered not evaluable for response.

Survival estimates were calculated using the Kaplan–Meier method, and groups were compared with the log-rank test. The Cox proportional hazards regression model was used to evaluate factors independently associated with OS and PFS. Baseline clinicopathological variables included in the multivariable analysis were selected based on statistical significance in the univariable analysis (cutoff, $P < 0.05$). The proportional hazards assumption was verified using the Schoenfeld residual method.

Factors associated with disease control (DC) and response were tested using univariable logistic regression. Variables included in the final multivariable model were selected according to their statistical significance in univariable analysis (cutoff, $P < 0.05$). Comparisons between patient and disease characteristics were carried out using Fisher´s exact test. All *P*-values were two-sided, and values < 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.3.2 (Vienna, Austria).

Results

Patient population

Between 10 December 2015 and 19 October 2021, a total of 222 patients were enrolled and received at least one dose of nivolumab. Baseline patient and disease characteristics are detailed in Table 1. The median age was 65 years (range, 22–87 years). Twenty-seven percent ($n = 60$) of patients were female, and 73% ($n = 162$) were male. Most patients (90%) had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 ($n = 45$, 20%) or 1 ($n = 156$, 70%). IMDC risk scores were favorable in 20% ($n = 45$), intermediate in 59% ($n = 131$), and poor in 19% ($n = 43$) of patients. Ninety percent ($n = 200$) had undergone prior nephrectomy. Clear cell renal cell carcinoma (ccRCC) was the predominant histologic subtype, present in 85% ($n = 188$) of cases.

The most common sites of metastasis were the lungs ($n = 139$, 63%), lymph nodes ($n = 128$, 57%), liver ($n = 61$, 27%), and bones ($n = 85$, 38%). Five percent ($n = 11$) of patients had central nervous system (CNS) metastases. Table 1 compares the baseline characteristics of our cohort with those reported in various clinical trials and real-world evidence (RWE) studies of nivolumab in aRCC.

Treatment exposure and safety

At the time of data collection, after a median follow-up of 14.6 months (range, 0.1–88.4 months), the median number of nivolumab cycles administered was 7 (range, 1–125). At that point, 91% of patients ($n = 203$) had discontinued treatment, most commonly due to disease progression (70%, $n = 156$). Ten percent ($n = 23$) discontinued due to adverse events, 4% ($n = 9$) due to death, and 11% ($n = 24$) for other reasons. Treatment was ongoing in 9% ($n = 19$) of patients at the time of data cut-off.

Nivolumab was administered as second-line therapy in 143 patients (64%), third-line in 55 patients (25%), and fourth-line or beyond in 24 patients (11%). The most commonly used first-line therapies were sunitinib ($n = 120$, 54%) and pazopanib ($n = 89$, 40%). Among patients who received nivolumab as third-line or later therapy ($n = 79$), cabozantinib was the most frequently used second-line treatment ($n = 23$, 33%) (Supplementary Table 2).

Efficacy

Overall survival At the time of data collection, 73% ($n = 163$) of enrolled patients had died. Median OS was 18.1 months (95% CI, 14.2–23.7) (Table 2, Fig. 1A), and the 6-, 12-, 24-, and 36-month OS rates were 78% (95% CI, 73–84), 62% (95% CI, 56–69), 42% (95% CI, 36–49), and 28% (95% CI, 22–35), respectively (Table 2). Among ten baseline variables analyzed, four were associated with worse OS in univariable analysis: ECOG-PS ≥ 2 (HR = 2.5, 95% CI, 1.5–4.1; $P = 0.0002$), poor IMDC risk score (HR = 2.68, 95% CI, 1.85–3.88; $P < 0.0001$), > 1 prior therapy for metastatic disease (HR = 1.4, 95% CI, 1–1.9; $P = 0.047$), and ≥ 3 metastatic sites (HR = 1.61, 95% CI, 1.2–2.2; $P = 0.0025$). One variable was associated with better OS: prior nephrectomy (HR = 0.58, 95% CI, 0.35–0.94; $P = 0.029$). Of these, only two remained independently associated with OS in multivariable analysis: poor IMDC risk score (HR = 2.06, 95% CI, 1.36–3.12; $P = 0.0007$) was linked to worse OS, and prior nephrectomy (HR = 0.59, 95% CI, 0.35–0.99; $P = 0.047$) to improved OS (Table 3).

Table 1 Baseline patient and disease characteristics for cases treated with nivolumab across different clinical trials and real-world evidence experiences

Characteristics	SOGUG (this study)	NORA [8]	ITALIAN EAP [9]	NIVOREN [10]	UK [11]	Check-Mate-025 (nivolumab arm) [4, 12]
Study design	Multicenter, retrospective cohort study	Multicenter, prospective, observational, non-interventional study	Multicenter, prospective, single arm observational study	Multicenter, single-arm phase 2 trial	Multicenter, retrospective cohort study	Multicenter, randomized, two-arm, open-label phase 3 trial
Population size, *n*	222	228	389	720	151	410
Sex, *n* (%)						
Female	60 (27)	65 (29)	98 (25)	164 (23)	42 (28)	95 (23)
Male	162 (73)	163 (71)	291 (75)	556 (77)	109 (72)	315 (77)
Median age—*years (range)*	65 (22–87)	70 (44–86)	65 (34–85)	64 (NA)	66.9 (NA)	62 (23–88)
ECOG-PS, *n* (%)						
0	45 (20)	96 (42)	176 (45)	612 (85)[a]	49 (32)	276 (68)
1	156 (70)	80 (36)	174 (45)	-	59 (39)	132 (32)
2	21 (10)	16 (7)	24 (7)	108 (15)[a]	19 (13)	2 (0.5)
3	-	-	-	-	3 (2)	-
Missing	-	36 (16)	15 (4)	-	21 (14)	-
IMDC risk score, *n* (%)						
Favorable	45 (20)	33 (14)	62 (20)	131 (18)	23 (15)	145 (35)
Intermediate	131 (59)	133 (58)	212 (69)	404 (56)	60 (40)	201 (49)
Poor	43 (19)	34 (15)	33 (11)	183 (25)	29 (19)	64 (16)
Missing	3 (2)	28 (12)	82	2	39 (26)	-
Histological subtype, *n (%)*						
Clear cell	188 (85)	184 (80)	356 (91)	720 (100)	131 (87)	410 (100)
Non-clear cell[b]	33 (15)	38 (17)	26 (7)	-	13 (9)	-
Missing	1 (0.4)	6 (3)	7 (2)	-	7 (5)	-
Prior nephrectomy, *n (%)*						
Yes	200 (90)	195 (86)	369 (95)	609 (85)	110 (73)	364 (89)
No	22 (10)	29 (12)	20 (5)	111 (15)	41 (27)	46 (11)
Missing	-	4 (2)	-	-	-	-
Corticosteroid use, *n (%)*[c]						
Yes	16 (7)	NA	Excluded	Excluded	NA	Excluded
No	205 (92)					
Missing	1 (1)					
Number of prior systemic therapies in the metastatic setting, *n (%)*						
1	143 (64)	177 (78)	80 (21)	359 (50)	109 (72)	294 (72)
2	55 (25)	32 (14)	137 (35)	200 (28)	36 (24)	116 (28)
≥ 3	24 (11)	19 (8)	170 (44)	161 (22)	6 (4)	-
Number of metastatic sites, *n (%)*						
1	43 (19)	NA	NA	NA	NA	68 (17)
2	79 (36)					341 (83)[d]
≥ 3	100 (45)					-
Site of metastases, *n (%)*						
Liver	61 (27)	63 (28)	128 (33)	NA	43 (29)	100 (24)
Lung	139 (63)	163 (71)	286 (74)	NA	116 (77)	278 (68)
Bone	85 (38)	72 (32)	193 (50)	NA	53 (35)	76 (19)
Lymph nodes	128 (57)	NA	238 (69)	NA	65 (43)	200 (49)
Brain	11 (5)	11 (5)	32 (8)	NA	19 (13)	0[e]
Adrenal glands	35 (16)	41 (18)	NA	83 (12)	NA	NA
Peritoneum	26 (10)	10 (4)	NA	NA	NA	NA

Table 1 (continued)

Characteristics	SOGUG (this study)	NORA [8]	ITALIAN EAP [9]	NIVOREN [10]	UK [11]	Check-Mate-025 (nivolumab arm) [4, 12]
Soft tissue	7 (3)	NA	NA	NA	12 (8)	NA
Other	59 (27)[f]	98 (43)	NA	NA	33 (22)	NA

Abbreviations: *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *NA* not available

[a]In the original publication ECOG-PS was reported as ECOG-PS 0–1 versus ECOG-PS 2–3

[b]The non-ccRCC histologies included papillary carcinoma ($n=24$) and chromophobe carcinoma ($n=9$)

[c]≥ 10 mg of prednisone or equivalent

[d]Recorded in the original publication as patients with ≥2 metastatic sites

[e]Central nervous system metastases were an exclusion criterion in the CheckMate-025 trial

[f]Pancreas, meninges, mediastinum, retroperitoneum, kidney, skin, spleen, heart, breast, bowel, gynecological, thyroid gland, and surgery site

Table 2 Efficacy endpoints across different clinical trials and real-world evidence experiences

Endpoints	SOGUG (this study)	NORA [8]	ITALIAN EAP [9]	NIVOREN [10]	UK [11]	Check-Mate-025 (nivolumab arm) [4, 12]
Response, n (%)						
Complete response	15 (7)	3 (1.3)	3 (1)	9 (1.3)	NA	4 (1)
Partial response	38 (17)	43 (19)	87 (22)	135 (19.7)	NA	99 (24)
Stable disease	62 (28)	60 (26)	124 (32)	214 (31.1)	NA	141 (34)
Progressive disease	93 (42)	75 (33)	141 (36)	329 (47.9)	NA	143 (35)
Not evaluable	14 (6)	47 (21)	34 (9)	7	NA	23 (6)
ORR % (95% CI)	23 (18–30)	20	23	20.8	NA	23 (19–27)
DCR % (95% CI)	52 (45–58)	46	NA	NA	NA	NA
Median OS, months (95% CI)	18.1 (14.2–23.7)	24.3 (19–28)	NA	24.5	19.2 (16.9–27)	25.8 (22.2–29.8)
6-month OS rate, % (95% CI)	78 (73–84)	79	80 (76–84)	NA	NA	NA
12-month OS rate, % (95% CI)	62 (56–69)	65 (59–71)	63 (58–68)	69 (66–73)	NA	76
24-month OS rate, % (95% CI)	42 (36–49)	51 (44–58)	NA	NA	NA	52
36-month OS rate, % (95% CI)	28 (22–35)	37 (28–45)	NA	NA	NA	39
Median PFS, months (95% CI)	4.96 (3.98–7.13)	5.3 (3.9–6.7)	4.4 (3.7–6.2)	3.2 (2.9–4.6)	NA	4.2 (3.7–5.4)
Median nivolumab doses (range)	7 (1–125)	10 (1–96)	13 (1–49)	10 (1–30)	NA	NA

Abbreviations: *CI* confidence interval, *DCR* disease control rate, *NA* Not available, *NR* not reached, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival

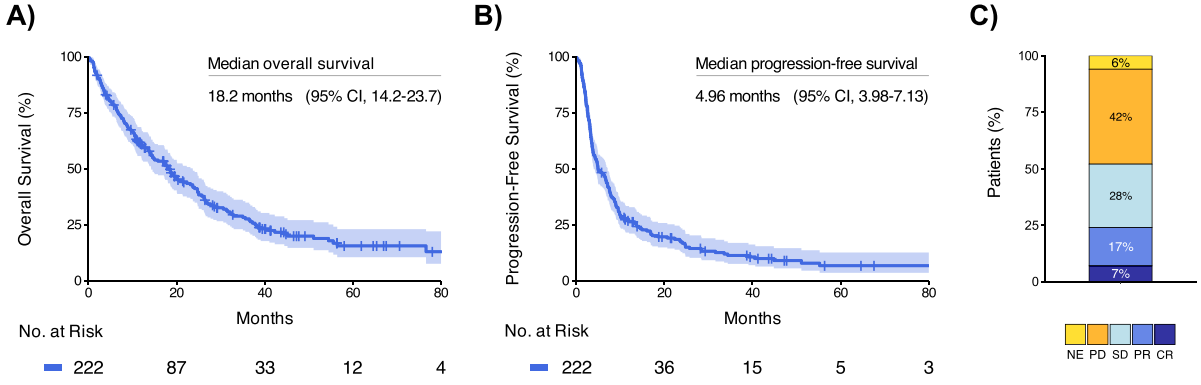

Fig. 1 Efficacy of nivolumab in the overall population. **A** Overall survival. **B** Progression-free survival. **C** Best response. Abbreviations: CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease

Table 3 Univariable and multivariable Cox regression analyses for overall survival and progression-free survival

Characteristics	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall survival				
Sex (Male *vs* female)	1.12 (0.79–1.59)	0.52	-	-
Age (< 75 *vs* ≥ 75 years)	1.2 (0.85–1.8)	0.26	-	-
ECOG PS (2 *vs* 0–1)	2.5 (1.5–4.1)	**0.0002**	1.57 (0.91–2.71)	0.1
IMDC risk score (poor *vs* intermediate/good/missing)	2.68 (1.85–3.88)	**< 0.0001**	2.06 (1.36–3.12)	**0.0007**
Histology (ccRCC *vs* non-ccRCC/missing)	0.91 (0.59–1.42)	0.69	-	-
Prior nephrectomy (yes *vs* no)	0.58 (0.35–0.94)	**0.029**	0.59 (0.35–0.99)	**0.047**
Corticosteroid use (yes *vs* no/missing)	1.04 (0.57–1.9)	0.9	-	-
CNS metastases (yes *vs* no)	0.74 (0.35–1.6)	0.45	-	-
Number of prior therapies (> 1 *vs* 1)	1.4 (1–1.9)	**0.047**	1.31 (0.94–1.83)	0.1
Number of metastatic sites (≥ 3 *vs* < 3)	1.6 (1.2–2.2)	**0.0025**	1.31 (0.95–1.82)	0.1
Progression-free survival				
Sex (Male *vs* female)	1.02 (0.74–1.39)	0.92	-	-
Age (< 75 *vs* ≥ 75 years)	1.34 (0.94–1.92)	0.11	-	-
ECOG PS (2 *vs* 0–1)	1.57 (0.97–2.52)	0.06		
IMDC risk score (poor *vs* intermediate/good/missing)	1.84 (1.3–2.61)	**0.0006**	1.7 (1.2–2.42)	**0.003**
Histology (ccRCC *vs* non-ccRCC/missing)	0.86 (0.58–1.27)	0.4	-	-
Prior nephrectomy (yes *vs* no)	0.84 (0.52–1.34)	0.46	-	-
Corticosteroid use (yes *vs* no/missing)	1.29 (0.76–2.2)	0.35	-	-
CNS metastases (yes *vs* no)	0.89 (0.47–1.69)	0.73	-	-
Number of prior therapies (> 1 *vs* 1)	1.28 (0.95–1.71)	0.1	-	-
Number of metastatic sites (≥ 3 *vs* < 3)	1.59 (1.20–2.11)	**0.0012**	1.50 (1.13–1.99)	**0.005**

Bold numbers indicate statistically significant values

Abbreviations: *ccRCC* clear cell renal cell carcinoma, *CI* confidence interval, *CNS* central nervous system, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *HR* hazard ratio, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium

Progression-free survival Median PFS was 4.96 months (95% CI, 3.98–7.13) (Table 2**,** Fig. 1B). Among the ten baseline variables assessed, two were associated with worse PFS in univariable analysis: poor IMDC risk score (HR = 1.84, 95% CI, 1.3–2.61; $P = 0.0006$) and ≥ 3 metastatic sites (HR = 1.59, 95% CI, 1.20–2.11; $P = 0.0012$). Both remained independently associated with shorter PFS in multivariable analysis: poor IMDC risk score (HR = 1.7, 95% CI, 1.2–2.42; $P = 0.003$) and ≥ 3 metastatic sites (HR = 1.50, 95% CI, 1.13–1.99; $P = 0.005$) (Table 3).

Disease control and response DCR and ORR were 52% (95% CI, 45–58) and 23% (95% CI, 18–30), respectively, including 15 (7%) complete responses and 38 (17%) partial responses (Table 2 and Fig. 1C). Of ten baseline variables assessed, none were associated with probability of response in univariable analysis, while four were associated with a lower probability of DC: ECOG-PS ≥ 2 (OR = 0.34, 95% CI, 0.12–0.88; $P = 0.03$), poor IMDC risk score (OR = 0.38, 95% CI, 0.18–0.76; $P = 0.007$), > 1 prior therapies (OR = 0.51, 95% CI, 0.28–0.88; $P = 0.02$), and ≥ 3 metastatic sites (OR = 0.34, 95% CI, 0.20–0.59; $P = 0.0001$). Among these, only ≥ 3 metastatic sites remained independently associated with a lower probability of DC in multivariable analysis (OR = 0.40, 95% CI, 0.23–0.70; $P = 0.002$) (Supplementary Tables 3 and 4).

To further explore the distribution of patient and disease characteristics based on variables of prognostic or predictive impact identified in the present study, as well as those defining subgroups traditionally underrepresented in clinical trials—such as non-ccRCC histologies and CNS metastases—we performed some additional analyses (Supplementary Tables 5–9). Among patients with poor IMDC risk, ECOG-PS ≥ 2 (30% *vs* 5%, $P < 0.0001$), receipt of only one prior therapy (49% *vs* 31%, $P = 0.03$), and ≥ 3 metastatic sites (63% *vs* 41%, $P = 0.02$) were more frequent compared with those patients with intermediate/good IMDC risk (Supplementary Table 6). Among patients with ≥ 3 metastatic sites, CNS metastases (9% *vs* 2%, $P = 0.03$) and receipt of only 1 prior therapy (44% *vs* 26%, $P = 0.007$) were more frequent compared with patients with < 3 metastatic sites (Supplementary Table 8). Among patients with CNS metastases, corticosteroid use was more frequent (45% *vs* 4%, $P < 0.0001$) compared with patients without CNS involvement (Supplementary Table 9). No other significant differences in baseline characteristics were observed beyond those already described (Supplementary Tables 5–9). Regarding treatment outcomes (Supplementary Tables 10–14), patients with intermediate/good IMDC risk had a higher DCR than those with poor risk (56% *vs* 33%, $P = 0.006$), while ORR was similar between groups (26% *vs* 14%, $P = 0.16$) (Supplementary Table 11). Similarly, patients with < 3 metastatic sites

had a higher DCR compared with those with ≥ 3 sites (63% *vs* 38%, $P = 0.0003$), with no significant difference in ORR (26% *vs* 21%, $P = 0.43$) (Supplementary Table 14).

Discussion

The treatment landscape of aRCC has undergone significant transformation since the approval of nivolumab in November 2015 for patients with accRCC who had received previous antiangiogenic therapy. This approval was based on the results of the multicenter, two-arm, randomized, open-label, phase 3 CM-025 clinical trial, which demonstrated that nivolumab improved OS and ORR compared to everolimus in aRCC patients, while also exhibiting a more favorable safety profile [4].

In recent years, RWE studies have gained substantial prominence in the clinical oncology community. While clinical trials conducted in highly controlled environments remain fundamental, they do not fully reflect the diversity and complexity of patients encountered in daily clinical practice. For instance, the CM-025 trial excluded patients with CNS metastases, prior mTOR inhibitor treatment, active or suspected autoimmune diseases, uncontrolled adrenal insufficiency, active chronic liver disease, and non-ccRCC histologies. Additionally, patients receiving systemic corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive agents were also excluded [4].

Consequently, real-world studies are essential for expanding evidence on efficacy and safety to broader patient populations, more accurately reflecting daily clinical practice [7]. Examples of such studies in aRCC include the Italian early access program (EAP) [9], the GETUG-AFU 26 NIVOREN trial [10], the NORA study [8], and the UK real-world experience [11], which provide additional insights into the impact of nivolumab in clinical settings across various European countries.

In this context, we conducted a multicenter retrospective study involving a cohort of 222 previously treated aRCC patients to evaluate the efficacy of nivolumab and the influence of baseline clinical factors on treatment outcomes in routine clinical practice in Spain. Furthermore, we reviewed similar experiences published from other countries and compared our results with theirs.

In our study, the real-world efficacy of nivolumab appeared consistent with previous reports. Median OS was 18.1 months, which is shorter than the 25.8 months observed in CM-025 [4, 12, 13] and other RWE studies such as the NORA [8] and NIVOREN [10] trials, but similar to findings from the Italian EAP [9] and the UK real-world experience [11]. Median PFS was 4.96 months, slightly longer than reported in CM-025 and other real-world studies, except for NORA, which reported a median PFS of 5.3 months. Our study showed an ORR of 23%, consistent with CM-025 [4, 12] and other RWE studies. Notably, the rate of complete responses in our study (7%) was higher than the ~ 1% reported in previous studies [4, 8–12]. However, a larger proportion of patients in our cohort experienced progressive disease as the best response (42%), similar to the NIVOREN trial (48%) [10].

Regarding the impact of clinical and pathological characteristics on nivolumab outcomes, several aspects merit discussion.

First, the median age in our cohort aligned with other studies [4, 8–12], falling between the sixth and seventh decades of life. However, CM-025 included a higher proportion of patients aged ≥ 75 years (18%) compared to our study (8%). As reported elsewhere, men outnumbered women at a ratio of approximately 2.5–3:1, slightly higher than the expected incidence ratio of 2:1. This discrepancy may reflect a lower proportion of female patients presenting with aRCC, as noted by other groups [14, 15]. Importantly, we found no statistically significant differences in survival or response based on age (< 75 *vs* ≥ 75 years) or sex.

Second, compared with some previous studies [4, 8, 11], our population included a greater proportion of patients with less favorable characteristics, such as having received three or more prior lines of therapy (11%) or having an ECOG-PS of 2 (10%). Of the four baseline variables associated with worse OS in univariable analysis (ECOG-PS ≥ 2, poor IMDC risk score, > 1 prior systemic therapy, and ≥ 3 metastatic sites), only a poor IMDC risk score remained statistically significant in multivariable analysis. Consistent with prior findings from Rebuzzi et al. [16], prior nephrectomy emerged as a factor independently associated with improved OS. In contrast, only poor IMDC risk score and ≥ 3 metastatic sites remained independently associated with worse PFS, while ≥ 3 metastatic sites was the only variable significantly associated with lower disease control. No baseline variables were associated with response.

Third, unlike CM-025, our study included patients with CNS metastases, non-ccRCC histologies, and those receiving corticosteroids > 10 mg/day of prednisone or equivalent. Of note, none of these features were associated with worse efficacy outcomes. However, data from the NIVOREN trial suggest that untreated brain metastases may limit immunotherapy efficacy, underscoring the potential benefit of combining focal brain-directed therapy with checkpoint inhibitors [17].

This study had several methodological limitations. First, although it included 222 patients across 13 medical centers in Spain, the sample may not fully represent the broader aRCC patient population nationwide. Nevertheless, it is the first report documenting the real-world use of nivolumab in this setting in Spain. Second, adverse events were not systematically recorded, although reasons for treatment discontinuation were collected. Third, tumor response assessments were performed according

to local protocols at each center, which may have introduced variability in PFS estimates. However, this limitation is mitigated by the availability of OS data and a broad follow-up period. Fourth, as with all retrospective studies, the use of medical records may introduce bias due to incomplete or inaccurate documentation. To minimize this risk, validation checks were implemented in the electronic case report form. Lastly, although our study primary reflects outcomes with nivolumab monotherapy, an approach whose use has declined since the introduction of first-line PD-1-based combination regimens–it remains a valuable option for patients who initially receive tyrosine kinase inhibitor monotherapy due to access limitations or prognostic considerations. These findings should therefore be interpreted in the context of current treatment paradigms, where patients, particularly those with intermediate and poor IMDC risk, are increasingly treated with combination therapies in the first-line setting. Because efficacy (and safety) profiles clearly differ between regimens, our study provides a relevant real-world scenario for characterizing patient and disease features that influence immunotherapy outcomes and identifying subgroups more likely to benefit from single-agent immunotherapy. Given the added complexity of drug–drug interactions in combination approaches, where enhanced efficacy may result from independent, additive, or synergistic mechanisms, it is essential to first elucidate the biological and clinical determinants of response and resistance to anti-PD-1 monotherapy. A deeper understanding of these mechanisms will improve the interpretation of treatment effects when these agents are used in combination and help guide the development of more rational therapeutic strategies.

In conclusion, this study supports the efficacy of nivolumab in routine clinical practice for a real-world cohort of previously treated aRCC patients in Spain, consistent with outcomes reported in clinical trials and other RWE studies.

Abbreviations

aRCC	Advanced renal cell carcinoma
ccRCC	Clear cell renal cell carcinoma
CI	Confidence interval
CM-025	CheckMate-025
CNS	Central nervous system
DCR	Disease control rate
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
HR	Hazard ratio
IMDC	International Metastatic RCC Database Consortium
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
RWE	Real-world evidence

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Conceptualization: NF-D and JR-B; software, NF-D and JR-B; validation, NF-D and JR-B; formal analysis, NF-D and JR-B; investigation: all authors; resources: all authors; data curation, all authors; writing – original draft, NF-D and JR-B; writing – review & editing, all authors; visualization, NF-D, YZB, and JR-B; supervision, JR-B; project administration, JR-B; funding acquisition, JR-B.

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Data availability

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

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Research with medicinal products of Galicia (2020/248), the Ethics Committee for Research with medicinal products of Euskadi (EPA2020065), the Ethics Committee for Research with medicinal products of Cantabria, the Ethics Committee for Research with medicinal products of Hospital Universitario La Paz (PI-4313), the Ethics Committee for Research with medicinal products of Córdoba (1584-N-20), and the Ethics Committee for Research at Hospital Universitario Elche-Vinalopó. The study was conducted in accordance with the guidelines of Good Clinical Practice and the Declaration of Helsinki. All living patients provided written informed consent before enrollment. Informed consent was waived for deceased patients before study initiation.

Consent for publication

Not applicable.

Competing interests

Natalia Fernández-Díaz — Travel, accommodations, and expenses: GlaxoSmithKline, Lilly, Roche, Pierre Fabre, Novartis, and Sanofi; María Mateos-González — Travel, accommodations, and expenses: AstraZeneca, Bristol-Myers Squibb, MSD, Roche, Sanofi, and Takeda; Educational activities: AstraZeneca, Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Roche, Sanofi, and Takeda; Honoraria for consultancies: MSD; Isabel Chirivella-González — Travel, accommodations, and expenses: Pfizer, Bristol-Myers Squibb, MSD, and Ipsen; Honoraria for consultancies: Pfizer, Bristol-Myers Squibb, Ipsen, MSD, and Roche; Honoraria as speaker: Pfizer, Bristol-Myers Squibb, and Ipsen; Ovidio Fernández-Calvo — Travel, accommodations, and expenses: Bristol-Myers Squibb, Ipsen, and Astellas; Honoraria for consultancies: Astellas, Pfizer, Bristol-Myers Squibb, Ipsen, Merck, and Eisai; Honoraria as speaker: Novartis, Bristol-Myers Squibb, Ipsen, Roche, Astellas, and Bayer; Martín Lázaro-Quintela — Honoraria as speaker: MSD, Bristol-Myers Squibb, and Ipsen; Advisory board: Ipsen, Astellas; Aurea Molina-Díaz — Travel, accommodations, and expenses: Eisai, Grünenthal Pharma, Kyowa Kirin, PharmaMar, Merck, Bristol-Myers Squibb, Roche, and Ipsen; Honoraria for educational activities: Pfizer, Bristol-Myers Squibb, MSD, Eisai, Kyowa Kirin, Merck, PharmaMar, AstraZeneca, Lilly, Sanofi, Takeda, Astellas, Roche, and Pierre Fabre; Advisory board: Bayer, Eisai, Pierre Fabre, PharmaMar, Pfizer, and Merck; Santiago Aguín-Losada — Travel, accommodations, and expenses: Merck, Roche, Bristol-Myers Squibb, and MSD; Honoraria for educational activities: Merck, MSD, Bristol-Myers Squibb, Sanofi, Roche, and Lilly; Honoraria for consultancies: Merck, MSD, and Bristol-Myers Squibb; Luis León-Mateos — Travel, accommodations,

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