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Clinical features and response to immune combinations in patients with renal cell carcinoma and sarcomatoid de-differentiation (ARON-1 study)

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Abstract

Metastatic renal cell carcinoma (mRCC) carrying sarcomatoid features (sRCC) has aggressive biology and poor prognosis. First-line immunotherapy (IO)-based combinations have improved the outcome of clear cell RCC patients, including that of sRCC. Real-world data confirming the adequate first-line management of sRCC is largely lacking. We investigated the clinical features and the outcome of sRCC patients treated with IO-based combinations within the ARON-1 study population (NCT05287464). The primary objective was to define the incidence and baseline clinical characteristics of sRCC compared with non-sRCC patients. The secondary objective was to describe the outcome of sRCC patients based on type of first-line treatment (IO + IO vs. IO + tyrosin kinase inhibitor [TKI]). We identified 1362 mRCC patients with IMDC intermediate or poor risk, 226 sRCC and 1136 non-sRCC. These two subgroups did not differ in terms of baseline characteristics. The median overall

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For affiliations refer to page 8

survival (OS) was 26.8 months (95%CI 21.6–44.2) in sRCC and 35.3 months (95% CI 30.2–40.4) in non-sRCC patients ($p = .013$). The median progression-free survival (PFS) was longer in non-sRCC patients compared to sRCC (14.5 vs. 12.3 months, $p = .064$). In patients treated with first-line IO + TKI the median OS was 34.4 months compared to 26.4 months of those who received IO + IO ($p = .729$). The median PFS was 12.4 months with IO + TKI and 12.3 months with IO + IO ($p = .606$). In conclusion, we confirm that sRCC are aggressive tumors with poor prognosis. IO-based combinations improve survival outcomes of sRCC patients, regardless from the type of strategy (IO + IO versus IO + TKI) adopted.

KEYWORDS
ARON-1 study, immune-based combinations, immunotherapy, NCT05287464, renal cell carcinoma, sarcomatoid differentiation, survival

What's new?

Patients who have metastatic renal cell carcinoma with sarcomatoid features (sRCC) have a very poor prognosis. Here, the authors describe the clinical characteristics and analyze outcomes of sRCC in patients in the ARON-1 study, the largest cohort of sRCC patients treated with first-line immunotherapy. Patients received immune checkpoint inhibitor therapy in combination with either anti-CTLA antibodies or VEGFR-tyrosine kinase inhibitor. They found no significant difference in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) between patients treated with the different immunotherapy combinations.

1 | INTRODUCTION

Renal cell carcinoma (RCC), either the most conventional clear cell histotype (ccRCC) or other rare histologic variants (non-clear cell RCC), may be associated with sarcomatoid de-differentiation.[1,2] The presence of sarcomatoid features, which occurs in about 5%–10% of cases (up to 20% when considering metastatic RCC), is associated with aggressive biology, very poor prognosis and metastatic disease at diagnosis in the vast majority of cases (more than 75%), regardless of the RCC prevalent histology.[3–9]

Morphologically, sarcomatoid RCC (sRCC) is an undifferentiated tumor characterized by epithelial to mesenchymal transition (EMT) pathological features, including presence in a variable proportion of spindle-shaped mesenchymal cells, expression of mesenchymal markers (i.e., N-cadherin and vimentin), and lack of the epithelial marker e-cadherin.[2,5] Recently, a molecular characterization of sRCC identified typical genomic alterations that may be responsible for the aggressive behavior of these tumors, comprising BAP 1 mutations, NF2 somatic alterations (and subsequent enrichment of Hippo pathway),[10] CDKN2A/B deep deletions, and increased expression of MYC transcriptional programs (the latter representing key factors correlated with aggressive phenotype and poor prognosis).[11]

From a therapeutic point of view, the aggressive phenotype of sRCC has been historically associated with limited benefit with vascular endothelial growth factor (VEGFR) tyrosine kinase inhibitors (VEGFR-TKIs) monotherapy, with objective response rate (ORR) of about 20% and primary refractory disease in more than 40% of cases.[6,12,13] Certainly, the recent advent of immunotherapy IO-based combinations, which represent the novel standard first-line therapy for clear cell RCC, has significantly improved the survival outcomes also of those aggressive tumors with sarcomatoid features.[14] Immunotherapy (IO) with immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 or programmed cell death ligand-1 (PD-1/PD-L1) either alone or associated with VEGFR-TKI (IO + TKI) or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies (IO + IO) have shown unprecedented antitumor activity in sRCC, reporting ORRs ranging from 47% to 61%.[15–19] Moreover, subgroup analyses of sRCC patients enrolled in the pivotal clinical trials of immune-based combinations confirmed the significant superiority of IO-based combinations also in this poor prognostic subgroup.[20–23] sRCC exhibits low gene expression signatures associated with angiogenesis, while it has a heavily immune-inflamed phenotype, characterized by increased cytotoxic immune infiltration, up-regulation of antigen presentation machinery genes, increased T_{eff} signature, and high PD-L1 expression.[11,24] All these features could explain the biology underlying the remarkable activity of immunotherapy in sarcomatoid tumors.

To date, real-world data confirming the adequate first-line management in daily clinical practice of this subgroup of sRCC at poor prognosis is largely lacking. The ARON-1 study (NCT05287464) has

been designed to analyze real-world data from metastatic RCC patients receiving first-line ICI-based combinations.[25–28] In this analysis, we aimed to describe the incidence of sRCC and the clinical characteristics associated to its metastatic presentation and its outcome in large real word dataset, finally we also investigated the activity and efficacy of different immune-based combinations.

2 | PATIENTS AND METHODS

2.1 | Study population

We retrospectively collected data from patients aged ≥18 years with a histologically confirmed diagnosis of RCC and a sarcomatoid component. We included patients with histologically or radiologically confirmed metastatic disease, International mRCC Database Consortium (IMDC) intermediate or poor-risk criteria treated with first-line IO + TKI or IO + IO combinations between 1 January 2016 and 1 October 2023 from 55 centers from 18 countries. Patients with good prognosis according to IMDC criteria were excluded from our analysis since they could not receive the IO + IO combination of nivolumab plus ipilimumab. We retrospectively collected from patients' medical records data related to age, gender, tumor histology, nephrectomy, sites of metastases, type of immuno-combination and response to therapy according to RECIST 1.1 criteria.[29] Patients with incomplete data on tumor assessment or response to therapy were excluded from the ARON-1 study.

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

2.2 | Study endpoints

The primary objective of our study was to define the incidence of sRCC and to describe baseline clinical characteristics at metastatic spread presentation compared with non-sRCC patients and correlation those associated with the outcome. Secondary objective was to describe the outcome of sRCC patients based on type of immune-combination used for first-line treatment. Data on tumor response (complete [CR] or partial responses [PR], stable [SD], or progressive disease [PD]) were collected and analyzed. Overall survival (OS) was calculated from the start of treatment to death for 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. Time to second progression (PFS2) was defined as the time from the start of first-line therapy to objective tumor progression on next-line treatment or death from any cause. Duration of response (DoR) was defined as the time from the start of first-line therapy to disease progression or death in patients who achieved CR or PR. Patients without a tumor progression to following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date.

The neutrophil to lymphocyte ratio (NLR) is based on neutrophil (N) and lymphocyte (L) counts and was defined as follows: NLR = N/L. NLR was calculated using data from the most recent laboratory tests prior to initiation of systemic treatment. As for Body Mass Index (BMI), it was defined as a person's weight in kilograms divided by the square of height in meters. Based on the World Health Organization (WHO) classification, patients were included in the overweight/obesity group when BMI was >25 kg/m^2.

2.3 | Statistical analysis

OS, PFS, PFS2, and DoR were estimated using the Kaplan–Meier method with Rothman's 95% confidence intervals (CIs), and comparisons between survival distributions were led by using the log-rank test. Univariate and multivariate analyses were carried out by using Cox proportional hazard models, hazard ratio (HR), and their 95% confidence intervals (95%CI). A survival receiver operating characteristic (ROC) analysis was used to identify potential cut-offs to better stratify patients in risk groups. The chi-square test was employed to compare groups for categorical variables. Significance levels were set at a value of .05, and all p values were two-sided. The statistical analysis was performed by MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

3 | RESULTS

3.1 | Study population

We evaluated 3902 RCC patients from the ARON-1 study, of these 3853 were evaluable for presence/absence of sarcomatoid dedifferentiation; of them 238 (6%) had sarcomatoid de-differentiation. When the analysis was restricted to 1362 patients with IMDC intermediate, or poor prognostic features the incidence of sarcomatoid de-differentiation was 16.6% (Figure S1).

The sRCC and non-sRCC patients did not differ in terms of baseline characteristics including tumor histology, rate of metastasis at diagnosis, sites of metastases, number of metastatic sites and IMDC features except for rate of nephrectomy that was higher in patients with sRCC compared to those who did not (79% vs. 56%; $p < .001$) (Table 1). Among sRCC patients, the median age was 64 year (range 25–89); 74% were males and 26% females. Tumor histology was clear cell RCC in 196 patients (87%); in the 30 non-clear cell RCC patients, papillary histology was observed in 27 cases, and chromophobe RCC in 3. Lung (68%) was the most common metastatic site. About treatments, 101 patients (45%) were treated with first-line IO + TKI (70 with pembrolizumab plus axitinib, 22 with nivolumab plus cabozantinib, and 9 with pembrolizumab plus lenvatinib), while 125 patients (55%) received first-line IO + IO combination (i.e., ipilimumab plus nivolumab) (Table 1).

3.2 | Survival analysis in sRCC and non-sRCC patients

After a median follow-up time of 15.6 months (95%CI 13.4–78.5), the median OS in the overall study population was 33.2 months (95%CI 29.6–40.2); respectively 26.8 months (95%CI 21.6–44.2) in sRCC patients and 35.3 months (95%CI 30.2–40.4) in non-sRCC patients ($p = .013$, Figure 1). The median PFS in the overall study population was 14.4 months (95%CI 12.9–15.5) and was longer in non-sRCC patients (14.5 months, 95%CI 13.2–15.9 vs. 12.3 months, 95%CI 8.0–16.3, $p = .064$, Figure 1).

TABLE 1 Baseline patients' characteristics.

	ARON-1 population			sRCC		
Patients	**Non-sRCC, 1136 (%)**	**sRCC, 226 (%)**	***p***	**IO + IO, 125 (%)**	**IO + TKI, 101 (%)**	***p***
Gender						
Male	845 (74)	146 (64)	.127	87 (69)	59 (58)	.107
Female	291 (26)	80 (36)		38 (31)	42 (42)	
Age, years (y)	64	63	–	63	64	–
Range	25–89	34–93		35–93	34–87	
Past nephrectomy	635 (56)	179 (79)	**<.001**	105 (84)	74 (73)	.059
Clear cell histology	969 (85)	196 (87)	.684	110 (88)	86 (85)	.536
NLR >5	297 (26)	52 (23)	.623	26 (21)	26 (26)	.406
BMI >25	605 (53)	104 (46)	.671	58 (46)	46 (45)	.887
Metastatic at diagnosis	710 (63)	143 (63)	1.000	77 (62)	66 (65)	.660
Number of metastatic sites >1	798 (70)	160 (71)	.877	83 (66)	77 (76)	.120
Common sites of metastasis						
Lung	765 (68)	163 (72)	.538	92 (74)	71 (70)	.530
Bone	410 (36)	67 (30)	.368	31 (25)	36 (35)	.124
Liver	220 (19)	48 (21)	.724	26 (21)	22 (22)	.864
Brain	85 (7)	18 (8)	.789	9 (7)	9 (9)	.603
IMDC risk group						
Intermediate-risk	817 (72)	163 (72)	1.000	93 (74)	70 (69)	.435
Poor-risk	319 (28)	63 (28)		32 (26)	31 (31)	

Note: The values marked in bold are statistically significant ($p < 0.05$).
Abbreviations: BMI, body mass index; IMDC, International Metastatic RCC Database Consortium; IO, immunotherapy; NLR, Neutrophil to lymphocyte ratio; sRCC, sarcomatoid renal cell carcinoma; TKI, tyrosine kinase inhibitor.

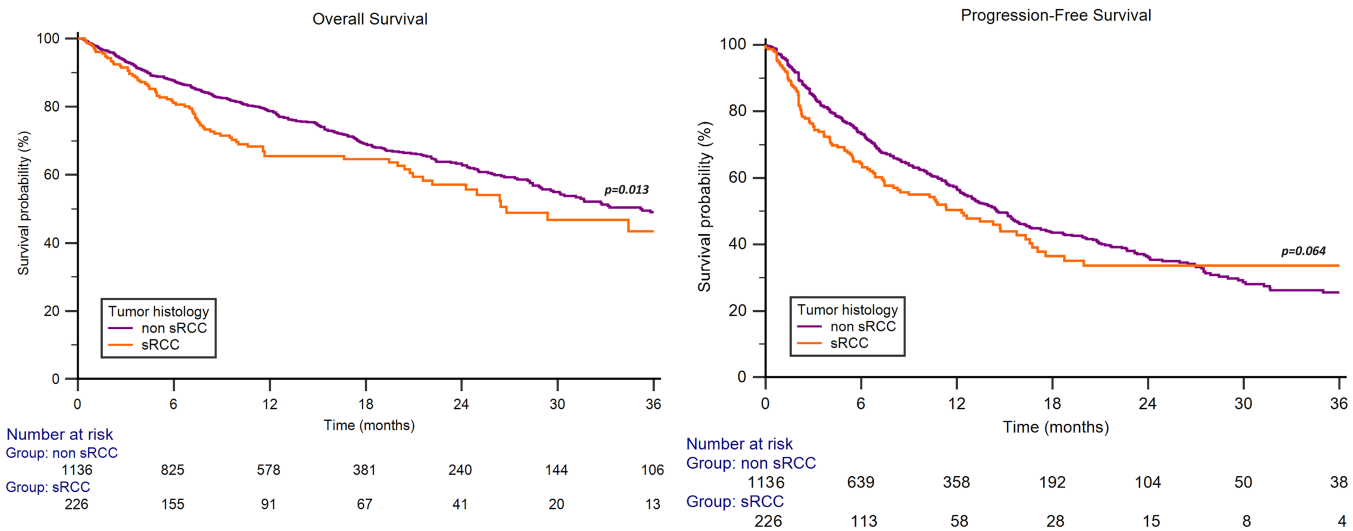

FIGURE 1 Overall survival and progression-free survival in renal cell carcinoma (RCC) patients at intermediate-poor IMDC prognosis with or without sarcomatoid de-differentiation (sRCC) in the overall ARON-1 population.

We further stratified patients according to IMDC group and sarcomatoid differentiation, showing significant differences in terms of both median OS and PFS between these subgroups. In particular, in the intermediate IMDC risk group the median OS was 40.3 (95%CI 31.7–52.5) and 34.4 months (95%CI 26.4–59.0) and the median PFS was 15.7 (95%CI 14.4–18.7) and 13.5 (95%CI 9.0–17.1) months in non-sRCC and sRCC patients, respectively ($p < .001$). In the poor IMDC risk group the median OS was 19.2 (95%CI 15.5–29.7) and 10.0 (95%CI 6.7–20.9) months and the median PFS was 11.0 (95%CI 7.2–12.7) and 7.3 (95%CI 3.1–14.7) months, in non-sRCC and sRCC patients, respectively ($p < .001$).

Due to the imbalance in terms of rate of nephrectomy between sRCC and non-sRCC patients, we further investigated if the prognostic role of sarcomatoid differentiation was independent or not from nephrectomy status. In patients who underwent nephrectomy, the median OS were 55.7 (95%CI 49.2–60.8) and 34.4 (95%CI 25.0–59.0) months ($p < .001$) and the median PFS were 19.9 (95%CI 15.2–22.7) and 14.7 (95%CI 10.8–17.6) months ($p = .076$), in non-sRCC and sRCC group, respectively. In patients who did not received nephrectomy, the median OS were 24.0 (95%CI 21.8–28.2) and 11.7 (95%CI 6.7–20.8), months ($p = .015$) and the median PFS were and 11.5 (95%CI 9.7–51.2) and 5.9 (95%CI 3.0–10.3) months ($p = .007$), in non-sRCC and sRCC group, respectively.

3.3 | Survival analysis in sRCC patients

The median OS was 29.4 months (95%CI 22.2–44.2) and 26.4 months (95%CI 11.7–26.4) in sRCC patients with clear cell and non-clear cell histology ($p = .854$, Figure 2). Similarly, no differences were found in terms of median PFS between sRCC patients with clear cell (13.5 months, 95%CI 8.0–16.7) and non-clear cell histology (10.3 months, 95%CI 3.3–11.3, $p = .679$).

Among patients with sRCC, the available baseline characteristics have been evaluated for correlation with PFS and OS as reported in the Table 2. At multivariable analysis for PFS, the only predictors of outcomes were female versus male sex (HR 1.49; 95%CI, 1.02–2.19; $p = .040$) and previous nephrectomy (HR 0.55; 95%CI, 0.36–0.86). At multivariable analysis for OS, the only predictors of outcomes were female versus male sex (HR 1.75; 95%CI, 1.12–2.72; $p = .014$), the IMDC prognostic group (HR 2.27; 95%CI, 1.41–3.67; $p < .001$) and the presence of liver metastases (HR 1.76; 95%CI 1.07–2.89; $p = .026$).

3.4 | Comparison between IO + IO and IO + TKI in sRCC patients

When considering only sRCC, there was no difference in the median follow up between those treated with IO + TKI or IO + IO (15.7 vs. 15.5 months; $p = .261$). The median OS was 34.4 months (95% CI 20.7–34.4) in patients treated with first-line IO + TKI and 26.4 months (95%CI 20.4–59.0) in those who received IO + IO ($p = .729$, Figure 3A). The median PFS was 12.4 months (95%CI 7.5–20.0) in patients receiving IO + TKI and 12.3 months (95%CI 6.4–17.1) in those treated with IO + IO ($p = .606$, Figure 3B). The overall response rate by treatment was reported in the Figure 4; the ORR (complete + partial response) was 48% for both patients treated with IO + TKI or IO + IO. No differences were found in terms of median DoR, which was NR for both groups ($p = .754$).

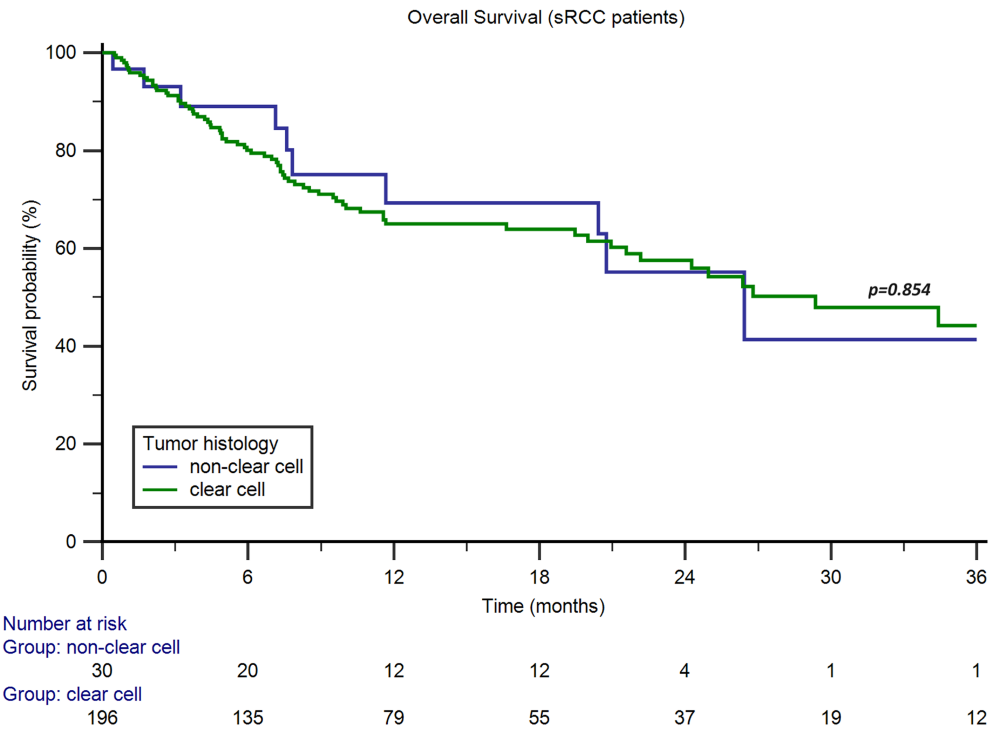

FIGURE 2 Overall survival in clear cell versus non-clear cell renal cell carcinoma (RCC) with sarcomatoid de-differentiation.

TABLE 2 Univariate and multivariate analyses in sarcomatoid RCC patients.

	Univariate Cox regression		Multivariate Cox regression	
Overall survival	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**
Sex (females vs. males)	1.88 (1.21–2.93)	**.005**	1.75 (1.12–2.72)	**.014**
Age (≥65 vs. <65 years)	1.41 (0.92–2.17)	.117		
BMI (>25 vs. ≤ 25)	0.98 (0.64–1.50)	.913		
Nephrectomy (yes vs. no)	0.47 (0.29–0.76)	**.002**	0.70 (0.42–1.19)	.189
Histology (nccRCC vs. ccRCC)	0.94 (0.48–1.82)	.852		
IMDC group (poor vs. intermediate)	2.53 (1.64–3.92)	**<.001**	2.27 (1.41–3.67)	**<.001**
Number of metastatic sites (>1 vs. 1)	1.89 (1.09–3.26)	**.023**	1.16 (0.64–2.10)	.615
Lung metastases (yes vs. no)	0.97 (0.60–1.58)	.901		
Bone metastases (yes vs. no)	1.53 (0.98–2.39)	.061		
Liver metastases (yes vs. no)	1.82 (1.13–2.94)	**.013**	1.76 (1.07–2.89)	**.026**
Brain metastases (yes vs. no)	1.48 (0.76–2.86)	.250		
First-line therapy (IO + IO vs. IO + TKI)	1.08 (0.70–1.67)	.729		
	Univariate Cox regression		**Multivariate cox regression**	
Progression-free survival	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**
Sex (females vs. males)	1.54 (1.05–2.25)	**.028**	1.49 (1.02–2.19)	**.040**
Age (≥65 vs. <65 years)	1.35 (0.93–1.97)	.115		
BMI (>25 vs. ≤25)	0.93 (0.64–1.36)	.724		
Nephrectomy (yes vs. no)	0.54 (0.35–0.82)	**.004**	0.55 (0.36–0.84)	**.005**
Histology (nccRCC vs. ccRCC)	1.12 (0.65–1.94)	.680		
IMDC group (poor vs. intermediate)	1.39 (0.93–2.07)	.111		
Number of metastatic sites (>1 vs. 1)	1.49 (0.94–2.34)	.087		
Lung metastases (yes vs. no)	0.96 (0.62–1.47)	.847		
Bone metastases (yes vs. no)	1.44 (0.97–2.15)	.071		
Liver metastases (yes vs. no)	1.45 (0.93–2.25)	.101		
Brain metastases (yes vs. no)	0.92 (0.46–1.82)	.801		
First-line therapy (IO + IO vs. IO + TKI)	1.10 (0.76–1.61)	.607		

Note: The values marked in bold are statistically significant ($p < 0.05$).
Abbreviations: BMI, body mass index; ccRCC, clear cell renal cell carcinoma; IMDC, International Metastatic RCC Database Consortium; IO, immunotherapy; nccRCC, non-clear cell renal cell carcinoma; TKI, tyrosine kinase inhibitor.

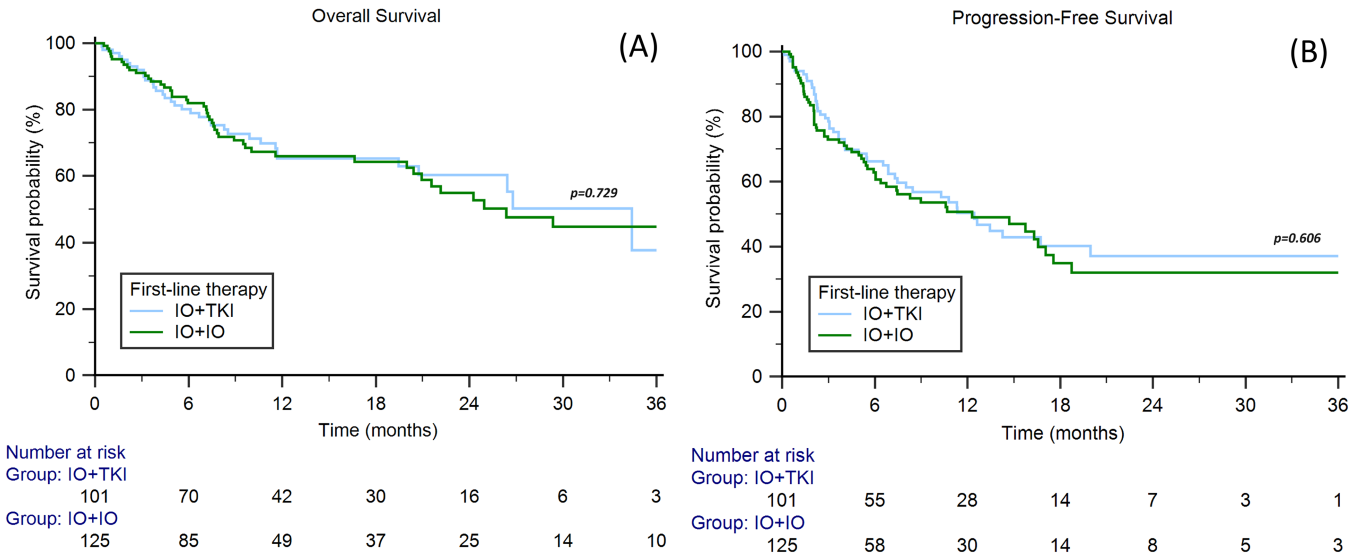

FIGURE 3 Overall survival (A) and progression-free survival (B) in sarcomatoid features (sRCC) patients treated with first-line IO + IO or IO + VEGFR-TKI.

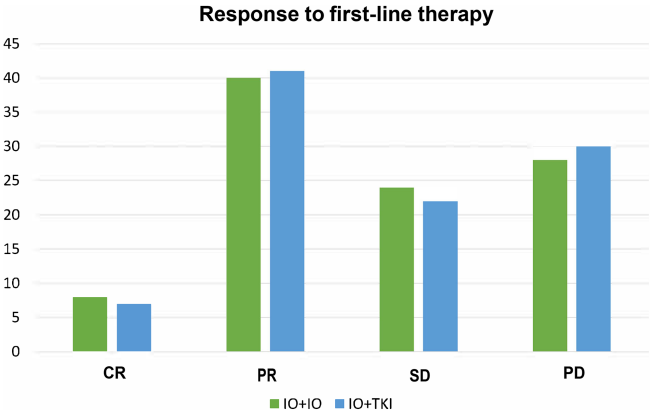

FIGURE 4 Overall response rate (ORR) in sarcomatoid features (sRCC) patients by type of first-line therapy.

About subsequent lines, one-hundred and nine patients (48%) progressed during first-line immune-based combinations; of them, 72 (65%) received second-line treatments (27/101 treated with IO + TKI and 45/125 receiving IO + IO). Second-line therapies consisted in cabozantinib in 44 patients, sunitinib in 15, clinical trials in 6, immune-based combinations in 3, axitinib in 2, and everolimus in 2 patients.

In patients who received second-line therapies, the median PFS2 was 16.5 months (95%CI 13.4–21.6) and was not statistically different between IO + IO (15.4 months, 95%CI 11.3–23.8) and IO + TKI (17.3 months, 95%CI 11.3–21.6, $p = .932$).

4 | DISCUSSION

To the best of our knowledge, this is the largest cohort of patients with advanced sRCC treated in the modern era with IO-based combination regimens reported so far. First of all, we confirmed that metastatic RCC harboring sarcomatoid de-differentiation have worse prognosis compared to non-sRCC, even in the era of IO-based combination therapies, with a significantly shorter OS regardless of the IMDC risk group and prior nephrectomy. Therefore, from one side we reinforced literature data about sarcomatoid feature as an independent factor of poor prognosis and we do support the accuracy of the IMDC risk model in predicting sRCC patients' outcomes.[6–9,30] However, conversely from what expected, we did not observed any significant differences in terms of rate of metastasis at diagnosis, sites of metastases, number of metastatic sites, and IMDC features between sRCC and non-sRCC, suggesting how the intrinsic biology of the sarcomatoid component could account for the aggressiveness of sRCC beyond the established clinical characteristics.[31] Indeed, carrying a sarcomatoid de-differentiation could be considered as a negative feature itself, irrespective from the disease burden or the sites of metastasis. Despite the recent revolution of the treatment landscape of advanced/metastatic RCC, responsible for a significant improvement in patients' outcomes, sarcomatoid de-differentiation still represents a feature independently correlated with poorer prognosis. An intrinsic resistance to therapies (and/or an earlier development of resistance) is another important factor that should be taken into account for explaining the aggressiveness of sRCC. Certainly, the advent of ICIs represent a great progress in the treatment of sRCC, given the constitutive high expression of PD-1/PD-L1 pathways and the high levels of tumor-infiltrating lymphocytes (TILs) associated with immune-responsiveness.[31] Further efforts are necessary for improving our understanding on the biology of sarcomatoid tumors, the presence of patterns with a predictive value and the mechanisms of resistance to therapies that might affect their activity.

Focusing on the cohort of sRCC patients, it is important to underline that prior nephrectomy was significantly associated with longer PFS compared to the lack of surgery; this correlation was maintained at both univariate and multivariate analyses thus supporting how the absence of primary tumor might prognostically affect the efficacy of the IO-based treatment. However, the loss of significance in terms of OS at multivariate analysis was probably due to the presence of other factors (including the IMDC risk group and the presence of liver metastasis) that could have a greater impact on long-term survival. The improvements in mRCC outcomes with the advent of immunotherapy have led to reconsider treatment algorithm, including the role of cytoreductive nephrectomy (CN) for those patients with a metastatic disease at the time of diagnosis. Data about the activity of IO-based combinations on the primary tumor are limited to a small subpopulation of patients without prior nephrectomy (around 20%–30%) included in the pivotal trials. Overall, IO-combos retain their antitumor activity also on the primary tumor, although it seems lower than on metastatic sites.[32–34] Certainly, the presence of sarcomatoid de-differentiation could hinder the decision-making for CN given the more aggressive course of the disease; while retrospective data suggested that CN improved outcomes for patients with sarcomatoid tumors in the targeted therapy era,[35] the role of CN for sRCC in the era of immunotherapy is still controversial, with no clear OS differences based on prior nephrectomy accordingly to our results.[36,37]

Patients with sRCC have a higher risk compared to clear cell RCC of developing liver metastasis, which are significantly associated with dismal outcomes.[38,39] Here, we confirmed liver metastasis as a poor prognostic factor associated with worse OS.

With regard to the type of first-line therapy for sRCC patients, we did not observed any significant difference between IO–IO and IO + VEGFR-TKI in terms of OS, PFS, and objective response rate. This data represents an important piece of evidence, albeit with the limit of the retrospective nature of our analysis. All the phase III trials investigating first-line IO-based combination therapies for RCC had demonstrated consistently superiority of ICI-based combos compared to sunitinib in the subgroup of sRCC patients.[14] In particular, not only the dual ICI combination of nivolumab plus ipilimumab showed (as expected) improved efficacy over sunitinib (PFS, HR 0.54; OS, HR 0.45; and ORR 60.8% vs. 23.1%) in the cohort of patients ($n = 139$) with sarcomatoid de-differentiation in the CheckMate 214 study,[20] but also the strategy of combining a VEGFR-TKI plus an ICI has appeared superior to single-agent VEGFR-TKIs. Thus, as shown in the subgroup analyses of the KEYNOTE-426,

CheckMate 9ER, CLEAR, JAVELIN Renal 101, and IMmotion151 studies, patients with sarcomatoid component had better outcomes (longer OS, PFS, and higher ORR) with the VEGFR-TKI + ICI combos compared to sutinitib.[18,19,21–23] Indeed, a strong biological rational supports a particular responsiveness of sRCC tumors to immunotherapy. Sarcomatoid de-differentiation is characterized by an immune-inflamed microenvironment, CD8+ T-cell infiltration, high expression by tumor infiltrating immune cells and tumor cells of PD-1 and PD-L1, and up-regulation of genes involved in the antigen presentation machinery.[11,19,40] Compared to clear cell RCC, sRCC seem to be less dependent on angiogenic signatures, with a lack of correlation between the expression of genes related to angiogenesis, hypoxia, and glycolytic pathways with patients outcomes, highlighting the crucial role of immunotherapy in the therapy of this population.[19] However, VEGFR-TKI, besides inhibiting the angiogenesis, elicits synergistic antitumor effects when combined to an ICI by enhancing the tumor infiltration of immune cells and reducing the immunosuppressive activity of myeloid-derived suppressor cells.[41] All these findings do support the use of both IO-based combination strategies for the treatment of this aggressive type of RCC. These results are in line with another recent retrospective analysis performed in a small cohort of sRCC patients, which showed the key role of IO treatment for this subgroup of tumors.[42]

Finally, we did provide interesting evidence about the absence of significant differences in terms of both PFS and OS between ccRCC and non-clear cell RCC (nccRCC) with sarcomatoid de-differentiation. As known, sarcomatoid features can occur over any RCC histology. As compared to ccRCC, nccRCC are less frequent (approximately 25% of all RCC tumors), broadly heterogeneous in terms of morphology, genetic profile and clinical behavior, and are associated with inferior survival outcomes. Furthermore, nccRCC are under-represented or excluded from pivotal phase 3 trials investigating novel therapies for RCC, with no major achievements in the therapeutic framework over the past decades.[43] Recently, IO-based combinations have demonstrated remarkable activity also in this subpopulation, with pembrolizumab + lenvatinib in the phase 2 KEYNOTE-B61 trial (the largest trial in this population so far, with 158 enrolled patients) showing 49% of ORR, and promising efficacy (1-year PFS rate of 63%, 1-year OS rate of 82%).[44] Of note, the activity of pembrolizumab + lenvatinib was consistent regardless of the presence of sarcomatoid features, which accounted for 12% of the overall population ($n = 19$).[44] Few data are currently available about the activity of the dual IO combination (i.e., nivolumab + ipilimumab) in nccRCC, with only 52 patients included in the phase 3b/4 CheckMate 920 study, 18.8% of which ($n = 15$) had sarcomatoid features.[45] Nivolumab + ipilimumab was responsible for an ORR of 35.7% in the sarcomatoid nccRCC subgroup (compared to 12.5% in tumors with no sarcomatoid aspects), underlining the relevant activity of immunotherapy in this subgroup at poor prognosis.[45] With the limit of the small proportion of sRCC with no-clear cell histology included in our study ($n = 30$), we reinforced the activity of IO-based combinations in RCC with sarcomatoid de-differentiation regardless from the predominant histology.

The retrospective nature of our data, and the consequent selection bias, represents the major limitations of our study; moreover, the small sample size of our study cohort suggests additional prospective studies to validate our findings. In addition, the lack of a centralized pathological revision of the tumor specimens could represent an important limitation, although coming from international reference cancer centers.

In conclusion, our findings report as the sarcomatoid component is expected in about 6% of patients with mRCC; we confirm that sRCC are aggressive tumors with poor prognosis that have significantly improved survival outcomes with IO-based combinations, regardless from the type of strategy (IO + IO versus IO + TKI) adopted. Further studies are needed to better characterize this histological de-differentiated component and identify potential molecular hallmarks for a tailored treatment approach.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, supervision, validation: Chiara Ciccarese, Roberto Iacovelli, Matteo Santoni. Methodology, data curating, writing—original draft preparation, supervision: Chiara Ciccarese, Thomas Büttner, Francesco Massari, Roberto Iacovelli, Matteo Santoni. Resources, Investigation: Linda Cerbone, Ilaria Zampiva, Fernando Sabino M. Monteiro, Umberto Basso, Martin Pichler, Maria Giuseppa Vitale, Ondrej Fiala, Giandomenico Roviello, Ray Manneh Kopp, Francesco Carrozza, Renate Pichler, Francesco Grillone, Esther Pérez Calabuig, Annalisa Zeppellini, Zsófia Küronya, Luca Galli, Gaetano Facchini, Kaisa Sunela, Alessandra Mosca, Javier Molina-Cerrillo, Giampaolo Spinelli, Jawaher Ansari, Alessandro Scala, Veronica Mollica, Enrique Grande, Sebastiano Buti, Ravindran Kanesvaran, Roubini Zakopoulou, Aristotelis Bamias, Mimma Rizzo. Project administration, validation: Roberto Iacovelli, Matteo Santoni. Data curating, writing—review & editing: Chiara Ciccarese, Thomas Büttner, Linda Cerbone. Writing—reviewing and editing: Francesco Massari, Roberto Iacovelli, Matteo Santoni. Resources, writing—review & editing: Chiara Ciccarese, Roberto Iacovelli, Matteo Santoni. Software, validation, supervision: Roberto Iacovelli, Matteo Santoni. The work reported in the article has been performed by the Authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Chiara Ciccarese has received honoraria for advisory boards, speaker engagements and scientific consultancy for educational purposes from Astellas, AstraZeneca, EISAI, MSD, Ipsen, BMS, Pfizer, Merck, Novartis; all unrelated to the present article. Linda Cerbone has received honoraria for advisory boards, speaker engagements and scientific consultancy for educational purposes from AstraZeneca, EISAI, MSD, Ipsen, BMS, A.A.A.; past MSD employee in Medical Affairs. Fernando Sabino M. Monteiro has received research support from Janssen, Merck Sharp Dome and honoraria from Janssen, Ipsen, Bristol Myers Squibb and Merck Sharp Dome. All unrelated to the present article. Ondrej Fiala received honoraria from Novartis, Janssen, Merck and Pfizer for consultations and lectures unrelated to this project. Ray Manneh Kopp: Speaker, Advisory: AstraZeneca, BMS, MSD, Amgen, Pfizer, Novartis, Roche, Ipsen. Clinical trials: BMS, MSD, Amgen, Novartis, Pfizer, Roche. Annalisa Zeppellini received honoraria for advisory boards, speaker engagements and scientific consultancy for educational purposes from BMS and Janssen, all unrelated to the present article. Javier Molina-Cerrillo declares consultant, advisory or speaker roles for IPSEN, Roche, Pfizer, Sanofi, Janssen, and BMS. JMC has received research grants from Pfizer, IPSEN and Roche. Gian Paolo Spinelli received honoraria for advisory boards from Novartis, Roche and BMS: all unrelated to the present article. Kanesvaran R. has received fees for speaker bureau and advisory board activities from the following companies; Pfizer, MSD, BMS, Eisai, Ipsen, Johnson and Johnson, Merck, Amgen, Astellas and Bayer. Enrique Grande has received honoraria for speaker engagements, advisory roles or funding of continuous medical education from Adacap, AMGEN, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, and Thermo Fisher Scientific. E.G. has received research grants from Pfizer, Astra Zeneca, Astellas, and Lexicon Pharmaceuticals. Sebastiano Buti has received honoraria for speaking at scientific events and advisory roles from AstraZeneca, Bristol Myers Squibb, Ipsen, Merck, Eisai, MSD, Novartis, and Pfizer and research funding from Novartis and Pfizer. Mimma Rizzo has received honoraria as a speaker/consultant from MSD, Bristol-Myers Squibb, Eisai, Astrazeneca, Gilead, Janssen, and Merk Serono, all unrelated to the present article. Francesco Massari has received research support and/or honoraria from Astellas, BMS, Janssen, Ipsen, MSD, and Pfizer outside the submitted work. Roberto Iacovelli has received honoraria for advisory boards, speaker engagements and scientific consultancy for educational purposes from Astellas, AstraZeneca, EISAI, MSD, Ipsen, BMS, Pfizer, Merck, Novartis, Jannsen; all unrelated to the present article. Matteo Santoni has received research support and honoraria from Janssen, Bristol Myers Squibb, Ipsen, MSD, Astellas, A.A.A. and Bayer, all unrelated to the present article. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The ARON-1 study was approved by the Ethical Committee of the Regione delle Marche (CERM) the April 21, 2022.

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REFERENCES

1. Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma: An examination of underlying histologic subtype and an analysis of associations with patient outcome. *Am J Surg Pathol*. 2004;28:435-441.
2. Delahunt B, Cheville JC, Martignonin G, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters the members of the ISUP renal tumor panel. *Am J Surg Pathol*. 2013;37:1490-1504.
3. Albiges L, Flippot R, Rioux-Leclercq N, Choueiri TK. Non-clear cell renal cell carcinomas: from shadow to light. *J Clin Oncol*. 2018;36:3624-3631. doi:10.1200/JCO.2018.79.2531
4. Jones TD, Eble JN, Wang M, Maclennan GT, Jain S, Cheng L. Clonal divergence and genetic heterogeneity in clear cell renal cell carcinomas with sarcomatoid transformation. *Cancer*. 2005;104(6):1195-1203.
5. Debien V, Thouvenin J, Lindner V, et al. Sarcomatoid dedifferentiation in renal cell carcinoma: from novel molecular insights to new clinical opportunities. *Cancers*. 2019;12(1):E99. doi:10.3390/cancers12010099
6. Kyriakopoulos CE, Chittoria N, Choueiri TK, et al. Outcome of patients with metastatic sarcomatoid renal cell carcinoma: results from the international metastatic renal cell carcinoma database consortium. *Clin Genitourin Cancer*. 2015;13:e79-e85.
7. Kim T, Zargar-Shoshtari K, Dhillon J, et al. Using percentage of sarcomatoid differentiation as a prognostic factor in renal cell carcinoma. *Clin Genitourin Cancer*. 2015;13(3):225-230.
8. de Velasco G, McKay RR, Lin X, et al. Comprehensive analysis of survival outcomes in non-clear cell renal cell carcinoma patients treated in clinical trials. *Clin Genitourin Cancer*. 2017;15:652-660.e1.
9. Zhang BY, Thompson RH, Lohse CM, et al. A novel prognostic model for patients with sarcomatoid renal cell carcinoma. *BJU Int*. 2015;115(3):405-411.
10. Malouf GG, Flippot R, Dong Y, et al. Molecular characterization of sarcomatoid clear cell renal cell carcinoma unveils new candidate oncogenic drivers. *Sci Rep*. 2020;10(1):701.
11. Bakouny Z, Braun DA, Shukla SA, et al. Integrative molecular characterization of sarcomatoid and rhabdoid renal cell carcinoma. *Nat Commun*. 2021;12:808. doi:10.1038/s41467-021-21068-9
12. Molina AM, Tickoo SK, Ishill N, et al. Sarcomatoid-variant renal cell carcinoma: treatment outcome and survival in advanced disease. *Am J Clin Oncol*. 2011;34:454-459.
13. Beuselinck B, Lerut E, Wolter P, et al. Sarcomatoid dedifferentiation in metastatic clear cell renal cell carcinoma and outcome on treatment with anti-vascular endothelial growth factor receptor tyrosine kinase inhibitors: a retrospective analysis. *Clin Genitourin Cancer*. 2014;12:e205-e214.
14. Iacovelli R, Ciccarese C, Bria E, et al. Patients with sarcomatoid renal cell carcinoma—re-defining the first-line of treatment: a meta-analysis of randomized clinical trials with immune checkpoint inhibitors. *Eur J Cancer*. 2020;136:195-203.
15. McKay RR, Bossé D, Xie W, et al. The clinical activity of PD-1/PD-L1 inhibitors in metastatic non-clear cell renal cell carcinoma. *Cancer Immunol Res*. 2018;6:758-765.
16. McDermott DF, Lee JL, Ziobro M, et al. Open-label, single-arm, phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. *J Clin Oncol*. 2021;39(9):1029-1039.
17. McGregor BA, McKay RR, Braun DA, et al. Results of a multicenter phase II study of atezolizumab and bevacizumab for patients with metastatic renal cell carcinoma with variant histology and/or sarcomatoid features. *J Clin Oncol*. 2020;38(1):63-70.
18. Rini BI, Motzer RJ, Powles T, et al. Atezolizumab plus bevacizumab versus sunitinib for patients with untreated metastatic renal cell carcinoma and sarcomatoid features: a prespecified subgroup analysis of the IMmotion151 clinical trial. *Eur Urol*. 2021;79:659-662.
19. Choueiri TK, Larkin JMG, Pal SK, et al. Efficacy and correlative analyses of avelumab plus axitinib versus sunitinib in sarcomatoid renal cell carcinoma: post hoc analysis of a randomized clinical trial. *ESMO Open*. 2021;6(3):100101.
20. Rini BI, Signoretti S, Choueiri TK, et al. Long-term outcomes with nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. *J Immunother Cancer*. 2022;10:e005445. doi:10.1136/jitc-2022-005445
21. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study. *J Clin Oncol*. 2019;37:4500.
22. Motzer RJ, Choueiri TK, Powles T, et al. Nivolumab + cabozantinib (NIVO + CABO) versus sunitinib (SUN) for advanced renal cell carcinoma (aRCC): outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. *J Clin Oncol*. 2021;39(6):308. doi:10.1200/JCO.2021.39.6_suppl.308
23. Grünwald V, Powles T, Eto M, et al. Phase e CLEAR study in patients with advanced renal cell carcinoma: outcomes in subgroups for lenvatinib-plus-pembrolizumab and sunitinib arms. *Front Oncol*. 2023;13:1223282.
24. McDermott DF, Huseni MA, Atkins MB, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med*. 2018;24(6):749-757.
25. Santoni M, Buti S, Myint ZW, et al. 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? *Eur Urol Oncol*. 2023;23:145. doi:10.1016/j.euo.2023.07.003
26. Santoni M, Massari F, Myint ZW, et al. Clinico-pathological features influencing the prognostic role of body mass index in patients with advanced renal cell carcinoma treated by immuno-oncology combinations (ARON-1). *Clin Genitourin Cancer*. 2023;21(5):e309-e319.e1. doi:10.1016/j.clgc.2023.03.006
27. Santoni M, Massari F, Myint ZW, et al. Global real-world outcomes of patients receiving Immuno-oncology combinations for advanced renal cell carcinoma: the ARON-1 study. *Target Oncol*. 2023;18(4):559-570. doi:10.1007/s11523-023-00978-2

28. Porta C, Bamias A, Zakopoulou R, et al. Geographical differences in the management of metastatic de novo renal cell carcinoma in the era of immune-combinations. *Minerva Urol Nephrol*. 2023;75(4):460-470. doi:10.23736/S2724-6051.23.05369-7
29. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-update and clarification: from the RECIST committee. *Eur J Cancer*. 2016;62:132-137.
30. Blum KA, Gupta S, Tickoo SK, et al. Sarcomatoid renal cell carcinoma: biology, natural history and management. *Nat Rev Urol*. 2020;17:659-678.
31. Li Y, Lih TSM, Dhanasekaran SM, et al. Histopathologic and proteogenomic heterogeneity reveals features of clear cell renal cell carcinoma aggressiveness. *Cancer Cell*. 2023;41:139-163.
32. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versusu sunitinib for first-line treatment in advanced renal cell carcinoma: extended 4-year follow-up of phase III CheckMate 214 trial. *ESMO Open*. 2020;5(6):e001079.
33. Powles T, Choueiri TC, Burotto M, et al. Final overall survival analysis and organ-specific target lesion assessments with two-year follow-up in CheckMate 9ER: Nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. 2022 ASCO Genitourinary Cancers Symposium.
34. Iacovelli R, Ciccarese C, Maruzzo M, et al. Primary tumor shrinkage and the effect on metastatic disease and outcomes in patients with advanced kidney cancer with intermediate or poor prognosis treated with Nivolumab plus Ipilimumab or Cabozantinib. *Clin Genitourin Cancer*. 2022;20(5):e1-e9.
35. Silagy AW, Mano R, Blum KA, et al. The role of cytoreductive nephrectomy for sarcomatoid renal cell carcinoma: a 29-year institutional experience. *Urology*. 2020;136:169-175.
36. Tully KH, Berg S, Paciotti M, et al. The natural history of renal-cell carcinoma with sarcomatoid differentiation, a stage-by-stage analysis. *Clin Genitourinary Cancer*. 2022;21(1):63-68.
37. Hahn AW, Kotecha RR, Viscuse PV, et al. Cytoreductive nephrectomy for patients with metastatic Sarcomatoid and/or Rhabdoid renal cell carcinoma treated with immune checkpoint therapy. *Eur Urol Focus*. 2023;9:2405-4569. doi:10.1016/j.euf.2023.02.008
38. Wei H, Miao J, Cui J, et al. The prognosis and clinicopathological features of different distant metastases patterns in renal cell carcinoma: analysis based on the SEER database. *Sci Rep*. 2021;11:17822.
39. Shan L, Shao X, Gu L, et al. Clinicopathologic factors linked to oncologic outcomes for renal cell carcinoma with sarcomatoid dedifferentiation: a PRISMA compliant systematic review and meta-analysis. *Front Surg*. 2022;9:922150.
40. Joseph RW, Millis SZ, Carballido EM, et al. PD-1 and PD-L1 expression in renal cell carcinoma with sarcomatoid differentiation. *Cancer Immunol Res*. 2015;3:1303-1307.
41. Hirsch L, Flippot R, Escudier B, Albiges L. Immunomodulatory roles of VEGF pathway inhibitors in renal cell carcinoma. *Drugs*. 2020;80:1169-1181.
42. Sawana GB, Dragomir A, Wood LA, et al. Real-world assessment of clinical outcomes in patients with metastatic renal cell carfcinoma with or without sarcomatoid features treated with first-line systemic therapies. *Eur Urol Oncol*. 2023;23:279.
43. Ciccarese C, Iacovelli R, Brunelli M, et al. Addressing the best treatment for non-clear cell renal cell carcinoma: a meta-analysis of randomized clinical trials comparing VEGFR-TKis versus mTORi-targeted therapies. *Eur J Cancer*. 2017;83:237-246.
44. Albiges L, Gurney H, Atduev V, et al. Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2023;24:881-891.
45. Tykodi SS, Gordan LN, Alter R, et al. Safety and efficacy if nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. *J Immunother Cancer*. 2022;10(2):e003844.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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