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Sarcomatoid Differentiation in Renal Cell Carcinoma: Clinical and Pathologic Heterogeneity and Outcomes With Immune Checkpoint Inhibitors—Data From the ARON-1 Study

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ABSTRACT

PURPOSE Sarcomatoid renal cell carcinoma (sRCC) represents a kidney malignancy with a sarcomatoid component associated with poor prognosis. Immunotherapy (IO)-based combinations demonstrated promising activity in sRCC, yet real-world evidence (RWE) remains limited. We aimed to characterize the clinicopathologic features and outcomes of patients with metastatic sRCC treated with first-line immune-based combinations.

PATIENTS AND METHODS This retrospective analysis from the ARON-1 study included 350 patients with histologically confirmed metastatic sRCC treated with first-line IO + IO, or IO + tyrosine kinase inhibitor across 66 centers in 21 countries (2016-2024). Overall survival (OS) was analyzed using Kaplan-Meier and Cox regression methods. Correlations between 2-year OS and clinical variables were assessed using Pearson's coefficient.

RESULTS After a median follow-up of 19.1 months, median OS was 26.9 months (95% CI, 21.6 to 43.3). OS was longer in males (43.3 *v* 15.3 months in females; $P < .001$), in whom underwent nephrectomy (32.3 *v* 20.7 months; $P = .002$), and in patients without hepatic (32.3 *v* 15.3 months; $P < .001$), without skeletal (41.0 *v* 20.0 months; $P = .007$), or without lymph node metastases (43.3 *v* 24.6 months; $P = .037$). Median OS varied by International Metastatic RCC Database Consortium (IMDC) risk group: 66.5, 29.4, and 11.7 months in favorable-, intermediate-, and poor-risk patients, respectively ($P < .001$). Different IO regimens showed variable outcomes by risk subgroup. Limitations include retrospective design and lack of central pathology review.

CONCLUSION First-line IO-based combinations provide clinically meaningful survival in sRCC, with outcomes affected by sex, metastatic sites, and IMDC risk. This RWE may support a tailored therapeutic approach on the basis of baseline prognostic factors.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

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INTRODUCTION

Renal cell carcinoma (RCC) with sarcomatoid features (sRCC) represents a highly aggressive variant of RCC that spans multiple histologic subtypes, most commonly clear cell RCC (ccRCC) as well as the much less common non–clear cell histologies, being associated with a worse prognosis across both localized and metastatic disease stages.[1] The presence of sarcomatoid differentiation was shown to occur in about 5%-10% of patients with more than 75% of these patients presenting with metastatic disease at the time of the diagnosis, irrespective of the underlying RCC-prevalent histology.[2-4] sRCCs are dedifferentiated RCC with a high-grade morphology (WHO grade 4) and histologically related to sarcoma-like features, including spindle-shaped cells, high cellularity, and marked cellular atypia, with immunohistochemical lack of the epithelial marker E-cadherin along with mesenchymal marker expression, and showing other high-risk microscopic features such as necrosis and microvascular invasion.[5] From a molecular point of view,

CONTEXT

Key Objective

What are the prognostic implications of clinical and pathologic heterogeneity in patients with metastatic renal cell carcinoma (RCC) with sarcomatoid differentiation treated with first-line immune-based combinations? This study analyzes outcomes in the largest real-world cohort of such patients across 66 centers worldwide, to the best of our knowledge, providing granular insight into survival patterns on the basis of baseline characteristics.

Knowledge Generated

Among 350 patients with sarcomatoid RCC, the median overall survival was 26.9 months. Sex, presence of liver metastases, and International Metastatic RCC Database Consortium risk group were independently associated with survival outcomes in multivariable analysis.

Relevance

These findings highlight the importance of individualized treatment strategies for patients with sarcomatoid RCC receiving immunotherapy combinations. Recognizing baseline prognostic factors may support therapeutic decision making and patient counseling in clinical practice.

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sRCCs are characterized by a plethora of genomic alterations (ie, overexpression of MYC-regulated genes, mutations involving the Hippo pathway, *CDKN2A/B* deletions, *BAP1* mutations, etc) related with a poor prognosis of these patients.[2,6] Moreover, programmed cell death ligand-1 (PD-L1) expression was shown to be particularly increased in sarcomatoid dedifferentiated RCCs, thus suggesting a potential benefit from PD-1/PD-L1 immune checkpoint inhibitors (ICIs) for patients with sRCC.[6]

As for the therapeutic management of sRCC, a surgical approach is considered the treatment of choice when diagnosed at an early stage. More recently, the pivotal KEYNOTE-564 study revealed that patients with resected sRCC derive greater benefit from adjuvant immunotherapy (IO) with pembrolizumab compared with patients without sarcomatoid features.[7] Sarcomatoid differentiation therefore represents a meaningful determinant in the therapeutic decision-making process for physicians. As for the metastatic disease, the role of cytoreductive nephrectomy is disputed. Previous studies demonstrated that sRCC responds poorly to vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), with a high rate of primary refractory patients (about 40%).[8] In the past decade, the advent of the IO-based combinations has dramatically revolutionized the therapeutic scenario of metastatic RCC (mRCC), leading to never-seen-before benefits in terms of survival outcomes and disease control also in this particularly aggressive histologic variant.[9] Of note, ICIs either alone or in combination with VEGFR TKIs (IO + IO, as nivolumab plus ipilimumab, and IO + TKI, as pembrolizumab plus axitinib or lenvatinib, and nivolumab plus cabozantinib) showed unprecedented antitumor activity in sRCC, reporting overall response rates (ORRs) ranging from 47% to 61%.[10-13] Although significant insights into the biology of sRCC have been gained from preclinical and clinical studies over the past years, real-world data on the clinical and pathologic heterogeneity of this subtype and its impact on prognosis and the efficacy of first-line IO-based combinations remain scarce.

The ARON-1 study (ClinicalTrials.gov identifier: NCT05287464) was designed to analyze real-world data from patients with metastatic RCC treated with first-line IO-based combination therapies.[14-18] Although the previous ARON-1 analysis aimed to determine the incidence and baseline clinical characteristics of patients with sRCC compared with non-sRCC patients and to explore outcomes in patients with sRCC on the basis of the type of first-line therapy, the present analysis seeks to investigate the prognostic significance of various clinical and pathologic features of sRCC in a real-world setting, thus assessing outcomes within a large data set. The aim was to more precisely characterize this specific mRCC population and evaluate the activity and efficacy of available immune-based combinations, focusing on their impact on survival outcomes.

PATIENTS AND METHODS

Study Population

This retrospective analysis included adult patients (age 18 years or older) diagnosed with RCC exhibiting sarcomatoid differentiation, confirmed through histologic evaluation. Patients selected for this study had either histologically or radiologically verified metastatic disease and were treated with first-line combinations of ICIs (IO) plus TKIs or dual ICIs (IO + IO). The study encompassed treatments initiated between January 1, 2016, and May 31, 2024, across 66 medical centers located in 21 different countries (Data Supplement, Fig S1).

Clinical data were extracted retrospectively from patient medical records, including demographic information (age

and sex), tumor histology, previous nephrectomy status, metastatic sites, International Metastatic RCC Database Consortium (IMDC) risk group, BMI, Eastern Cooperative Oncology Group performance status, treatment regimens, and therapeutic response based on RECIST 1.1.[19]

Patients generally remained on first-line therapy until clinical or radiologic evidence of disease progression at the clinicals' discretion, occurrence of intolerable adverse effects, or death. Imaging evaluations, including computed tomography or magnetic resonance imaging, followed institutional protocols and were typically performed every 8-12 weeks. Routine physical examinations and laboratory assessments were conducted at intervals of 4-6 weeks throughout the follow-up period as per clinical practice.

Study End Points

The primary goal of the present investigation was to assess how various clinical and pathologic features influenced prognosis in patients with metastatic sRCC. A secondary aim was to explore treatment outcomes according to the type of IO-based regimen administered as first-line therapy. Tumor response was categorized as complete response (CR), partial response, stable disease, or progressive disease, and these outcomes were systematically evaluated.

Overall survival (OS) was defined as the duration from the initiation of therapy to the time of death from any cause. For patients who were still alive or lost to follow-up at the time of data analysis, survival was censored at the date of the most recent clinical evaluation.

BMI was calculated by dividing an individual's weight in kilograms by the square of the height in meters (kg/m^2).

Statistical Analysis

Survival outcomes were analyzed using the Kaplan-Meier method, with 95% CI computed using Rothman's approach. Median follow-up was calculated using the inverse Kaplan-Meier method. Differences between survival curves were evaluated using the log-rank test. Cox proportional hazards models were used to conduct both univariable and multivariable analyses, with results presented as hazard ratios (HRs) and corresponding 95% CI. Pearson's correlation coefficient was used to assess associations between variables. A two-sided P value of <.05 was considered statistically significant. All statistical analyses were performed using MedCalc software, version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

Ethical Considerations

The ARON-1 study was conducted after approval from the Ethics Committee of the Marche Region (approval number 2021-492), along with clearance from the institutional review boards of all participating institutions, in alignment with the regulatory frameworks of each respective country. All research activities were carried out in adherence to Good Clinical Practice guidelines and the ethical standards governing international biomedical research. The study protocol was developed in accordance with the principles outlined in the Declaration of Helsinki, ensuring the ethical treatment and protection of human subjects.

RESULTS

Study Population

We evaluated 5537 patients with RCC from the ARON-1 study; of them, 350 (6%) had sarcomatoid dedifferentiation and were treated with first-line IO combinations (Data Supplement, Fig S2).

The median age of patients with sarcomatoid differentiation was 64 years (range, 34-92); 232 patients (66%) were males and 118 (34%) females. Two hundred and sixty-seven patients (76%) underwent nephrectomy. Tumor histology was clear cell RCC in 298 patients (85%). Among the 52 patients with non–clear cell RCC, papillary histology was observed in 15 patients (4%) and chromophobe RCC in 10 patients (3%), and the remaining 27 (8%) were reported as poorly differentiated or unclassified. Lung (69%) and distant lymph nodes (51%) were the most frequent metastatic sites. A total of 182 patients (52%) were treated with first-line IO + TKI, including 91 (26%) with pembrolizumab plus axitinib, 53 (15%) with nivolumab plus cabozantinib, and 38 (11%) with pembrolizumab plus lenvatinib, while 168 patients (48%) received first-line ipilimumab plus nivolumab combination (Table 1).

Survival Analysis

After a median follow-up time of 19.1 months (95% CI, 15.6 to 111.4), the median OS in patients with sarcomatoid differentiation was 26.9 months (95% CI, 21.6 to 43.3).

The median OS was 43.3 months (95% CI, 26.4 to 57.4) in males and 15.3 months (95% CI, 9.9 to 66.5) in females (P < .001; Fig 1), while no statistically significant differences were found between patients age ≥70 years versus < 70 years (24.6 months [95% CI, 15.2 to 32.3 *v* 34.4 months; 95% CI, 24.3 to 52.5]; P = .187) and between patients with a BMI ≥25 kg/m^2 versus < 25 kg/m^2 (32.3 months [95% CI, 24.3 to 56.8 *v* 24.6 months; 95% CI, 16.8 to 44.2]; P = .433).

The median OS was 32.3 months (95% CI, 25.0 to 52.5) and 20.7 months (95% CI, 7.0 to 57.4) in patients who did or did not undergo nephrectomy, respectively (P = .002; Fig 1).

Median OS was 29.4 months (95% CI, 22.2 to 44.2) in patients with clear cell RCC and 20.8 months (95% CI, 11.7 to 66.5) in patients with non–clear cell histology (P = .478).

The median OS was 25.0 months (95% CI, 20.0 to 44.2) in patients with synchronous mRCC and 41.0 months (95% CI, 22.2 to 59.0) in patients with metachronous mRCC (P = .114).

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TABLE 1. Baseline Patients' Characteristics

Patients	No. (%)
Sex	
Male	232 (66)
Female	118 (34)
Age, years	64
Range	34-92
Past nephrectomy	267 (76)
Clear cell histology	298 (85)
BMI ≥25	176 (50)
Metastatic at diagnosis	221 (63)
Common sites of metastasis	
Lung	240 (69)
Distant lymph nodes	180 (51)
Bone	108 (31)
Liver	74 (21)
Brain	33 (9)
IMDC risk group	
Good-risk	19 (6)
Intermediate-risk	221 (63)
Poor-risk	110 (31)
First-line therapy	
Nivolumab plus ipilimumab	168 (48)
Pembrolizumab plus axitinib	91 (26)
Nivolumab plus cabozantinib	53 (15)
Pembrolizumab plus lenvatinib	38 (11)

Abbreviations: IMDC, International Metastatic RCC Database Consortium; IO, immunotherapy; sRCC, sarcomatoid renal cell carcinoma; TKI, tyrosine kinase inhibitor.

We further stratified patients by site of metastases. A statistically significant difference was found between patients with versus without metastases to distant lymph nodes (24.6 months [95% CI, 16.8 to 34.4 *v* 43.3 months; 95% CI, 25.0 to 59.0]; $P = .037$; Fig 1), bones (20.0 months [95% CI, 11.6 to 66.5 *v* 41.0 months; 95% CI, 25.0 to 56.8]; $P = .007$; Fig 1), and liver (15.3 months [95% CI, 7.5 to 57.4 *v* 32.3 months; 95% CI, 25.5 to 56.8]; $P < .001$; Fig 1), while no differences were observed in patients with versus without lung (29.4 months [95% CI, 22.2 to 52.5 *v* 25.5 months; 95% CI 12.1 to 66.5]; $P = .470$) or brain metastases (11.7 months [95% CI, 7.6 to 57.4 *v* 27.0 months; 95% CI, 22.2 to 52.5]; $P = .094$).

As for the IMDC classification, the median OS was 66.5 months (95% CI, 17.8 to 78.5), 29.4 months (95% CI, 24.6 to 44.2), and 11.7 months (95% CI, 7.1 to 27.0) in patients with favorable-, intermediate-, and poor-risk features, respectively ($P < .001$; Fig 1).

Survival and Response by First-Line Therapy

We further stratified the overall study population by type of first-line immune combination and IMDC risk group. Among the 19 patients with favorable-risk features, 10 were treated with pembrolizumab plus axitinib, four with nivolumab plus cabozantinib, and five with pembrolizumab plus lenvatinib. The median OS was not reached (NR) with all three IO combinations, with 2-year OS rates of 83% for pembrolizumab plus axitinib, 90% for pembrolizumab plus lenvatinib, and 100% for nivolumab plus cabozantinib. The rate of response by IO combination therapy is illustrated in Figure 2.

In patients with intermediate-risk criteria, the median OS was NR for both pembrolizumab plus axitinib and nivolumab plus cabozantinib, 25.0 months (95% CI, 20.8 to 43.3) for nivolumab plus ipilimumab, and 29.4 months (95% CI, 24.6 to 44.2) for pembrolizumab plus lenvatinib ($P = .681$; Fig 3), with 2-year OS rates of 64%, 48%, 70%, and 73%, respectively. The rate of response by IO combination therapy is illustrated in Figure 2.

In the poor-risk subgroup, 22 patients received pembrolizumab plus axitinib, 45 nivolumab plus ipilimumab, 23 nivolumab plus cabozantinib, and 20 pembrolizumab plus lenvatinib. The median OS was 15.2 months (95% CI, 4.0 to 71.1) for pembrolizumab plus axitinib, 20.9 months (95% CI, 6.9 to 57.4) for nivolumab plus ipilimumab, 8.5 months (95% CI, 3.9 to 56.8) for nivolumab plus cabozantinib, and 7.2 months (95% CI, 4.9 to 26.9) for pembrolizumab plus lenvatinib ($P = .597$; Fig 3), with 2-year OS rates of 42%, 48%, 31%, and 45%, respectively. The rate of response by immune-combination therapy is illustrated in Figure 2.

Correlation Between 2-Years OS Rates and Patients' Clinical and Pathologic Characteristics

We found a statistically significant correlation between 2-year OS rate and IMDC risk group ($P < .001$; correlation coefficient −0.21 [95% CI, −0.31 to −0.10]; Fig 4), the presence of liver metastases ($P < .001$; correlation coefficient −0.23 [95% CI, −0.32 to −0.12]; Fig 4), and sex ($P = .002$; correlation coefficient −0.17 [95% CI, −0.27 to −0.06]; Fig 4).

In patients receiving pembrolizumab plus axitinib, a significant correlation was found between 2-year OS rate and IMDC ($P = .012$; correlation coefficient −0.26 [95% CI, −0.44 to −0.06]; Data Supplement, Fig S3) and sex ($P < .001$; correlation coefficient −0.06 [95% CI, −0.26 to 0.15]; Data Supplement, Fig S3), while in patients treated with nivolumab plus ipilimumab, the 2-year OS rate was significantly correlated with the presence of liver metastases ($P = .009$; correlation coefficient −0.20 [95% CI, 0.19 to 0.38]; Data Supplement, Fig S4) and sex ($P = .002$; correlation coefficient −0.24 [95% CI, 0.19 to 0.38]; Data Supplement, Fig S4).

However, patients treated with nivolumab plus cabozantinib showed a significant correlation between 2-year OS rate and IMDC ($P = .033$; correlation coefficient −0.30 [95% CI, −0.53 to −0.03]; Data Supplement, Fig S5), presence of liver metastases ($P = .016$; correlation coefficient −0.33 [95% CI, −0.56 to −0.06]; Data Supplement, Fig S5), and sex ($P < .001$;

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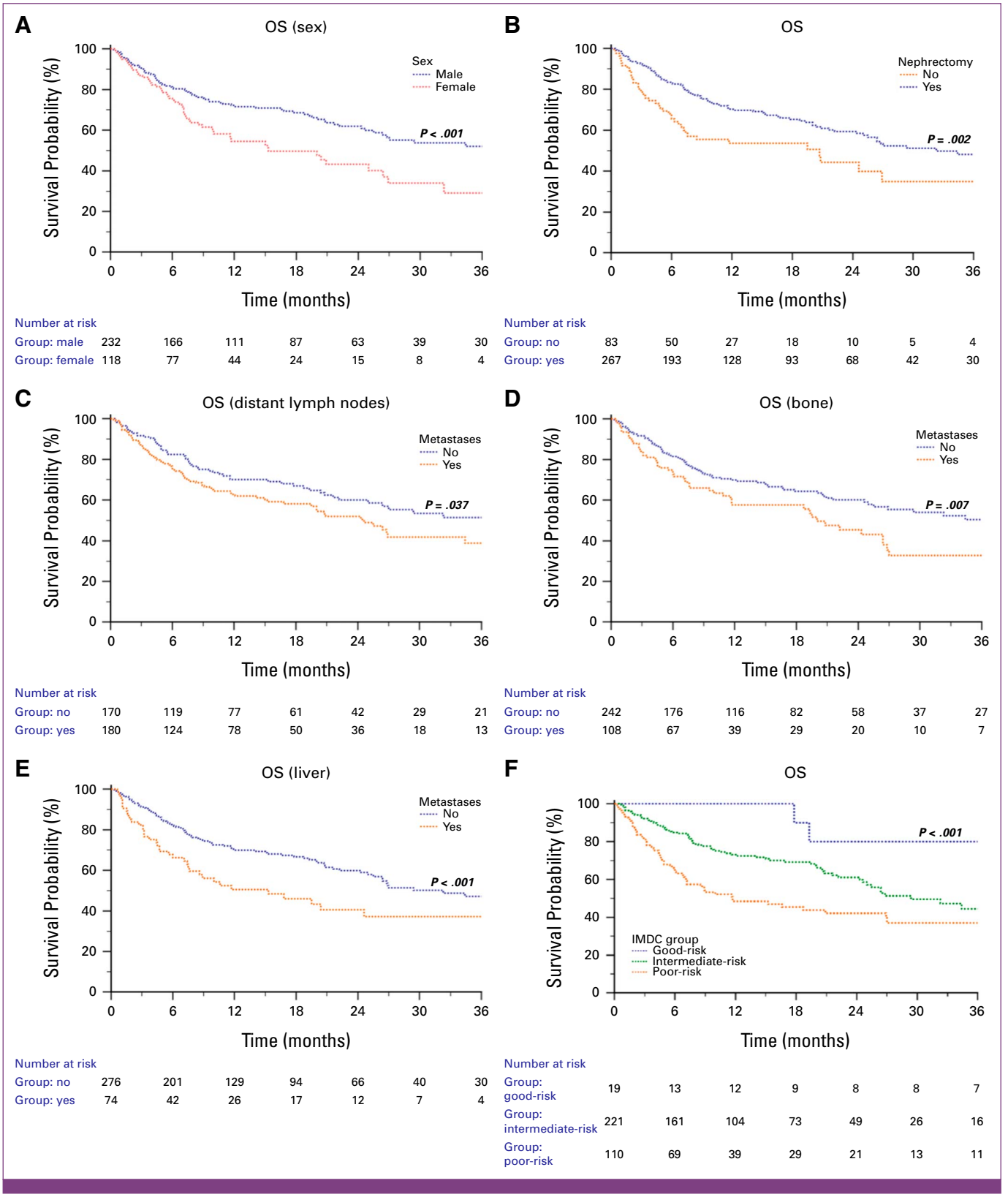

FIG 1. OS in RCC patients with sarcomatoid dedifferentiation (sRCC) in the overall ARON-1 population stratified by clinic-pathologic features. (A) Sex, (B) previous nephrectomy, (C) distant lymph node, (D) bone, (E) liver metastasis and (F) IMDC group. IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma; sRCC, sarcomatoid renal cell carcinoma.

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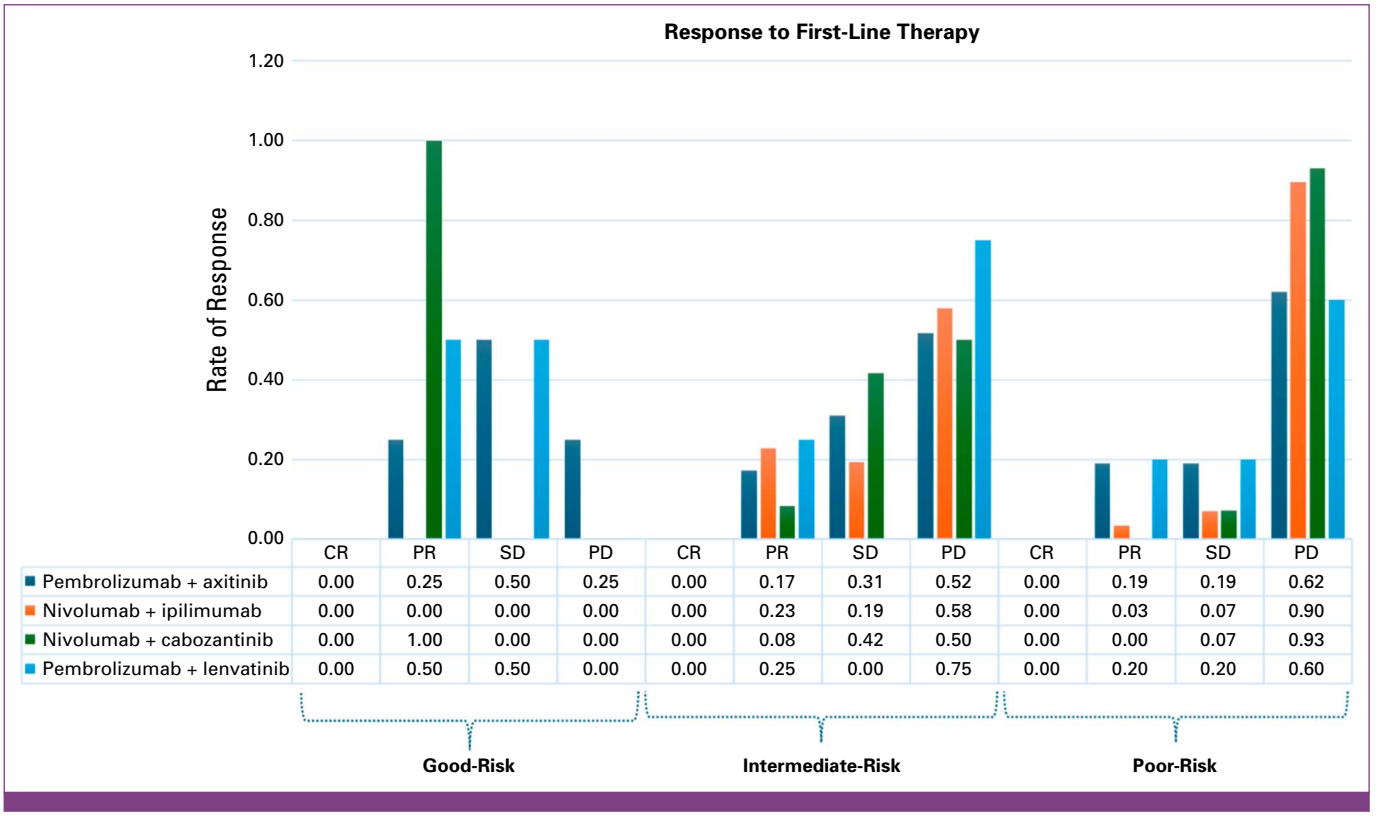
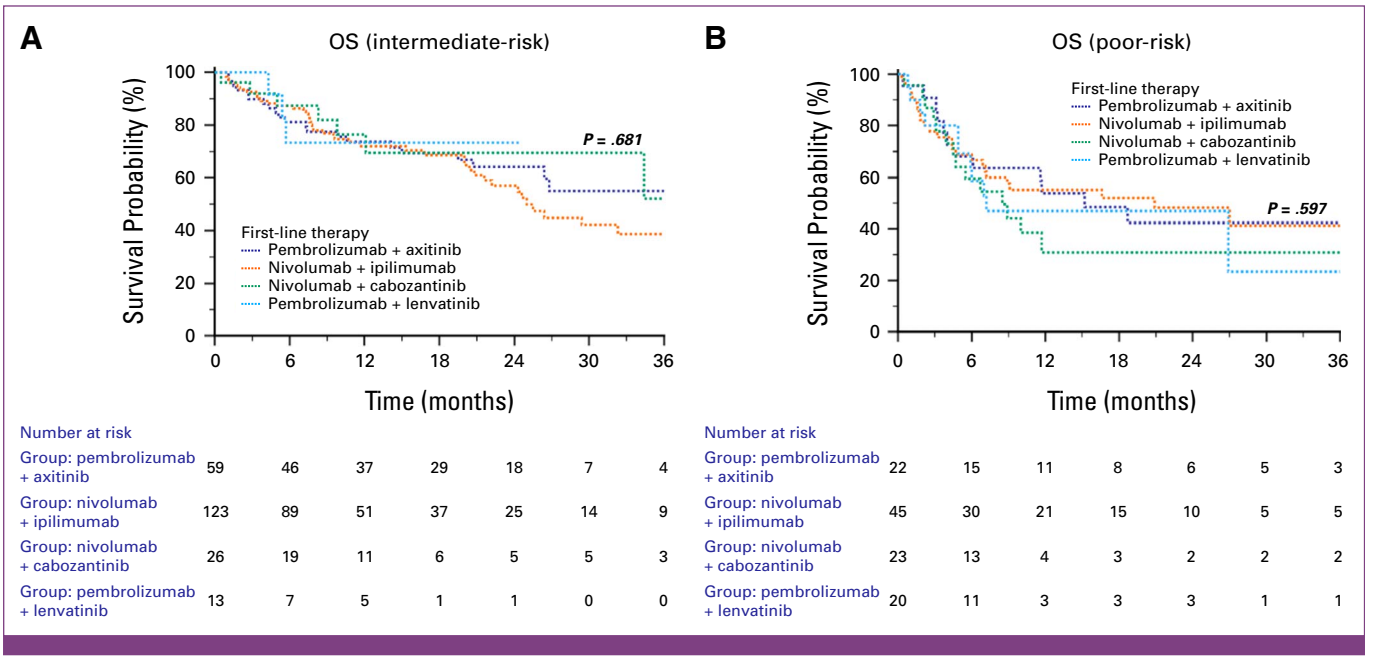


	Good-Risk				Intermediate-Risk				Poor-Risk			
	CR	PR	SD	PD	CR	PR	SD	PD	CR	PR	SD	PD
Pembrolizumab + axitinib	0.00	0.25	0.50	0.25	0.00	0.17	0.31	0.52	0.00	0.19	0.19	0.62
Nivolumab + ipilimumab	0.00	0.00	0.00	0.00	0.00	0.23	0.19	0.58	0.00	0.03	0.07	0.90
Nivolumab + cabozantinib	0.00	1.00	0.00	0.00	0.00	0.08	0.42	0.50	0.00	0.00	0.07	0.93
Pembrolizumab + lenvatinib	0.00	0.50	0.50	0.00	0.00	0.25	0.00	0.75	0.00	0.20	0.20	0.60

FIG 2. Rates of response by immune-combination therapy and IMDC group. CR, complete response; IMDC, International Metastatic RCC Database Consortium; PD, progressive disease; PR, partial response; SD, stable disease.

correlation coefficient −0.05 [95% CI, −0.32 to 0.23]; Data Supplement, Fig S5), while no significant correlations were found between 2-year OS rate and patients' clinicopathologic features in the pembrolizumab plus lenvatinib subgroup, in which only the correlation with sex was slightly significant (P = .084; Data Supplement, Fig S6).



Number at risk							
Group: pembrolizumab + axitinib	59	46	37	29	18	7	4
Group: nivolumab + ipilimumab	123	89	51	37	25	14	9
Group: nivolumab + cabozantinib	26	19	11	6	5	5	3
Group: pembrolizumab + lenvatinib	13	7	5	1	1	0	0

Number at risk							
Group: pembrolizumab + axitinib	22	15	11	8	6	5	3
Group: nivolumab + ipilimumab	45	30	21	15	10	5	5
Group: nivolumab + cabozantinib	23	13	4	3	2	2	2
Group: pembrolizumab + lenvatinib	20	11	3	3	3	1	1

FIG 3. OS in patients with sRCC treated with first-line immune-combinations stratified by IMDC risk group: (A) intermediate-risk and (B) poor-risk. IMDC, International Metastatic RCC Database Consortium; OS, overall survival; sRCC, sarcomatoid renal cell carcinoma.

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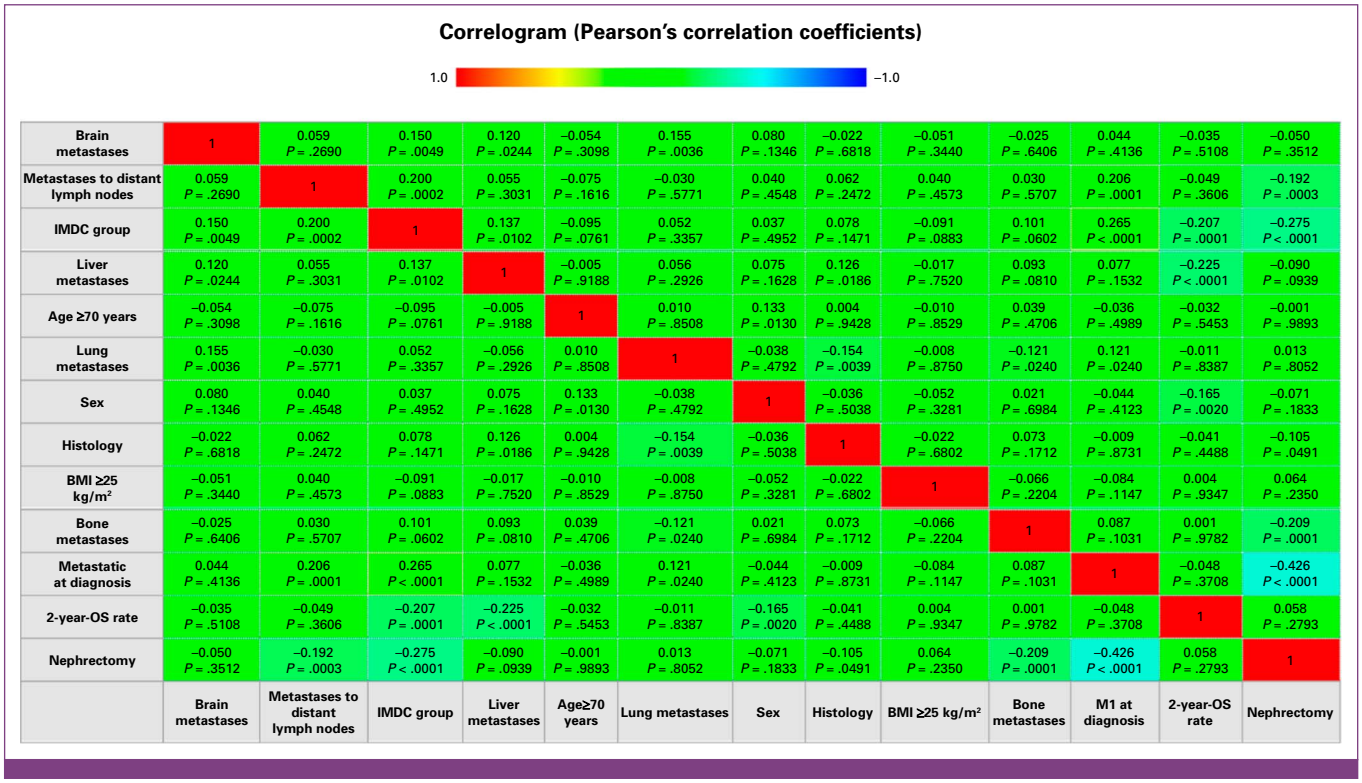

	Brain metastases	Metastases to distant lymph nodes	IMDC group	Liver metastases	Age≥70 years	Lung metastases	Sex	Histology	BMI ≥25 kg/m²	Bone metastases	M1 at diagnosis	2-year-OS rate	Nephrectomy
Brain metastases	1	0.059 P = .2690	0.150 P = .0049	0.120 P = .0244	−0.054 P = .3098	0.155 P = .0036	0.080 P = .1346	−0.022 P = .6818	−0.051 P = .3440	−0.025 P = .6406	0.044 P = .4136	−0.035 P = .5108	−0.050 P = .3512
Metastases to distant lymph nodes	0.059 P = .2690	1	0.200 P = .0002	0.055 P = .3031	−0.075 P = .1616	−0.030 P = .5771	0.040 P = .4548	0.062 P = .2472	0.040 P = .4573	0.030 P = .5707	0.206 P = .0001	−0.049 P = .3606	−0.192 P = .0003
IMDC group	0.150 P = .0049	0.200 P = .0002	1	0.137 P = .0102	−0.095 P = .0761	0.052 P = .3357	0.037 P = .4952	0.078 P = .1471	−0.091 P = .0883	0.101 P = .0602	0.265 P < .0001	−0.207 P = .0001	−0.275 P < .0001
Liver metastases	0.120 P = .0244	0.055 P = .3031	0.137 P = .0102	1	−0.005 P = .9188	0.056 P = .2926	0.075 P = .1628	0.126 P = .0186	−0.017 P = .7520	0.093 P = .0810	0.077 P = .1532	−0.225 P < .0001	−0.090 P = .0939
Age ≥70 years	−0.054 P = .3098	−0.075 P = .1616	−0.095 P = .0761	−0.005 P = .9188	1	0.010 P = .8508	0.133 P = .0130	0.004 P = .9428	−0.010 P = .8529	0.039 P = .4706	−0.036 P = .4989	−0.032 P = .5453	−0.001 P = .9893
Lung metastases	0.155 P = .0036	−0.030 P = .5771	0.052 P = .3357	−0.056 P = .2926	0.010 P = .8508	1	−0.038 P = .4792	−0.154 P = .0039	−0.008 P = .8750	−0.121 P = .0240	0.121 P = .0240	−0.011 P = .8387	0.013 P = .8052
Sex	0.080 P = .1346	0.040 P = .4548	0.037 P = .4952	0.075 P = .1628	0.133 P = .0130	−0.038 P = .4792	1	−0.036 P = .5038	−0.052 P = .3281	0.021 P = .6984	−0.044 P = .4123	−0.165 P = .0020	−0.071 P = .1833
Histology	−0.022 P = .6818	0.062 P = .2472	0.078 P = .1471	0.126 P = .0186	0.004 P = .9428	−0.154 P = .0039	−0.036 P = .5038	1	−0.022 P = .6802	0.073 P = .1712	−0.009 P = .8731	−0.041 P = .4488	−0.105 P = .0491
BMI ≥25 kg/m²	−0.051 P = .3440	0.040 P = .4573	−0.091 P = .0883	−0.017 P = .7520	−0.010 P = .8529	−0.008 P = .8750	−0.052 P = .3281	−0.022 P = .6802	1	−0.066 P = .2204	−0.084 P = .1147	0.004 P = .9347	0.064 P = .2350
Bone metastases	−0.025 P = .6406	0.030 P = .5707	0.101 P = .0602	0.093 P = .0810	0.039 P = .4706	−0.121 P = .0240	0.021 P = .6984	0.073 P = .1712	−0.066 P = .2204	1	0.087 P = .1031	0.001 P = .9782	−0.209 P = .0001
Metastatic at diagnosis	0.044 P = .4136	0.206 P = .0001	0.265 P < .0001	0.077 P = .1532	−0.036 P = .4989	0.121 P = .0240	−0.044 P = .4123	−0.009 P = .8731	−0.084 P = .1147	0.087 P = .1031	1	−0.048 P = .3708	−0.426 P < .0001
2-year-OS rate	−0.035 P = .5108	−0.049 P = .3606	−0.207 P = .0001	−0.225 P < .0001	−0.032 P = .5453	−0.011 P = .8387	−0.165 P = .0020	−0.041 P = .4488	0.004 P = .9347	0.001 P = .9782	−0.048 P = .3708	1	0.058 P = .2793
Nephrectomy	−0.050 P = .3512	−0.192 P = .0003	−0.275 P < .0001	−0.090 P = .0939	−0.001 P = .9893	0.013 P = .8052	−0.071 P = .1833	−0.105 P = .0491	0.064 P = .2350	−0.209 P = .0001	−0.426 P < .0001	0.058 P = .2793	1

FIG 4. Correlogram of Pearson's correlation coefficients in the overall study population. IMDC, International Metastatic RCC Database Consortium; OS, overall survival.

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Univariable and Multivariable Analyses

At univariable analysis, sex, nephrectomy, IMDC group, and metastases to distant lymph nodes, bone, or liver were significantly associated with OS (Table 2), while at multivariable analysis, only sex, IMDC group, and liver metastases were predictors of OS (Table 2).

DISCUSSION

To the best of our knowledge, this is the largest real-world cohort of patients with advanced sRCC treated with first-line IO-based combinations, offering insights into clinicopathologic features, treatment patterns, and survival outcomes, and informing contemporary management of this aggressive disease subset.

Historically, metastatic RCC patients with sarcomatoid features had a median OS (mOS) of 6-13 months, varying with histology (ccRCC *v* nccRCC), individual patient characteristics, and therapies used.[1,20] sRCC is consistently characterized by poor prognosis, rapid progression, and limited response to targeted therapies. The observed mOS of 26.9 months in our cohort highlights the efficacy of IO-based regimens in this population.

Consistent with previous reports, most patients with sRCC were male with a median diagnosis age of 64 years.[18,21] Clear cell histology predominated (85%), in line with epidemiologic data.[18,22,23] Previous nephrectomy was associated with improved mOS (32.3 *v* 20.7 months; $P = .002$), possibly because of tumor debulking and immunomodulatory effects.[24] Female patients showed significantly shorter mOS than males (15.3 *v* 43.3 months; $P < .001$). Sex remained an independent OS predictor, indicating a prognostic role in sRCC. A similar trend was noted by Ishihara et al,[25] where female patients with mRCC treated with IO-based regimens had worse PFS, although OS differences were not significant. This sex-based disparity aligns with broader oncology literature[26-28] and findings from additional analyses of the ARON-1 study,[17,18] also including patients with pretreated sRCC receiving cabozantinib.[29] Sex-based outcome disparities may stem from hormonal effects on the tumor microenvironment (TME)[30] and distinct mutational patterns—for example, higher *KDM5C* mutation rates in males versus *BAP1* in females, the latter linked to poor prognosis.[31] *BAP1* mutations are notably enriched in sRCC.[6] Additionally, androgens may modulate gut microbiota, potentially influencing immune responses.[32]

In our cohort, histology (clear *v* non–clear cell) did not significantly affect OS ($P = .478$), reinforcing that sarcomatoid differentiation likely outweighs histologic subtype in predicting IO response.[1,33]

Metastatic patterns significantly influenced outcomes. Liver, bone, and distant lymph node metastases correlated with worse OS, as opposed to lung and brain metastases. These

TABLE 2. Univariate and Multivariate Analyses in Patients With sRCC

	Univariate Cox Regression		Multivariate Cox Regression	
OS	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex (females *v* males)	1.77 (1.27 to 2.48)	**<.001**	1.70 (1.21 to 2.39)	**.002**
Age, years (≥70 *v* <70)	1.26 (0.89 to 1.78)	.189		
BMI (>25 *v* ≤ 25)	0.88 (0.64 to 1.22)	.435		
Nephrectomy (yes *v* no)	0.56 (0.39 to 0.81)	**.002**	0.79 (0.53 to 1.16)	.230
Histology (nccRCC *v* ccRCC)	1.17 (0.75 to 1.84)	.479		
IMDC group (poor *v* intermediate *v* good)	1.84 (1.38 to 2.44)	**<.001**	1.66 (1.22 to 2.25)	**.001**
Metastases to distant lymph nodes (yes *v* no)	1.41 (1.02 to 1.96)	**.038**	1.09 (0.78 to 1.54)	.612
Lung metastases (yes *v* no)	0.88 (0.62 to 1.25)	.471		
Bone metastases (yes *v* no)	1.59 (1.13 to 2.22)	**.007**	1.35 (0.95 to 1.92)	.090
Liver metastases (yes *v* no)	1.84 (1.27 to 2.65)	**.001**	1.55 (1.07 to 2.25)	**.022**
Brain metastases (yes *v* no)	1.52 (0.93 to 2.49)	.097		

NOTE. The bold entries refer to statistically significant *P*-values.
Abbreviations: ccRCC, clear cell renal cell carcinoma; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; OS, overall survival; nccRCC, non–clear cell renal cell carcinoma; sRCC, sarcomatoid renal cell carcinoma.

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data are principally consistent with previous findings establishing the poor prognostic implication of these sites, and notably skeletal and liver metastases, which are also typically less responsive to IO.[34,35] Although brain metastases typically predict worse prognosis,[36] they showed no OS impact in the current analysis.

The IMDC risk model retained prognostic relevance: mOS decreased from favorable- (66.5 months) to intermediate- (29.4) and poor-risk groups (11.7; $P < .001$). These results support its continued use in sRCC despite IO-era limitations.[33] The presence of sarcomatoid features may guide therapy choice, favoring IO + TKI in favorable-risk and indicating poor outcomes for poor-risk patients regardless of regimen.[37]

No significant OS differences emerged among IO-based regimens across IMDC subgroups. In favorable-risk patients, all IO + TKI combinations showed high 2-year OS rates. In intermediate-risk patients, mOS was highest with pembrolizumab/lenvatinib (29.4 months) and was NR with pembrolizumab/axitinib and nivolumab/cabozantinib. Among poor-risk patients, mOS ranged from 7.2 to 20.9 months. Nivolumab/ipilimumab, despite being mostly reserved for poor-risk patients, yielded the highest median OS (20.9 months) and 2-year OS rate (48%). It should be remarked that those patients with sRCC receiving IO + IO combination were the most numerous within the poor-risk group. Furthermore, no statistically significant OS differences were found between IO + IO and IO + TKI regimens in intermediate- and poor-risk groups, supporting all IO-based combinations as viable options for sRCC. These findings echo previous real-world evidence and phase III trials of IO-based therapies in sRCC,[18,38] highlighting the role of these regimens in managing this challenging disease subset.

Immunocombinations have consistently outperformed sunitinib in sRCC.[39] Molecular profiling has revealed frequent alterations—*BAP1*, *NF2* (affecting Hippo signaling), *CDKN2A/B* deletions, and *MYC*-driven transcriptional activity—linked to aggressiveness and IO responsiveness.[6,33,39] Sarcomatoid differentiation also exhibit a highly immune-inflamed TME, with prominent $CD8^+$ T-cell infiltration and elevated PD-1/PD-L1 expression.[6] In the CheckMate 214 study, nivolumab/ipilimumab showed superior PFS (HR, 0.54), OS (HR, 0.45), and ORR (60.8% *v* 23.1%) compared with sunitinib, with higher CR rates (23.0% *v* 6.2%) in sarcomatoid mRCC.[10] IO + TKI combinations also proved beneficial for sRCC, overcoming their lower angiogenic gene expression and relative resistance to VEGFR-targeted therapy.[40] VEGF's immunosuppressive role may explain synergy between VEGFR-TKIs and ICIs. VEGFR-TKIs may boost immune infiltration and suppress myeloid-derived suppressor cells when paired with ICIs.[41] These mechanisms support the rationale for IO + TKI in sRCC. Subgroup analyses from KEYNOTE-426, CLEAR, and CheckMate 9ER showed improved outcomes with IO + TKI versus sunitinib in patients with sRCC.[11-13] Our findings reinforce this, confirming IO-based combinations—whether dual ICIs or ICI + VEGFR-TKI—as effective strategies. The superior outcomes observed with nivolumab/ipilimumab in poor-risk patients align with molecular evidence of immune-rich tumor profiles in this group.[42]

Comparative analyses confirmed the influence of IMDC risk, liver metastases, and sex on 2-year OS. The strength of these associations varied by regimen: that is, pembrolizumab/axitinib outcomes varied with IMDC group and sex, while liver metastases and sex were more impactful in the nivolumab/ipilimumab group. These findings highlight potential treatment-biologic interactions, although subgroup heterogeneity and confounders (nephrectomy rates, histology mix, sarcomatoid proportion, etc) warrant cautious interpretation.

Our study's strengths include a large cohort and robust multivariable survival analysis. However, its retrospective nature introduces biases and limits causal inference. Treatment access varied across regions and time. Absence of centralized pathology review and incomplete sarcomatoid quantification are additional limitations. Future prospective studies should validate these findings and clarify the impact of sex and metastatic patterns. The ongoing CARE-1 trial, comparing nivolumab/ipilimumab to IO + TKI, may provide further insights.[43]

In conclusion, this analysis from the ARON-1 study highlights the complex interplay of patient demographics, disease characteristics, and treatment selection in sRCC treated with first-line immune-combination therapies. Sex, IMDC risk group, and the presence of liver metastases emerged as key prognostic factors. The comparable efficacy across approved IO-based combinations reinforces the importance of personalized therapy decisions, while underscoring the need for continued research to refine treatment strategies in this challenging patient population.

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