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Real-world Outcome of Patients with Advanced Renal Cell Carcinoma and Intermediate- or Poor-risk International Metastatic Renal Cell Carcinoma Database Consortium Criteria Treated by Immune-oncology Combinations: Differential Effectiveness by Risk Group?

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Abstract

Background: Renal c carcinoma (RCC) is one of the most common urinary cancers worldwide, with a predicted increase in incidence in the coming years. Immunotherapy, as a single agent, in doublets, or in combination with anti–vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs), has rapidly become a cornerstone of the RCC therapeutic scenario, but no head-to-head comparisons have been made. In this setting, real-world evidence emerges as a cornerstone to guide clinical decisions.

Objective: The objective of this retrospective study was to assess the outcome of patients treated with first-line immune combinations or immune oncology (IO)-TKIs for advanced RCC.

Design, setting, and participants: Data from 930 patients, 654 intermediate risk and 276 poor risk, were collected retrospectively from 58 centers in 20 countries. Special data such as sarcomatoid differentiation, body mass index, prior nephrectomy, and metastatic localization, in addition to biochemical data such as hemoglobin, platelets, calcium, lactate dehydrogenase, neutrophils, and radiological response by investigator's criteria, were collected.

Outcome measurements and statistical analysis: Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method. The median follow-up was calculated by the inverse Kaplan-Meier method.

Results and limitations: The median follow-up time was 18.7 mo. In the 654 intermediate-risk patients, the median OS and PFS were significantly longer in patients with the intermediate than in those with the poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (38.9 vs 17.3 mo, 95% confidence interval [CI] $p < 0.001$, and 17.3 vs 11.6 mo, 95% CI $p < 0.001$, respectively). In the intermediate-risk subgroup, the OS was 55.7 mo (95% CI 31.4–55.7) and 40.2 mo (95% CI 29.6–51.6) in patients treated with IO + TKI and IO + IO combinations, respectively ($p = 0.047$). PFS was 30.7 mo (95% CI 16.5–55.7) and 13.2 mo (95% CI 29.6–51.6) in intermediate-risk patients treated with IO + TKI and IO + IO combinations, respectively ($p < 0.001$). In the poor-risk subgroup, the median OS and PFS did not show a statistically significant difference between IO + IO and IO + TKI. Our study presents several limitations, mainly due to its retrospective nature.

Conclusions: Our results showed differences between the IO + TKI and IO + IO combinations in intermediate-risk patients. A clear association with longer PFS and OS in favor of patients who received the IO + TKI combinations compared with the IO-IO combination was observed. Instead, in the poor-risk group, we observed no significant difference in PFS or OS between patients who received different combinations.

Patient summary: Renal cancer is one of the most frequent genitourinary tumors. Treatment is currently based on immunotherapy combinations or immunotherapy with tyrosine kinase inhibitors, but there are no comparisons between these.In this study, we

have analyzed the clinical course of 930 patients from 58 centers in 20 countries around the world. We aimed to analyze the differences between the two main treatment strategies, combination of two immunotherapies versus immunotherapy + antiangiogenic therapy, and found in real-life data that intermediate-risk patients (approximately 60% of patients with metastatic renal cancer) seem to benefit more from the combination of immunotherapy + antiangiogenic therapy than from double immunotherapy. No such differences were found in poor-risk patients. This may have important implications in daily practice decision-making for these patients.

1. Introduction

Renal cell carcinoma (RCC) accounts for about 3% of all adult malignancies, but its global incidence has increased by 2% a year over the past 20 yr [1]. About 75% of RCC cases per year are at an early stage at the time of diagnosis, thus requiring a surgical approach. Of the RCC patients, 25–30% have metastases at the time of diagnosis, and around 30% relapse with distant metastases after surgical approaches [2].

The therapeutic scenario of metastatic RCC (mRCC) has changed dramatically over the past decades, moving from first-line treatment strategies based on tyrosine kinase inhibitors (TKIs) targeting either the vascular endothelial growth factor (VEGF) or the VEGF receptors, to combination of two immune checkpoint inhibitors (ICIs) or coadministration of an ICI plus a TKI [3–8]. At present, nivolumab plus ipilimumab has been approved by the US Food and Drug Administration in patients with intermediate and poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk class [9], while nivolumab plus cabozantinib as well as pembrolizumab plus axitinib, pembrolizumab plus lenvatinib, and avelumab plus axitinib (without overall survival [OS] data) have been approved as first-line therapies regardless of the IMDC risk profile.

These combinations showed improved survival benefits and impressive response rates when compared with sunitinib in treatment-naive mRCC patients, leading to their approval as novel standards of care in this setting [10]. Considering these widely available first-line strategies, the current notable challenge for physicians is to define the best tailored therapy for each untreated mRCC patient, assessing several patient- and tumor-related variables. Indeed, due to the existence of tumor molecular heterogeneity [11,12], even patients presenting similar clinicopathological characteristics could have vastly different survival rates.

The ARON-1 study (NCT05287464) has been designed to globally collect real-world experiences on the use of immune combinations in mRCC patients. In this subanalysis, we focused on the real-world effectiveness of these therapeutic approaches in patients with intermediate or poor IMDC risk factors.

2. Patients and methods

2.1. Study population

We retrospectively collected data from patients aged ≥18 yr with a histologically confirmed diagnosis of RCC, and histologically or radiologically confirmed metastatic disease. We included patients with IMDC intermediate- and poor-risk criteria treated with first-line immune combinations between January 1, 2016 and October 1, 2022, from 58 centers in 20 countries. Ethical committee approval was obtained from the ARON-1 study (NCT05287464).

We retrospectively extracted data, from patients' paper and electronic charts, about age, gender, tumor histology, nephrectomy, sites of metastases, type of immune combination, and response to therapy. Patients with insufficient data on tumor assessment or response to therapy were excluded from the ARON-1 study.

First-line therapy was continued until there was clinical and/or radiological tumor progression, unacceptable toxicities, or death. Computed tomography or magnetic resonance imaging scans were performed every 8–12 wk following standard local procedures. Physical and laboratory tests were carried out every 4–6 wk during patients' follow-up.

2.2. Study endpoints

The primary objective of our retrospective study was to assess the outcome of patients treated with first-line immune combinations or TKIs for advanced RCC. Tumor radiological assessment was performed according to the RECIST 1.1 criteria [13], and data on tumor response (complete [CR] or partial [PR] response, and stable [SD] or progressive [PD] disease) were collected and analyzed by investigator criteria. The objective response rate (ORR) was defined as the proportion of patients who achieve a CR or PR as per the RECIST criteria. OS was calculated from the start of treatment to death from any cause. Progression-free survival (PFS) was defined as the time from the start of first-line therapy to progression or death from any cause, whichever occurred first. Patients without tumor progression to the following line of treatment or death or those lost to follow-up at the time of analysis were censored at their last follow-up date. The median follow-up was calculated by the inverse Kaplan-Meier method.

2.3. Statistical analysis

OS and PFS were estimated using the Kaplan-Meier method with Rothman's 95% confidence intervals (CIs), and comparisons between survival distributions were performed by using the log-rank test. Univariate and multivariate analyses were carried out using Cox proportional hazard models, hazard ratio (HR), and their 95% CIs. A landmark analysis

was performed designating 6 mo as the time point during the follow-up period.

The chi-square test was employed to compare groups for categorical variables. Significance levels were set at a value of 0.05, and all *p* values were two sided. Body mass index (BMI) was defined as a person's weight in kilograms divided by the square of their height in meters. Based on the World Health Organization classification, patients were included in the overweight/obesity group when BMI was >25 kg/m^2.

The statistical analysis was performed by MedCalc version 19.6.4 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Baseline characteristics

In this analysis, we included from the ARON-1 dataset 654 (70%) and 276 (30%) patients with intermediate- and poor-risk criteria, respectively (Supplementary Fig. 1). The median follow-up time was 18.7 mo (95% CI 13.5–88.8); 678 patients (73%) were male. The median age was 64 yr (range 25–92). The tumor histology was clear cell RCC in 811 patients (87%); among the 119 non–clear cell RCC patients, papillary histology was observed in 41 cases and chromophobe RCC in 13; sarcomatoid differentiation was reported in 145 patients (16%). In the total sample size, 539-patients underwent a nephrectomy (58%). Distant metastases confined to the lungs were identified in 655 patients (70%). BMI was ≥25 in 443 patients (48%).

A total of 485 patients (52%) received immune-oncology (IO) + TKI combinations and 445 patients (48%) were treated by dual IO therapy in the first-line setting. Baseline clinical and pathological characteristics of the overall population are shown in Table 1. We did not find statistically significant differences between the clinicopathological characteristics of patients treated by IO + TKI or IO + IO combinations in both the intermediate- and the poor-risk subgroup (Table 1).

3.2. Survival analyses in the overall study population

The median OS was 38.9 mo (95% CI 29.7–51.6), 51.6 mo (95% CI 35.3–55.7) in patients with intermediate IMDC criteria and 18.4 mo (95% CI 12.9–38.3) in patients with poor-risk features ($p < 0.001$; Fig. 1).

The median PFS was 15.4 mo (95% CI 13.2–19.1) and was significantly longer in patients with intermediate IMDC criteria than in those with poor IMDC criteria (17.3 mo, 95% CI 14.5–22.6 vs 11.6 mo, 95% CI 7.1–14.9, $p < 0.001$; Fig. 1).

3.3. OS and PFS analyses in intermediate-risk patients

Among the 654 intermediate-risk patients, the median OS was longer in patients with BMI ≥25 kg/m^2 than in those with BMI <25 kg/m^2 (51.6 mo, 95% CI 40.6–55.7 vs 31.4 mo, 95% CI 28.1–40.2, $p = 0.004$; Fig. 2). Shorter OS was associated with the presence of sarcomatoid differentiation (26.4 mo, 95% CI 21.6–26.4 vs 51.6 mo, 95% CI 38.9–55.7, $p = 0.046$; Fig. 2), bone metastases (28.4 mo, 95% CI 25.9–55.7 vs 51.6 mo, 95% CI 40.2–51.6, $p = 0.009$; Fig. 2), or liver metastases (30.2 mo, 95% CI 25.9–55.7 vs 51.6 mo, 95% CI 38.9–51.6, $p = 0.030$; Fig. 2).

By contrast, no significant OS differences were found based on sex (males = 51.6 mo, 95% CI 35.3–55.7 vs females = not reached [NR], 95% CI NR–NR, $p = 0.815$), age <65 vs ≥65 yr (51.6 mo, 95% CI 38.9–55.7 vs NR, 95% CI NR–NR, $p = 0.051$), tumor histology (clear cell RCC = 51.6 mo, 95% CI 38.9–55.7 vs non–clear cell RCC = 29.6 mo, 95% CI 24.8–29.6, $p = 0.325$), presence of metastases at RCC diagnosis (35.3 mo, 95% CI 28.2–51.6 vs 41.0 mo, 95% CI 28.9–55.7, $p = 0.892$), lung metastases (yes = 51.6 mo, 95% CI 31.4–51.6

Table 1 – Baseline patients' characteristics

Patients	Overall 930 (%)	Intermediate-risk patients			Poor-risk patients		
		IO + TKI 353 (%)	IO + IO 301 (%)	*p* value	IO + TKI 132 (%)	IO + IO |144 (%)	*p* value
Gender				0.748			0.877
Male	678 (73)	257 (73)	226 (75)		94 (71)	101 (70)	
Female	252 (27)	96 (27)	75 (25)		38 (29)	43 (30)	
Age (yr), median (range)	64 (25–92)	63 (31–88)	65 (25–92)	–	63 (27–88)	65 (30–92)	–
BMI ≥25 kg/m^2	443 (48)	158 (45)	163 (54)	0.204	52 (39)	70 (49)	0.155
Metastatic at diagnosis	599(64)	206 (58)	176 (58)	1.000	107 (81)	110 (76)	0.391
Past nephrectomy	539 (58)	216 (61)	207 (69)	0.237	50 (38)	66 (46)	0.253
Clear cell histology	811 (87)	302 (86)	269 (89)	0.522	112 (85)	128 (89)	0.402
Non–clear cell histology							
Papillary	41	13 (4)	13 (4)	0.571	10 (7)	5 (3)	0.12
Chromophobe	13	7 (2)	3 (1)	0.235	2 (2)	1 (1)	0.841
Other types	65	28 (8)	19 (6)	0.312	8 (6)	10 (7)	0.786
Sarcomatoid differentiation	145 (16)	41 (12)	54 (18)	0.236	21 (16)	29 (20)	0.463
Sites of metastasis							
Lung	655 (70)	223 (63)	214 (71)	0.230	101 (77)	117 (81)	0.489
Lymph nodes	492 (53)	168 (48)	162 (54)	0.397	83 (63)	79 (55)	0.251
Bone	345 (37)	127 (36)	93 (31)	0.455	65 (39)	60 (42)	0.666
Liver	186 (20)	63 (18)	58 (19)	0.856	37 (28)	28 (19)	0.134
Brain	75 (8)	26 (7)	14 (5)	0.553	16 (12)	19 (13)	0.831
Type of immunocombination				–			–
Nivolumab + ipilimumab	445 (48)	–	301 (100)		–	144 (100)	
Pembrolizumab + axitinib	402 (43)	301 (85)	–		101 (77)	–	
Nivolumab + cabozantinib	67 (7)	41 (12)	–		26 (20)	–	
Pembrolizumab + lenvatinib	16 (2)	11 (3)	–		5 (3)	–	

BMI = body mass index; IO = immune oncology; TKI = tyrosine kinase inhibitor.

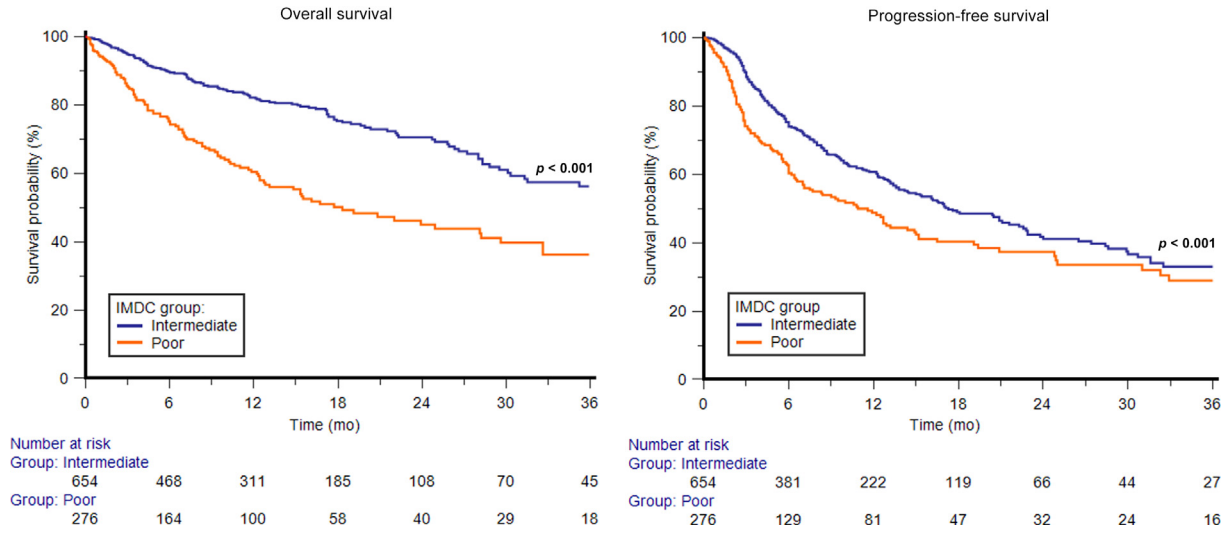

Fig. 1 – Overall and progression-free survival in patients with intermediate or poor IMDC criteria treated by immune combinations. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

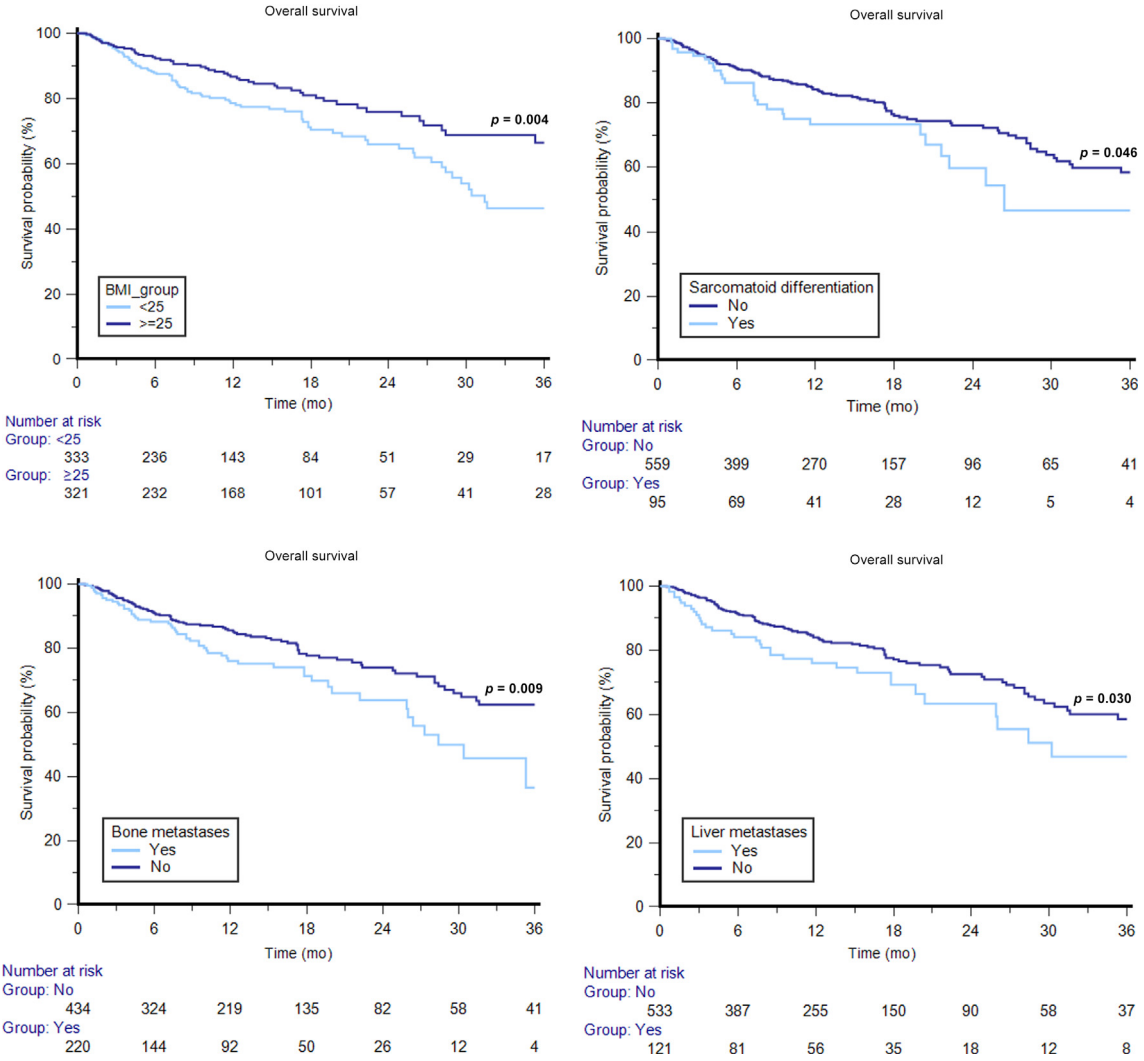

Fig. 2 – Overall survival in patients with intermediate IMDC criteria treated by immune combinations stratified by BMI, sarcomatoid differentiation, and presence of bone or liver metastases. BMI = body mass index; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

Table 2 – Univariate and multivariate analyses of the predictors of overall survival and progression-free survival in intermediate-risk mRCC patients[a]

	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
OS				
Gender (female vs male)	1.05 (0.72–1.52)	0.815		
Age (≥65 vs <65 yr)	1.39 (1.00–1.93)	0.051		
BMI (≥25 vs <25 kg/m^2)	0.61 (0.44–0.85)	**0.004**	0.71 (0.55–0.92)	**0.009**
Nephrectomy (yes vs no)	0.50 (0.36–0.70)	**<0.001**	0.47 (0.36–0.60)	**<0.001**
Histology (ccRCC vs nccRCC)	0.80 (0.50–1.26)	0.324		
Sarcomatoid features (yes vs no)	1.53 (1.00–2.33)	**0.048**	1.84 (1.35–2.52)	**<0.001**
Metastases at diagnosis (yes vs no)	1.02 (0.73–1.43)	0.892		
Lung metastases (yes vs no)	1.03 (0.73–1.47)	0.852		
Lymph node metastases (yes vs no)	1.12 (0.81–1.55)	0.502		
Bone metastases (yes vs no)	1.56 (1.11–2.20)	**0.010**	1.57 (1.22–2.02)	**<0.001**
Liver metastases (yes vs no)	1.52 (1.04–2.23)	**0.031**	1.34 (1.01–1.78)	**0.042**
Brain metastases (yes vs no)	1.51 (0.79–2.88)	0.211		
IO + IO vs IO + TKI combinations	1.37 (0.97–1.93)	**0.047**	1.37 (1.06–1.77)	**0.016**
PFS				
Gender (female vs male)	0.95 (0.72–1.24)	0.685		
Age (≥65 vs <65 yr)	0.99 (0.78–1.25)	0.915		
BMI (≥25 vs <25 kg/m^2)	0.86 (0.68–1.09)	0.212		
Nephrectomy (yes vs no)	0.68 (0.53–0.87)	**0.002**	0.62 (0.50–0.75)	**<0.001**
Histology (ccRCC vs nccRCC)	0.97 (0.68–1.38)	0.857		
Sarcomatoid features (yes vs no)	1.53 (1.00–2.33)	**0.048**	1.66 (1.29–2.14)	**<0.001**
Metastases at diagnosis (yes vs no)	1.02 (0.80–1.30)	0.883		
Lung metastases (yes vs no)	1.08 (0.83–1.39)	0.581		
Lymph node metastases (yes vs no)	1.26 (1.00–1.60)	0.052		
Bone metastases (yes vs no)	1.53 (1.20–1.97)	**<0.001**	1.56 (1.27–1.90)	**<0.001**
Liver metastases (yes vs no)	1.29 (0.97–1.73)	0.085		
Brain metastases (yes vs no)	1.71 (1.12–2.64)	**0.013**	1.53 (1.11–2.10)	**0.009**
IO + IO vs IO + TKI combinations	1.65 (1.29–2.11)	**<0.001**	1.48 (1.21–1.81)	**<0.001**

ccRCC = clear cell renal cell carcinoma; CI = confidence interval; HR = hazard ratio; IO = immune oncology; mRCC = metastatic cell renal cell carcinoma; nccRCC = non–clear cell renal cell carcinoma; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.
[a] Statistically significant values are reported in bold.

vs no = 55.7 mo, 95% CI 28.9–55.7, $p = 0.853$), lymph node metastases (yes = 51.6 mo, 95% CI 35.3–51.6 vs no = 55.7 mo, 95% CI 30.4–55.7, $p = 0.755$), or brain metastases (yes = 26.7 mo, 95% CI 18.0–26.7 vs no = 51.6, 95% CI 35.3–55.7, $p = 0.207$).

At the univariate analysis, BMI ≥25 kg/m^2, no previous nephrectomy, sarcomatoid differentiation, bone metastases, liver metastases, and the IO + IO combination were significant predictors of worst OS in intermediate-risk patients, and their prognostic role was confirmed at the multivariate analysis (Table 2). Regarding PFS, no previous nephrectomy, sarcomatoid differentiation, bone metastases, brain metastases, and the IO + IO combination were significant predictors of the worst PFS in the intermediate RCC subgroup.

3.4. OS and PFS analyses in poor-risk patients

In the 276 patients with poor-risk features, no previous nephrectomy (12.9 mo, 95% CI 10.3–17.8, vs 32.7 mo, 95% CI 20.9–41.0, $p = 0.003$; Fig. 3) as well as the presence of metastases at RCC diagnosis (15.4 mo, 95% CI 11.7–25.0 vs 32.7 mo, 95% CI 19.2–41.0, $p = 0.023$; Fig. 3), bone metastases (12.3 mo, 95% CI 9.3–17.8 vs 28.2 mo, 95% CI 16.8–41.0, $p = 0.002$; Fig. 3), or brain metastases (yes = 11.7 mo, 95% CI 4.5–25.0 vs no = 20.9 mo, 95% CI 14.9–32.7, $p = 0.019$; Fig. 3) were significantly associated with shorter OS.

By contrast, no statistically significant OS differences were found based on sex (males = 19.2 mo, 95% CI 12.8–29.7 vs females = 15.5 mo, 95% CI 11.1–41.0, $p = 0.934$), age (<65 yr = 25.0 mo, 95% CI 16.8–32.7 vs ≥65 yr = 12.3 mo, 95% CI 9.5–18.4, $p = 0.051$), BMI (≥25 kg/m^2 = 25.0 mo, 95% CI 14.9–32.7 vs <25 kg/m^2 = 15.6 mo, 95% CI 10.0–29.0, $p = 0.086$), tumor histology (clear cell RCC = 20.9 mo, 95% CI 15.4–32.7 vs non–clear cell RCC = 10.7 mo, 95% CI 6.1–15.4, $p = 0.122$), sarcomatoid differentiation (10.0 mo, 95% CI 6.7–41.0 vs 22.1 mo, 95% CI 15.4–32.7, $p = 0.112$), presence of lung metastases (yes = 18.4 mo, 95% CI 12.8–28.2 vs no = NR, 95% CI NR–NR, $p = 0.258$), lymph node metastases (yes = 16.2 mo, 95% CI 12.5–28.2 vs no = 29.7 mo, 95% CI 12.3–29.7, $p = 0.222$), or liver metastases (yes = 15.4 mo, 95% CI 8.9–32.7 vs no = 20.9 mo, 95% CI 12.9–32.7, $p = 0.123$).

At the univariate analysis, previous nephrectomy, the presence of metastases at RCC diagnosis, and bone and brain metastases were significant predictors of OS. At the multivariate analysis, only bone and brain metastases confirmed their prognostic role (Table 3). Furthermore, previous nephrectomy, the presence of metastases at RCC diagnosis, and bone and brain metastases were significantly correlated with PFS at the univariate analysis, while only bone metastases proved to be associated with PFS at the multivariate analysis (Table 3).

3.5. Impact of immune-combination type on PFS and OS by IMDC risk group

We further stratified the overall study population based on the IMDC criteria and types of immune combinations. In the intermediate-risk subgroup, OS was 55.7 mo (95% CI

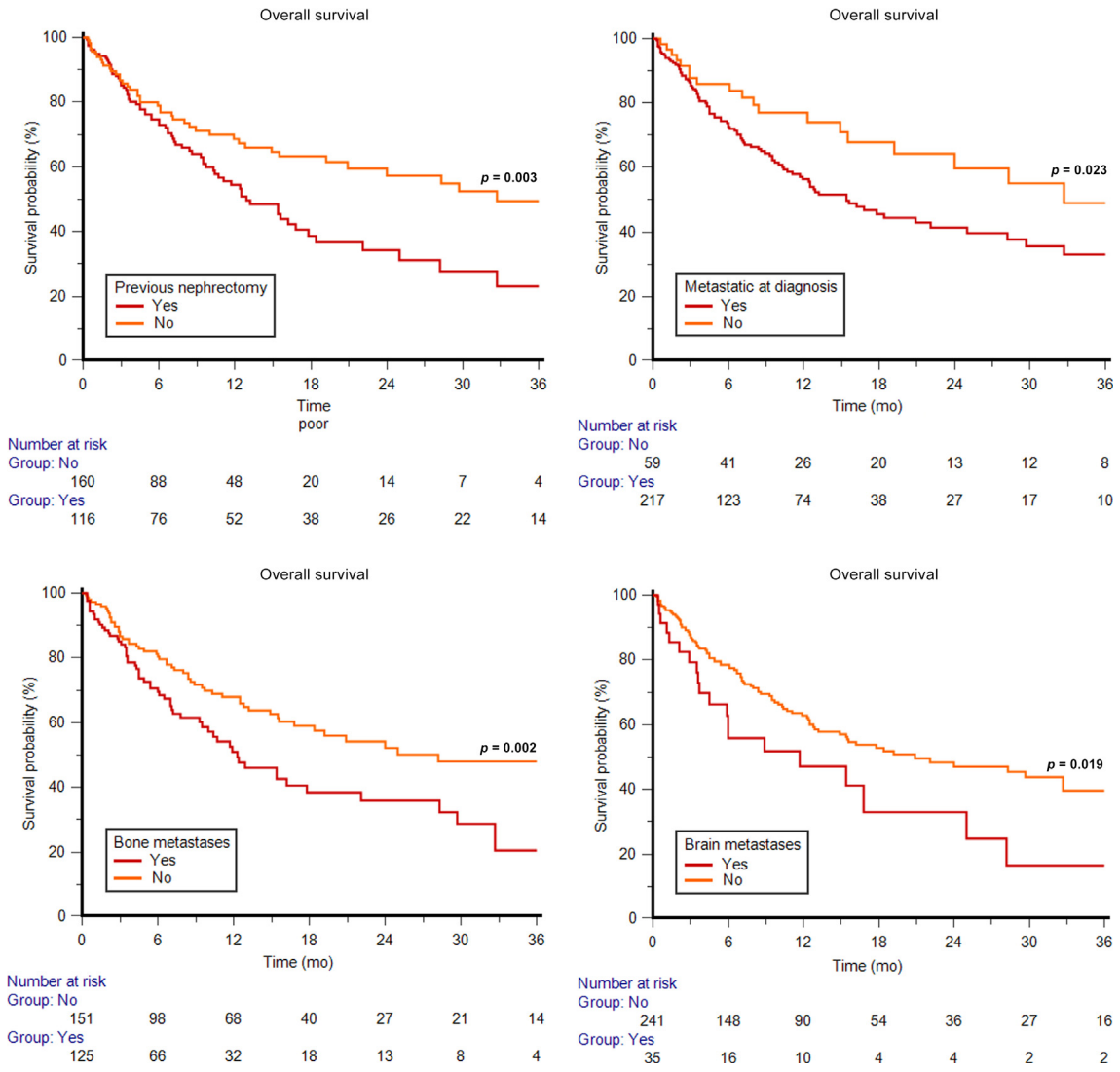

Fig. 3 – Overall survival in patients with poor IMDC criteria treated by immune combinations stratified by previous nephrectomy, presence of metastases at RCC diagnosis, bone metastases, and brain metastases. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; RCC = renal cell carcinoma.

31.4–55.7) and 40.2 mo (95% CI 29.6–51.6) in patients treated with IO + TKI and IO + IO combinations, respectively ($p = 0.047$; Fig. 4). Analogously to OS, the median PFS was 30.7 mo (95% CI 16.5–55.7) and 13.2 mo (95% CI 29.6–51.6) in intermediate-risk patients treated with IO + TKI and IO + IO combinations, respectively ($p < 0.001$; Fig. 4).

In the poor-risk subgroup, the median OS was numerically longer with dual immunotherapy (18.4 mo, 95% CI 11.9–29.7) than with the combination of IO + TKIs (15.5 mo, 95% CI 12.4–32.7, $p = 0.613$; Fig. 4). Moreover, no statistically significant differences were found between IO + TKI and IO + IO combinations in terms of PFS in the poor-risk subgroup (11.6 mo, 95% CI 7.0–14.9 vs 10.0 mo, 95% CI 6.0–19.4, $p = 0.614$; Fig. 4).

Furthermore, we performed a 6-mo landmark analysis for OS to compare the outcomes of patients treated by IO + TKI or IO + IO combinations. In the intermediate-risk subgroup, the median OS was 55.7 mo (95% CI 55.7–55.7) in patients receiving IO + TKIs and 51.6 mo (95% CI 35.3–51.6) in those treated by IO + IO ($p = 0.127$; Supplementary Fig. 2). In the poor-risk subgroup, the median OS was 32.7 mo (95% CI 22.1–32.7) in patients receiving IO + TKIs and 32.7 mo (95% CI 20.9–41.0) in those treated by IO + IO ($p = 0.643$; Supplementary Fig. 2).

3.6. *Tumor response to therapy*

In the overall study population, the percentages of patients experiencing CR, PR, SD, and PD were 6%, 40%, 30%, and 24%, respectively. In the intermediate-risk group, we observed CR = 6%, PR = 41%, SD = 33%, and PD = 20%. Stratified by the type of immune combination, intermediate-risk patients treated by IO + TKIs showed CR = 3%, PR = 47%, SD = 5%, and PD = 15%, with an ORR of 50%. By contrast, patients receiving the IO + IO combination reported CR = 8%, PR = 35%, SD = 30%, and PD = 27%, with an ORR of 43%. The

Table 3 – Univariate and multivariate analyses of the predictors of overall and progression-free survival in poor-risk mRCC patients

	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
OS				
Gender (female vs male)	1.02 (0.68–1.52)	0.935		
Age (≥65 vs <65 yr)	1.43 (1.00–2.06)	0.053		
BMI (≥25 vs <25 kg/m^2)	0.72 (0.50–1.05)	0.088		
Nephrectomy (yes vs no)	0.56 (0.38–0.82)	**0.003**	0.69 (0.42–1.07)	0.090
Histology (ccRCC vs nccRCC)	0.68 (0.41–1.11)	0.126		
Sarcomatoid features (yes vs no)	1.42 (0.92–2.20)	0.115		
Metastases at diagnosis (yes vs no)	1.74 (1.07–1.83)	**0.025**	1.18 (0.66–2.14)	0.574
Lung metastases (yes vs no)	1.33 (0.81–2.21)	0.261		
Lymph node metastases (yes vs no)	1.27 (0.86–1.87)	0.224		
Bone metastases (yes vs no)	1.79 (1.24–2.59)	**0.002**	1.70 (1.18–2.46)	**0.005**
Liver metastases (yes vs no)	1.37 (0.92–2.04)	0.126		
Brain metastases (yes vs no)	1.75 (1.09–2.80)	**0.021**	1.71 (1.06–2.75)	**0.027**
IO + IO vs IO + TKI combinations	1.10 (0.76–1.59)	0.615		
PFS				
Gender (female vs male)	1.18 (0.83–1.68)	0.350		
Age (≥65 vs <65 yr)	1.09 (0.78–1.52)	0.627		
BMI (≥25 vs <25 kg/m^2)	0.96 (0.69–1.33)	0.790		
Nephrectomy (yes vs no)	0.61 (0.43–0.85)	**0.004**	0.68 (0.45–1.03)	0.069
Histology (ccRCC vs nccRCC)	0.87 (0.54–1.40)	0.569		
Sarcomatoid features (yes vs no)	1.43 (0.97–2.12)	0.075		
Metastases at diagnosis (yes vs no)	1.53 (1.01–2.33)	**0.049**	1.05 (0.62–1.76)	0.856
Lung metastases (yes vs no)	1.45 (0.93–2.26)	0.104		
Lymph node metastases (yes vs no)	0.98 (0.70–1.37)	0.904		
Bone metastases (yes vs no)	1.60 (1.15–2.21)	**0.005**	1.51 (1.09–2.11)	**0.015**
Liver metastases (yes vs no)	1.09 (0.74–1.58)	0.672		
Brain metastases (yes vs no)	1.58 (1.01–2.49)	**0.049**	1.54 (0.97–2.43)	0.066
IO + IO vs IO + TKI combinations	1.09 (0.78–1.52)	0.616		

ccRCC = clear cell renal cell carcinoma; CI = confidence interval; HR = hazard ratio; IO = immune oncology; mRCC = metastatic cell renal cell carcinoma; nccRCC = non–clear cell renal cell carcinoma; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.
Statistically significant values are reported in bold.

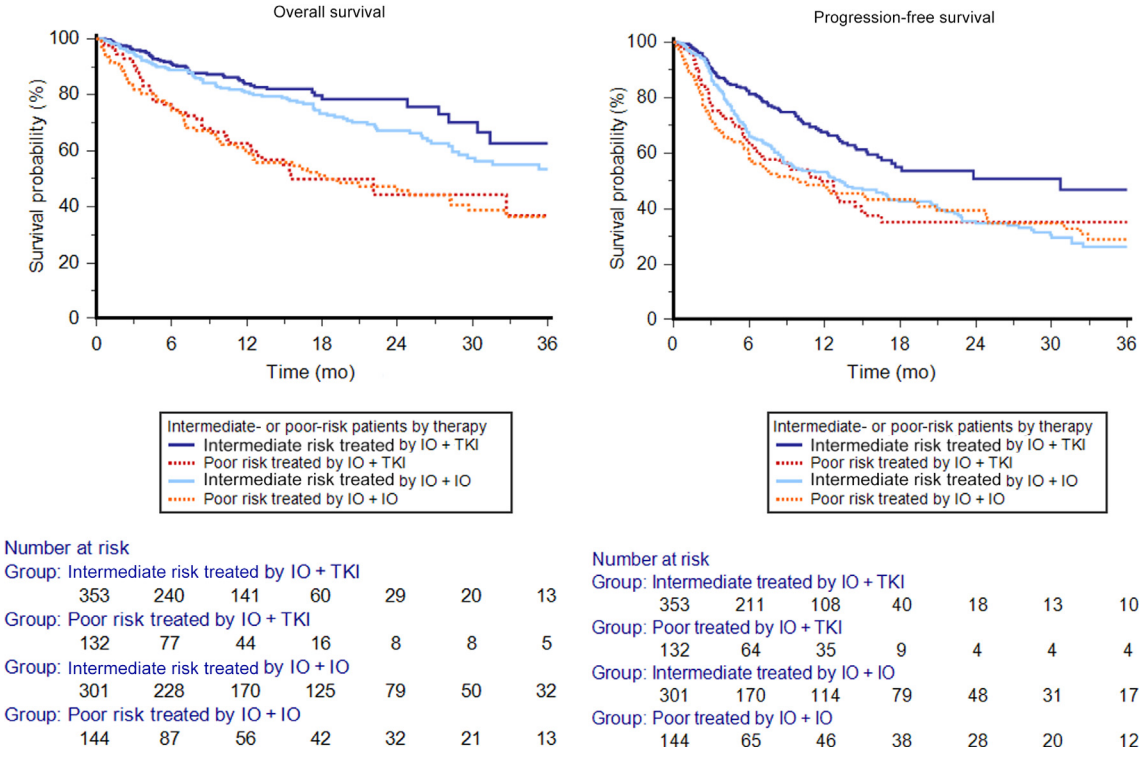

Fig. 4 – Overall and progression-free survival in patients with intermediate or poor IMDC risk criteria treated by IO + TKI or IO + IO combinations. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO = immune oncology; TKI = tyrosine kinase inhibitor.

difference in terms of ORR between the two combinations was not statistically significant ($p = 0.322$).

Among patients with the poor-risk IMDC criteria, the percentages of patients experiencing CR, PR, SD, and PD were 5%, 37%, 24%, and 34%, respectively. Patients receiving IO + TKI combinations registered CR = 1%, PR = 45%, SD = 25%, and PD = 29%, with an ORR of 46%, while patients treated by dual immunotherapy combination reported CR = 9%, PR = 29%, SD = 22%, and PD = 40%, with an ORR of 38% ($p = 0.253$). The difference in terms of CR between patients treated by IO + TKIs or IO + IO was statistically significant ($p = 0.009$).

4. Discussion

In the present study, we reported the outcomes of 930 patients with intermediate- and poor-risk mRCC, treated with first-line immune combinations, around the world. To our knowledge, this is the largest study in a real-life setting. Our results confirmed the prognostic impact of the IMDC score, for both PFS and OS (Fig. 1). Moreover, for intermediate-risk patients, some clinical factors were significantly associated with poor outcome (ie, BMI $\geq$25 kg/m^2, no prior nephrectomy, sarcomatoid differentiation, and bone, brain, and liver metastases); these results are expected and in line with previous observations [3–7].

Of note, only bone and brain metastases were significantly associated with a dismal prognosis in poor-risk patients. Prior nephrectomy for these patients did not affect OS or PFS, and this observation is in line with previous observations [14].

When we compared the IO + TKI with the IO + IO combinations in intermediate-risk patients, we observed a clear association with longer PFS and OS in favor of patients who received the IO + TKI combinations compared with those receiving the IO-IO combination. Instead, in the poor-risk group, we observed no significant difference in PFS or OS between patients who received different combinations (Fig. 4). In addition, the CR rate was significantly higher for patients who received the IO-IO combination and differed from the CR rates in phase 3 trials. These results may generate the hypothesis of differential effectiveness of the IO + TKI and IO + IO combinations in the intermediate- and poor-risk groups. The molecular signatures developed and validated in the immune combinations including an anti-VEGF agent supported this hypothesis [15–17]. Indeed, while for IMDC intermediate-risk patients the HIF-VEGF pathway activation may still play a crucial role, for IMDC poor-risk patients, the main pathway involves stromal-immune/context T cells. Furthermore, at ESMO 2022, Choueiri et al. [7] presented the results of the COSMIC 313 trial, which evaluated the triple combination of cabozantinib, nivolumab, and ipilimumab, compared with placebo, nivolumab, and ipilimumab, as first-line treatment in patients with IMDC intermediate- or poor-risk mRCC. The study reached its primary endpoint (PFS) in the overall population, but patients with poor-risk disease appeared to have no benefit from the addition of the TKI cabozantinib (HR 1.04, 95% CI 0.65–1.69). Of note, the randomization provided for stratification by the IMDC group.

Our study presents several limitations, mainly due to its retrospective nature. A centralized review of radiological imaging was not performed, and patients not assessable for a response were excluded. Furthermore, we had no available data on concomitant medications or other comorbidities that could affect the efficacy of first-line therapy. Moreover, to address the follow-up time limitation for OS, we included a 6-mo OS landmark analysis (S2). Therefore, our results should be interpreted with caution and are in need of a larger prospective validation.

5. Conclusions

We can conclude that the results of our study, the biological background in different IMDC groups, and the results of the COSMIC 313 trial might question the usefulness of administering VEGF receptor TKI–containing combinations in IMDC poor-risk patients. Ad hoc studies are needed to test our hypothesis.

Author contributions: Javier Molina-Cerrillo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Santoni, Molina-Cerrillo.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Santoni, Buti.
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Supervision: Porta.
Other: None.

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Appendix A. Supplementary data

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