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Toxicity-related immunotherapy discontinuation and outcome in patients with advanced renal cell carcinoma treated with immune-based combinations (ARON-1 study)

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Abstract

The advent of immunotherapy (IO) has revolutionized the therapeutic landscape of advanced renal cell carcinoma (RCC). The aim of this study is to analyze clinical outcomes in patients who discontinued IO in metastatic RCC first line in a real-world setting. We retrospectively collected data about 1077 patients aged ≥18 years with a histologically confirmed diagnosis of clear cell RCC and histologically or radiologically confirmed metastatic disease, treated in 52 centers from 20 countries, between January 1, 2016 and April 1, 2024, from all three International metastatic renal cell carcinoma (mRCC) Database Consortium risk groups (favorable, intermediate, and poor). Each patient was treated in front-line with IO + Tirosine Kinase Inhibitor or IO + IO combinations. In this study we analyzed survival outcomes comparing patients who interrupted IO versus patients who continuously received it and multivariable analysis. We analyzed the clinical behavior of 185 patients who interrupted IO treatment due to SAE, 127 patients with IO-tyrosine kinase inhibitor, 58 patients with IO–IO versus 892 patients who do not discontinue IO treatment. No significant differences in OS were found in patients who discontinue treatment versus no discontinuation. Moreover, time to discontinuation seemed to be an OS predictor, being

Abbreviations: CR, complete response; ECOG, eastern cooperative oncology group; ICIs, immune checkpoint inhibitors; IMDC, International mRCC Database Consortium; IO, Immunotherapy; iAE, immune adverse event; irAE, immune-related adverse event; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; RCC, renal cell carcinoma; RWE, real world evidence; SAE, serious adverse event; SD, stable disease; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

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inferior in patients who interrupted IO in the first to third month versus patients who discontinued treatment after this time data. The ARON-1 study offers a comprehensive examination of toxicity-related IO discontinuation in advanced RCC, contributing to a better understanding of balancing treatment efficacy with tolerability.

KEYWORDS

immunotherapy, immunotherapy interruptions, kidney cancer

What's New?

New immunotherapy drugs have expanded treatment options for renal cell carcinoma (RCC). However, a significant proportion of patients ultimately discontinue immunotherapy, typically because of impacts on quality of life. This study analyzed clinical outcomes among such patients, focusing specifically on those with metastatic RCC who had to permanently discontinue immunotherapy. No statistically significant difference was observed in overall survival between patients with and without treatment discontinuation. Survival was shorter, however, in patients who stopped immunotherapy within the first 3 months compared to those who discontinued later. The findings can potentially inform therapeutic strategies for the management of advanced RCC.

1 | INTRODUCTION

Renal cell carcinoma (RCC) represents the most common type of kidney cancer, accounting for approximately 90% of cases. It is estimated that over 430,000 new cases of RCC are diagnosed annually worldwide, resulting in over 175,000 deaths each year. The incidence of RCC has been steadily rising, partly due to the increased use of imaging techniques leading to the diagnosis of asymptomatic kidney tumors.[1]

The treatment landscape for advanced RCC has evolved significantly over the past decade. Traditionally, cytokine therapies such as interferon-alpha and interleukin-2 were the mainstay of treatment, with limited efficacy and substantial toxicity. The introduction of targeted therapies, including tyrosine kinase inhibitors (TKIs) such as sunitinib, pazopanib, cabozantinib and lenvatinib, and mammalian target of rapamycin (mTOR) inhibitors, represented a significant advance in the treatment in terms of efficacy and tolerability.[2]

Recently, the advent of immune checkpoint inhibitors (ICIs) has changed the management of advanced RCC. ICIs, such as nivolumab, ipilimumab, and pembrolizumab, alone or in combination with TKIs or other ICIs, have demonstrated improved overall survival (OS) and progression-free survival (PFS) compared to previous standards of care. The four approved combinations—nivolumab-ipilimumab, pembrolizumab-lenvatinib, pembrolizumab-axitinib and nivolumab-cabozantinib—have set new benchmarks for efficacy in this patient population.[3–10] Some real world evidence (RWE) reports and prospective trials are trying to determine the optimal sequence of treatment in patients with metastatic disease, but we are lacking prospective data comparing these combinations in the first-line setting.[3–21]

However, these immunotherapy (IO) combinations carry potential risks. Immune-mediated adverse effects are of particular interest, leading, in some cases, to the IO discontinuation, which may impact its efficacy.[3–10,22,23] Understanding the incidence, causes, and outcomes associated with IO discontinuations is crucial for optimizing treatment strategies and making clinical decisions.

IO interruptions occur in a notable proportion of patients receiving ICI-based therapies.[3–10] Some studies provided valuable insights into the real-world incidence of these interruptions and their impact on patient outcomes in RCC and other solid tumors. While interruptions were common, they did not necessarily correlate with poorer survival outcomes, suggesting that some patients may still gain substantial benefit from IO despite discontinuations.[24–27]

We are lacking prospective data about clinical outcomes in patients who interrupted ICI in mRCC. In Checkmate 214 about 22.7% of patients interrupted ICI due to adverse events and 29.1% of patients required a high corticosteroid dose (≥40 mg prednisone daily) due to immune-related adverse events (irAEs). In Checkmate 9ER 20% of patients receiving nivolumab-cabozantinib discontinued at least one agent due to serious adverse events (SAEs) and 6% discontinued both. Nineteen percent of patients in the combination arm required a high dose of steroids for immune adverse event (iAE) management.[28–30]

In CLEAR study, 28.7% of patients receiving pembrolizumab-lenvatinib discontinued pembrolizumab due to adverse events and 14.8% of patients receiving high corticosteroids to manage irAEs.[7,31] In Keynote 426, 30.5% patients in pembrolizumab-axitinib group discontinue at least one of the drugs and 10.7% discontinue both due to adverse events.[3]

Across the four pivotal studies, results on discontinuing IO after an irAE varied. However, there is still a lack of prospective evidence on these patients and their clinical outcomes. While ICIs have dramatically improved the outcome for patients with advanced RCC, the management of treatment-related toxicities remains a critical aspect of care. Research into the implications of IO interruptions is essential to guide clinical practice. Therefore, the aim of our study is to shed

light on the clinical evolution of these patients who discontinue IO and even receive high doses of steroids in this context.[3–20]

The ARON-1 project has been designed to create a global network of RWE to retrospectively collect the use of IO and other emerging drugs on patients with kidney from participant centers (NCT05287464). In this analysis, we evaluated clinical outcomes in patients with advanced RCC who had to permanently discontinue IO, either IO–IO or IO following IO–TKI, due to severe adverse events, defined as grade ≥3 according to the Common Terminology Criteria for Adverse Events version 5.0, or intolerable toxicity as determined by the investigator's clinical judgment. The latter was based on a comprehensive assessment including persistence or worsening of symptoms despite optimal supportive care, significant impairment in quality of life or daily functioning, or patient preference after discussion of risks and benefits. These patients were compared with those who remained on treatment. More than 1000 patients were included, making this one of the most robust real-world evidence datasets in this patient population.

2 | PATIENTS AND METHODS

2.1 | Study population

We included patients aged ≥18 years with a histologically confirmed diagnosis of clear cell RCC and histologically or radiologically confirmed metastatic disease. The patients were treated in 52 centers from 20 countries, between January 1, 2016 and April 1, 2024, from all three International mRCC Database Consortium (IMDC) risk groups (favorable, intermediate, and poor). Each patient was treated in frontline with IO + TKI or IO + IO combinations.

We retrospectively collected data about age, gender, histology, IMDC risk group, nephrectomy, sites of metastases, immune-combinations administered, response to treatment and SAEs from patients' electronic charts and paper. Patients were excluded if any of the following mandatory variables were missing: age, gender, histology, IMDC risk group, nephrectomy status, metastatic sites, type of immune-combination administered, tumor assessment results, or response to therapy. Missing data were handled using case-wise deletion, as the retrospective nature of the study and heterogeneity of source records did not allow for reliable imputation. First-line therapy was continued until the evidence of clinical and/or radiological tumor progression, unacceptable toxicities, or death. Computed tomography or magnetic resonance imaging scans were carried out following standard local procedures every 8 or 12 weeks. Physical examinations and laboratory tests were performed every 4 or 6 weeks during patients' follow-up.

2.2 | Study endpoints

The primary objective of our analysis was to assess the real-world rate of IO discontinuations during first-line immune combination therapies. Tumor radiological assessment was conducted according to the RECIST 1.1 criteria[20] and designated as complete responses (CRs) or partial responses (PRs), stable disease (SD) or progressive disease (PD). Overall response rate (ORR) was defined as the proportion of patients who achieved a CR or PR per RECIST criteria. OS was calculated from the start of first-line treatment to death for any cause, while PFS was defined as the time from the start of the therapy to progression or death from any cause. Time to immunotherapy interruption (TII) was calculated from the start of first-line immune combinations to the date of IO interruption due to SAEs. Patients who continued treatment without progression, those who had died or been lost to follow-up, were censored at their last follow-up date.

Landmark analysis was performed designating 6 months as the time point during the follow-up period to reduce potential biases related to IO combinations exposure time.

2.3 | Statistical analysis

The statistical analysis was performed by MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

Regarding OS, PFS, and follow-up, the Kaplan–Meier method was used, and comparisons between survival distributions were analyzed with the log-rank test. Confidence intervals (CIs) (95% CI) were calculated by Rothman's formula. Cox proportional hazards models, using Schoenfeld residuals, were applied to assess the multivariable impact on patient survival, providing hazard ratios and 95% CIs and including clinical and pathological variables related to patients' outcomes: gender, age >70 years, nephrectomy, tumor histology, sarcomatoid de-differentiation, lung, bone, liver or brain metastases and IO discontinuation due to SAEs.

The chi-square test was used to compare groups for categorical variables. Significance levels were set at a value of 0.05, and all *p* values were two-sided.

Harrell's C-index (concordance index)[21] has been used to measure the separation between two survival distributions with censored data, providing an assessment of the quality of survival models.

3 | RESULTS

3.1 | Patients' population

We included 1077 patients treated with immune-based combinations from the ARON-1 dataset; 804 (75%) were males. Median age was 63 years. Clear cell histology was predominant (88%), with 139 patients (13%) reporting sarcomatoid de-differentiation. Lung (69%) and bone (33%) were the most common metastatic sites. Most patients (63%) underwent nephrectomy. Favorable, intermediate, and poor IMDC features were present in 17%, 61%, and 22% of all cases, respectively.

Two hundred and thirty-four patients received nivolumab-ipilimumab as first-line therapy (21%) and 843 were treated by

IO + TKI combinations: 590 pembrolizumab-axitinib (55%), 165 nivolumab-cabozantinib (15%), and 88 pembrolizumab-lenvatinib (8%). We summarized in Table 1 the list of clinical-pathological characteristics of patients who interrupted or did not interrupt IO due to SAEs. Interestingly, no statistically significant differences were found between patients who interrupted or continued IO.

One hundred and eighty-five patients (17%) interrupted IO due to SAEs, with 5 treatment-related deaths (<1%). The incidence of IO interruption was 24% and 15% in patients treated with IO + IO or IO + TKI, respectively. In the IO-TKI group, we found 16% of IO interruptions in patients treated with pembrolizumab-axitinib, 11% with cabozantinib-nivolumab, and 19% with pembrolizumab-lenvatinib.

Table 2 summarizes the type of SAEs that led to IO interruption.

Median time to IO interruption was 3.5 months (95% CI 2.3–58.8); among the 185 patients who interrupted IO due to SAEs, 24 patients (13%) interrupted within 1 month, 62 (34%) between 1 and 3 months and 99(53%) >3 months.

Median follow-up time from the start of first-line therapy was 27.1 months (95% CI 21.1–90.0).

3.2 | Survival analysis

The median OS in the overall study population was 49.2 months (95% CI 33.2–61.8). Median OS was 44.2 months (95% CI 33.1–78.5) in patients who continued and 52.2 months (95% CI 30.4–59.6) in patients who discontinued IO due to SAEs ($p = 0.719$, Figure 1). No differences were found between patients who continued versus discontinued due to SAEs in the subgroup of patients who underwent (61.8 months, 95% CI 44.2–78.5 vs. 59.6 months, 95% CI 52.2–60.6, $p = 0.880$) or not nephrectomy (24.5 months, 95% CI 20.8–32.5 vs. 29.6 months, 95% CI 14.3–30.4, $p = 0.938$).

In patients treated with IO + TKI combination, no significant differences were found between subjects who interrupted IO due to

TABLE 1 Patient characteristics.

Characteristics	Overall no. (%)	Patients who interrupted immunotherapy due to SAEs	Patients who continued immunotherapy	*p*-Value
Total patients	1077 (100)	185 (100)	892 (100)	-
Gender				
Male	804 (75)	129 (70)	675 (76)	0.525
Female	273 (25)	56 (30)	217 (24)	
Age (years) median (range)	63 (27–88)	64 (27–88)	62 (32–88)	0.898
Clear cell histology	950 (88)	165 (89)	785 (88)	1.000
Non-clear cell histology	127 (12)	20 (11)	107 (12)	1.000
Papillary	60 (6)	9 (5)	51 (6)	1.000
Cromophobe	20 (2)	2 (1)	18 (5)	0.212
Other	47 (4)	9 (5)	38 (4)	1.000
Sarcomatoid de-differentiation	139 (13)	21 (11)	118 (13)	0.828
Metastatic at diagnosis	585 (54)	92 (50)	493 (55)	0.571
Previous nephrectomy	683 (63)	126 (68)	557 (62)	0.459
Site of metastasis, individual				
Lung	740 (69)	134 (72)	606 (68)	0.644
Liver	198 (18)	26 (14)	172 (19)	0.446
Bone	360 (33)	54 (29)	306 (34)	0.542
Brain	81 (8)	14 (8)	67 (8)	1.000
IMDC prognostic risk group				
Favorable	186 (17)	36 (19)	150 (17)	0.718
Intermediate	655 (61)	117 (64)	538 (60)	0.662
Poor	236 (22)	32 (17)	204 (23)	0.377
Type of first-line therapy				
Nivolumab + Ipilimumab	234 (22)	58 (32)	176 (20)	0.163
Pembrolizumab + Axitinib	590 (55)	92 (50)	498 (56)	
Nivolumab + Cabozantinib	165 (15)	18 (9)	147 (16)	
Pembrolizumab + Lenvatinib	88 (8)	17 (9)	71 (8)	

Abbreviations: IMDC, International mRCC Database Consortium, SAEs, serious adverse events.

TABLE 2 List of SAEs leading to immunotherapy interruption in patients treated with distinct first-line immune combinations.

Patients	IO + IO 58 patients (%)	IO + TKI 127 patients (%)
Any SAEs	14 (24)	19 (15)
Endocrine SAEs		
Hypothyroidism	1 (2)	1 (1)
Adrenal insufficiency	1 (1)	1 (1)
Dermatologic SAEs		
Rash	2 (3)	1 (1)
Gastrointestinal SAEs		
Diarrhea	3 (5)	4 (3)
Stomatitis/mucositis	0 (0)	0 (0)
Nausea	0 (0)	0 (0)
Liver toxicity	1 (2)	5 (4)
Other SAEs		
Fatigue	3 (5)	4 (3)
Pneumonitis	1 (2)	1 (1)
Renal toxicity	1 (1)	1 (1)
Neuropathy	1 (1)	1 (1)
Heart failure	1 (1)	1 (1)
Artritis	1 (1)	1 (1)
Other	1 (2)	1 (1)

Abbreviations: IO, immunotherapy; SAEs, serious adverse events; TKI, tyrosine kinase inhibitor.

SAEs and those who continued IO (52.2 months, 95% CI 30.4–59.6 vs. 44.2 months, 95% CI 32.7–78.5, $p = 0.921$, Figure 1). We further analyzed the role of toxicity-related TKI interruptions in patients who discontinued IO due to SAEs. We found no statistically significant differences in terms of median OS between patients who stopped TKIs (59.6 months, 95% CI 27.9–59.6) versus subjects who continued TKIs (52.2 months, 24.0–52.2, $p = 0.682$).

The median OS of the 58 patients treated with IO + IO combination who interrupted IO was not reached while it was 33.1 months (95% CI 18.4–49.2) in the 186 patients who continued ($p = 0.644$, Figure 1).

Furthermore, we performed a 6-month landmark analysis for OS (Figure S1) to reduce potential biases related to the time of exposure to immune combinations. We showed that the median OS was 55.7 months (95% CI 40.2–78.5) in patients who continued and 52.2 months (95% CI 34.4–59.6) in patients who discontinued IO due to SAEs ($p = 0.663$).

We further stratified the 185 patients who interrupted IO due to SAEs based on TII. The median OS was 11.4 months (95% CI 3.7–52.2) in patients who interrupted within 1 month, 30.4 months (95% CI 20.9–34.4) in subjects who interrupted between 1 and 3 months and 59.6 months (95% CI 59.6–59.6) in those who interrupted after 6 months ($p < 0.05$, Figure 2). No statistical differences were found between patients who interrupted IO + IO or IO + TKI therapy within the first 3 months in terms of median OS (27.9 months, 95% CI 3.7–34.4 vs. 32.0 months, 95% CI 7.1–52.2, $p = 0.163$).

3.3 | Harrell's C index

We further calculated Harrell's C Index to assess the quality of our survival models. By comparing patients who discontinued due to SAEs to those who continued, we found that the C Index was 0.506 in the overall study population, 0.516 in patients receiving IO + TKI and 0.499 in subjects treated with IO + IO. All these values near 0.500 would indicate no correlation between survival time and IO discontinuation due to SAEs.

3.4 | Response to first-line therapy

In the overall study population, we reported 6% CR, 46% PR, 30% SD and 18% PD, with an ORR of 52%. In patients who interrupted IO due to SAEs, we observed 7% CR, 54% PR, 29% SD and 10% PD, with an ORR of 61%.

In the subgroup treated with IO + TKI combinations, we reported 8% CR, 53% PR, 34% SD and 5% PD in patients who interrupted IO due to SAEs and 7% CR, 46% PR, 30% SD and 17% in patients who continued immunotherapy. The difference in terms of the rate of primary refractory patients (5% vs. 17%) was statistically significant ($p < 0.05$).

In patients receiving IO + IO combination, we showed 7% CR, 55% PR, 18% SD, and 20% PD in patients who interrupted IO due to SAEs and 5% CR, 36% PR, 32% SD, and 27% PD in patients who continued IO. The ORR was higher in patients who interrupted IO due to SAEs (62% vs. 41%, $p < 0.05$).

3.5 | Prognostic factors

We further performed univariable and multivariable analyses to assess the presence of prognostic factors in our study population. We showed that age, nephrectomy, sarcomatoid de-differentiation, IMDC group, bone, liver, and brain metastases were significantly associated with OS at univariable analysis and confirmed their prognostic role at the multivariable analyses.

4 | DISCUSSION

Immune-based combinations, either IO + TKI or IO + IO, have further improved the outcome of mRCC patients.[21] However, the increased efficacy of these regimens is often accompanied by a higher incidence of SAEs, leading to treatment interruptions.[22] The occurrence of SAEs poses a critical challenge in the management of cancer patients receiving IO. Adverse events can range from mild to life-threatening, and their onset can significantly impact the patient's quality of life, treatment adherence, and overall prognosis.[23] The decision to interrupt IO due to SAEs involves a complex assessment of the risks and benefits, aiming to mitigate toxicity while maintaining therapeutic efficacy. Despite its clinical importance, there is limited prospective and

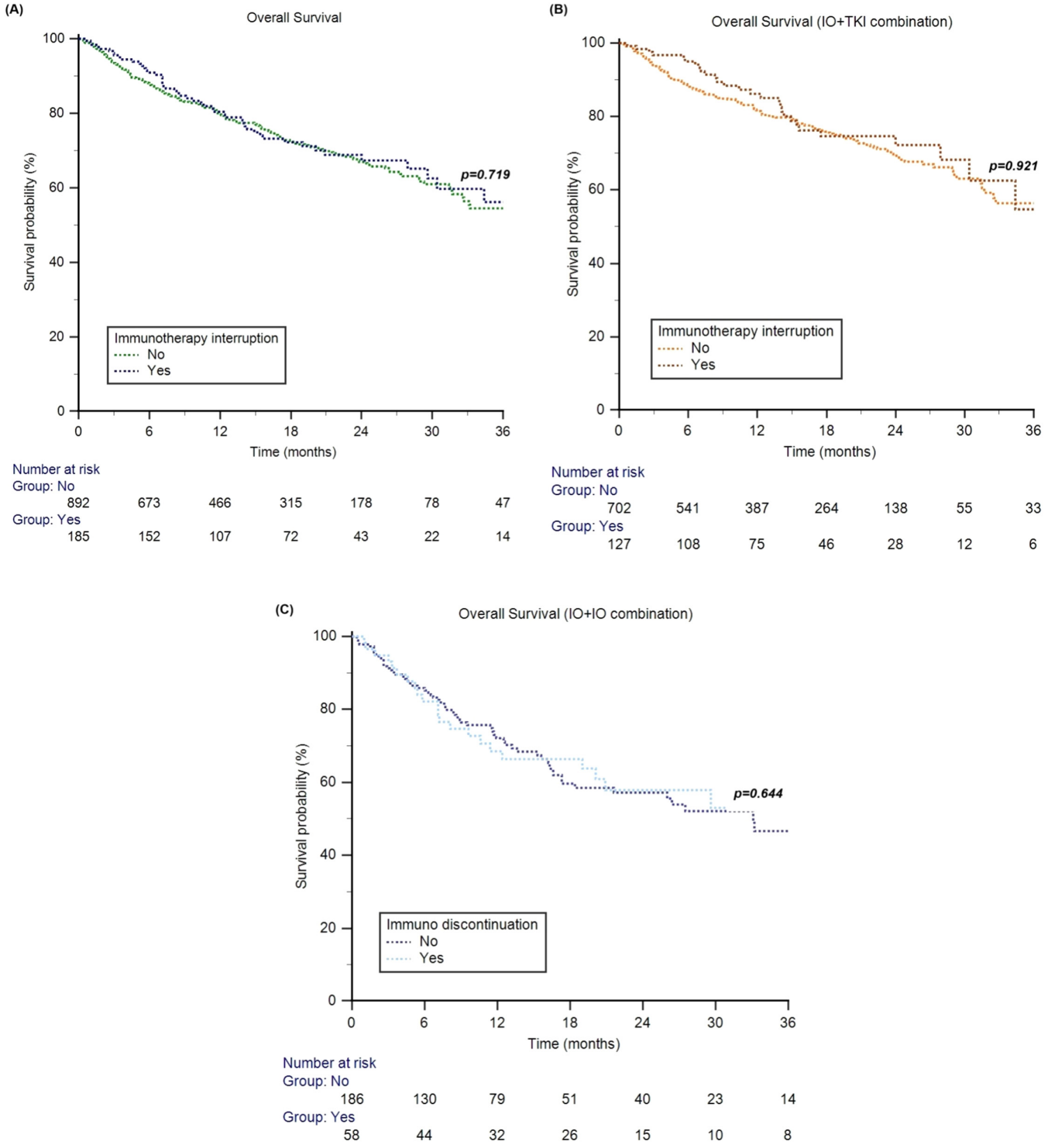

FIGURE 1 Overall Survival in patients who interrupted immunotherapy due to SAEs. (A) Overall survival in the entire population. (B) Overall survival in patients who received immunotherapy plus tyrosine kinase inhibitor (IO + TKI). (C) Overall survival in patients who received IO combinations (IO + IO). IO, immunotherapy; TKI, tyrosine kinase inhibitor. [Color figure can be viewed at wileyonlinelibrary.com]

real-world evidence on the prevalence, timing, and impact of IO interruptions caused by severe adverse events.

Understanding the factors linked to IO interruptions, and their impact on patient outcomes, is essential for optimizing treatment strategies. Phase III studies of IO–IO and IO–TKI regimens have reported differing rates of treatment discontinuation and varying requirements for high-dose steroids. The ARON-1 study provides critical insights into the implications of IO interruptions due to SAEs in patients with mRCC treated with immune combinations. Survival analysis revealed no significant difference in median OS between patients who continued IO and those who interrupted due to SAEs. Specifically, the median OS was 44.2 months for continuous treatment and

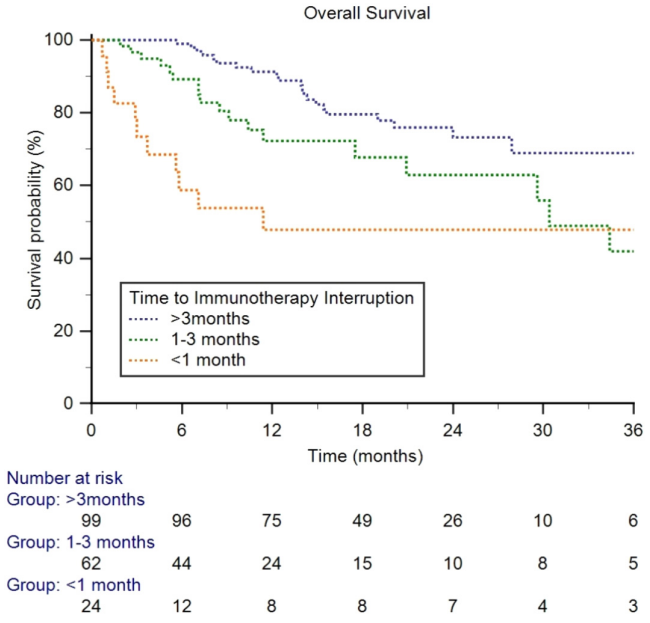

FIGURE 2 Overall survival in patients who interrupted immunotherapy due to SAEs stratified by time to immunotherapy interruption (TII). [Color figure can be viewed at wileyonlinelibrary.com]

52.2 months for interrupted treatment regardless of the combination received, with no statistical differences. This finding suggests that managing SAEs with therapy interruptions does not negatively impact long-term survival outcomes in other tumor types.[24–26]

Patients who interrupted IO due to SAEs showed a noteworthy ORR of 61%, with a CR of 7% and a PR of 54%. These results suggest that interruptions due to SAEs do not necessarily compromise treatment efficacy, achieving a higher ORR than the 52% observed in patients who continued therapy. The subgroup analysis revealed differences based on the type of IO combination. For IO + TKI combinations, the primary refractory rate was significantly lower in patients who interrupted therapy compared to those who continued (5% vs. 17%, $p < 0.05$). Similarly, in IO + IO combinations, patients who interrupted therapy had a higher ORR (62% vs. 41%, $p < 0.05$). These findings suggest that different combination therapies may have varied resilience to interruptions, impacting their effectiveness and patient outcomes. Similar observations were made in the CheckMate 214 trial, where patients with advanced RCC treated with nivolumab-ipilimumab who experienced TRAEs had comparable response rates and survival outcomes to those without such events.[4]

Other studies have similarly found that IO interruptions do not necessarily lead to poorer outcomes. In the KEYNOTE-006 trial, patients with melanoma treated with pembrolizumab who discontinued treatment due to adverse events showed no significant difference in OS compared with those who continued therapy, suggesting that discontinuation did not impact survival.[25]

Cook et al. reported that patients with advanced non-small cell lung cancer (NSCLC) who had IO interruptions due to adverse events also achieved high response rates and long-term survival benefits comparable to those who continued uninterrupted treatment.[24]

In the recent real-world retrospective study conducted by Lievense et al., 47% of patients with metastatic NSCLC who discontinued ICIs due to irAEs achieved a durable response, with a median duration of 18 months without requiring further treatment. Additionally, 23% of patients experienced disease oligoprogression after ICI discontinuation, which was successfully managed with local radiotherapy, leading to disease control. Similar findings have been reported in other small retrospective studies. Santini et al. observed that retreatment with ICIs did not improve outcomes among 20 patients with metastatic NSCLC who had initially responded but discontinued therapy due to irAEs. Moreover, a study by Russano et al. investigated the prognostic significance of early irAEs, comparing 24 patients with metastatic NSCLC who discontinued ICIs after a single administration due to severe irAEs to a control group, and found no difference in survival outcomes between the groups.

In this analysis of the ARON-1 study, the timing of IO interruption significantly influenced patient outcomes. Patients who interrupted therapy within 1 month had a median OS of 11.4 months, whereas those who interrupted after 6 months had a median OS of 59.6 months. This suggests that early interruptions are associated with poorer outcomes, emphasizing the importance of managing and potentially delaying interruptions when feasible to optimize survival benefits.

In contrast, a study by Teraoka et al. on NSCLC patients treated with nivolumab found that those who discontinued treatment early had poorer outcomes compared to patients who were able to continue therapy longer.[26]

Conversely, in the Stellato et al. retrospective study, the outcomes demonstrated the sustained efficacy of ICIs even after early discontinuation due to irAEs. Notably, 66.6% of patients remained progression-free 6 months post-interruption, indicating a long-term benefit from ICIs.[27]

While our study provides robust real-world evidence, several limitations must be acknowledged. The retrospective nature of the data collection may introduce selection bias. Moreover, variations in local clinical practices across the 52 centers (e.g., variable imaging intervals) could affect the generalizability of the results. The use, timing, and dose of corticosteroids were not uniformly collected across centers, which may influence both toxicity resolution and treatment outcomes. Eastern Cooperative Oncology Group (ECOG) performance status at baseline and during follow-up was not consistently available, limiting adjustment for this important prognostic factor. Additionally, the follow-up duration may be insufficient to capture long-term outcomes for some patients. These variably recorded variables could introduce residual confounding, and our findings should therefore be interpreted with appropriate caution.

Future prospective studies, with standardized treatment protocols and longer follow-up periods, are warranted to validate our findings and refine strategies for managing SAEs in mRCC patients.

4.1 | Conclusion

The ARON-1 study highlights the complex but important role of IO interruptions due to SAEs in treating advanced RCC. These

interruptions do not always reduce treatment effectiveness and can often be managed to maintain favorable patient outcomes. This study aligns with and expands upon existing evidence from other studies in various types of cancer. These insights are invaluable for guiding clinical decisions and optimizing therapeutic strategies in the management of advanced RCC. In our knowledge this is the largest data reported in the RCC setting regarding IO discontinuation outcomes due to SAEs.

AUTHOR CONTRIBUTIONS

Javier Molina-Cerrillo: Conceptualization; writing – original draft; methodology; validation; formal analysis; supervision; writing – review and editing; data curation. **Giandomenico Roviello:** Conceptualization; writing – original draft; validation; writing – review and editing; data curation. **Maria T. Bourlon:** Writing – original draft; writing – review and editing; data curation. **Hana Studentova:** Data curation; writing – original draft; writing – review and editing. **Ondrej Fiala:** Writing – original draft; writing – review and editing; data curation. **Linda Cerbone:** Writing – original draft; writing – review and editing; data curation. **Jakub Kucharz:** Writing – original draft; writing – review and editing; data curation. **Jawaher Ansari:** Writing – original draft; writing – review and editing; data curation. **Annalisa Zeppellini:** Writing – original draft; writing – review and editing; data curation. **Tarek Taha:** Writing – review and editing; writing – original draft; data curation. **Sebastiano Buti:** Writing – original draft; writing – review and editing; data curation. **Yuksel Urun:** Writing – original draft; writing – review and editing; data curation. **Sarah Scagliarini:** Writing – original draft; writing – review and editing; data curation. **Haoran Li:** Writing – original draft; writing – review and editing; data curation. **Kaisa Sunela:** Writing – original draft; writing – review and editing; data curation. **Se Hoon Park:** Writing – original draft; writing – review and editing; data curation. **Mimma Rizzo:** Writing – original draft; writing – review and editing; data curation. **Anca Zgura:** Writing – original draft; writing – review and editing; data curation. **Rita Chiari:** Writing – original draft; writing – review and editing; data curation. **Emmanuel Seront:** Writing – review and editing; writing – original draft; data curation. **Martina Catalano:** Writing – original draft; writing – review and editing; data curation. **Marwan Ghosn:** Writing – original draft; writing – review and editing; data curation. **Alessandra Filosa:** Writing – original draft; writing – review and editing; data curation. **Andrey Soares:** Writing – review and editing; writing – original draft; data curation. **Francesco Massari:** Writing – original draft; writing – review and editing; data curation. **Fernando Sabino Marques Monteiro:** Writing – original draft; data curation; writing – review and editing. **Enrique Grande:** Writing – original draft; writing – review and editing; data curation. **Camillo Porta:** Writing – original draft; writing – review and editing; data curation. **Sergio Bracarda:** Writing – original draft; writing – review and editing; data curation. **Matteo Santoni:** Writing – original draft; writing – review and editing; conceptualization; investigation; methodology; validation; formal analysis; data curation; supervision.

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CONFLICT OF INTEREST STATEMENT

Javier Molina-Cerrillo declares consultant, advisory or speaker roles for IPSEN, Roche, Pfizer, Sanofi, Janssen, AAA, Astellas, MSD, Recordati, Exelisis, Adium, and BMS. He has received research grants from Pfizer, IPSEN and Roche, all outside the submitted work. Francesco Massari has received research support and/or honoraria from Advanced Accelerator Applications, Astellas, Astra Zeneca, Bayer, BMS, Janssen, Ipsen, MSD, Pfizer outside the submitted work. 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. Ondrej Fiala received honoraria from Novartis, Janssen, Merck and Pfizer for consultations and lectures unrelated to this project. Fernando Sabino Marques Monteiro has received research support provided by MSD and Foundation Medicine. Honoraria from Janssen, Ipsen, BMS, Novartis, AstraZeneca, Bayer, ADIUM and MSD. Travel expenses by Novartis, Bayer, ADIUM, Merck and MSD. Consulting or Advisory Role from Novartis and ADIUM. Ownership: BIO, Brazilian Information Oncology. All are unrelated to this study. Enrique Grande has received honoraria for ad boards, meetings and/or lectures from Pfizer, BMS, IPSEN, Roche, Eisai, Eusa Pharma, MSD, Sanofi-Genzyme, Adacap, Novartis, Pierre Fabre, Lexicon and Celgene. Enrique Grande has received unrestricted research grants from Pfizer, Astra Zeneca, MTEM/Threshold, Roche, IPSEN and Lexicon. Camillo Porta has received honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, Ipsen and MSD and acted as a Protocol Steering Committee Member for BMS, Eisai and MSD. Jakub Kucharz declares advisory boards, support for attending meetings, honoraria from Angelini, Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, IPSEN, Janssen, Merck MSD, Novartis, Pfizer; and Research funding: Novartis. All unrelated to the present paper. 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. 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 paper. The other authors declare no conflicts of interest. [Correction added on 29 November 2025, after first online publication: The conflict of interest statement section has been revised.].

DATA AVAILABILITY STATEMENT

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

ETHICAL STATEMENT

The "ARON-1" project (NCT05287464) was approved was conducted in accordance with the "Declaration of Helsinki" and approved by local and central ethics committees (committee of Marche Region; approval number: 2021-492). Due to the retrospective nature of the study, informed signed consent was not required.

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SUPPORTING INFORMATION

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

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