Received: 15 November 2025 | Revised: 23 November 2025 | Accepted: 3 December 2025

DOI: 10.1002/ijc.70289

IJC INTERNATIONAL JOURNAL of CANCER | UICC

LETTER TO THE EDITOR

Reply to: Comments on "Toxicity-related immunotherapy discontinuation and outcome in patients with advanced renal cell carcinoma treated with immune-based combinations (ARON-1 study)"

Dear Editor,

We thank Dr. Wen-Jiang Yang for his thoughtful appraisal of our study exploring the clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) who discontinued first-line immune-based combinations due to serious adverse events (SAEs). We appreciate his recognition of ARON-1 as the largest real-world effort to date to examine this timely and clinically relevant issue.[1]

ARON-1 was conceived to leverage a broad international, multi-institutional network encompassing 52 centers across 20 countries, capturing contemporary practice patterns in a rapidly evolving therapeutic landscape. We fully acknowledge that the retrospective nature of the analysis carries inherent limitations, particularly the heterogeneity of local management strategies, incomplete capture of certain variables, and potential residual confounding. Nevertheless, our primary intent was to provide hypothesis-generating, real-world evidence (RWE) complementing the insights from pivotal randomized trials. In this respect, ARON-1 represents a pragmatic reflection of day-to-day clinical decision-making rather than a substitute for prospective validation.

We concur with the correspondents that the use of corticosteroids constitutes a potentially important modifier of immune response and could influence both toxicity outcomes and survival. In our large multinational dataset, information on corticosteroid timing, dose, and duration was inconsistently available and therefore excluded from multivariate modeling to avoid unreliable inferences as well as misinterpretation. Nonetheless, we explicitly acknowledged this limitation in the Discussion section. Importantly, evidence from melanoma and non-small cell lung cancer (NSCLC) suggests that the deleterious impact of corticosteroids is most pronounced when used at baseline or early during treatment for non-immune indications, whereas steroids administered for immune-related adverse events (irAEs) do not appear to compromise efficacy. This body of evidence supports our interpretation that, despite unmeasured variation in steroid exposure, the overall neutrality of outcomes between continuation and discontinuation groups is biologically plausible.[2–6]

We agree that the prognostic significance of irAEs may differ according to organ system and severity. In ARON-1, hepatic and pulmonary events were less frequent but were indeed associated with earlier discontinuation. Conversely, endocrine irAEs were often manageable, allowing treatment resumption in routine practice. Our results, showing similar overall survival (OS) and even numerically higher objective response rates (ORR 61% vs. 52%) among patients who discontinued, suggest that treatment interruption per se is not synonymous with therapeutic failure. This aligns with mechanistic hypotheses that durable immune activation can persist beyond treatment exposure once an effective immune memory has been established.

ARON-1 identified timing of interruption as a key determinant of outcome. Patients discontinuing within the first 3 months had inferior OS compared with those discontinuing later, while those treated ≥3 months achieved survival comparable to continuously treated counterparts. This "early versus late" effect is consistent with observations in NSCLC, melanoma, and urothelial carcinoma cohorts, where early cessation, often driven by aggressive disease biology, portends poorer prognosis independent of treatment duration. Therefore, our landmark analyses at 6 months were deliberately designed to mitigate immortal-time bias and reinforce that adequate initial exposure, rather than indefinite continuation, underlies sustained benefit.[3]

Multiple prospective and retrospective series across solid tumors corroborate our findings. In melanoma and NSCLC, patients discontinuing immune checkpoint inhibitors due to toxicity maintained long-term survival comparable to those treated continuously. Stellato et al. reported analogous results in RCC, showing that early discontinuation due to severe irAEs did not abrogate clinical benefit. Collectively, these data suggest that durable responses can persist even after treatment cessation, reflecting immune memory and sustained T-cell activation. ARON-1 thus extends this evidence to the largest RCC cohort evaluated to date, providing real-world reassurance that toxicity-related discontinuation does not necessarily compromise outcomes.[1–7]

The correspondents' conceptual framework of unmeasured confounders is reasonable in this type of study. To minimize bias, we applied multivariable Cox regression including established prognostic variables (age, nephrectomy, International Metastatic RCC Database Consortium (IMDC) risk, sarcomatoid features, and metastatic sites)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; irAEs, immune-related adverse events; IMDC, International Metastatic RCC Database Consortium; mRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rates; OS, overall survival; RWE, real-world evidence; SAEs, serious adverse events.

and performed a 6-month landmark analysis. The Harrell's *C*-index near 0.5 underscores the absence of association between treatment interruption and survival beyond chance, reinforcing the neutrality of the effect. While unmeasured factors such as Eastern Cooperative Oncology Group (ECOG) status and steroid dose remain possible confounders, their omission would likely introduce random rather than directional bias in a cohort exceeding 1000 patients.

Randomized trials remain the gold standard for causal inference, but RWE offers indispensable complementary insight into treatment feasibility, adherence, and toxicity management outside clinical trial restrictions. This is particularly important as clinical practice outcomes may diverge from those reported in clinical trials, largely due to differences in patient populations and selection biases.[8–10] Our consortium intentionally incorporated both community and academic centers, thereby enhancing external validity and accurately reflecting routine clinical practice.

The convergent findings across tumor types further strengthen confidence in the biological robustness of our observations.

The ARON-1 study is a dynamic project that is evolving over time, not only improving the collection of prospective cohort data but also continuing to evolve by integrating prospective and translational analyses to try to determine biomarkers of response and prognosis in renal cancer.

AUTHOR CONTRIBUTIONS

Javier Molina-Cerrillo: Conceptualization; writing – original draft; writing – review and editing. **Giandomenico Roviello:** Writing – review and editing; conceptualization. **Ondrej Fiala:** Conceptualization; writing – review and editing. **Tarek Taha:** Conceptualization; writing – review and editing. **Sebastiano Buti:** Writing – review and editing; conceptualization. **Mimma Rizzo:** Conceptualization; writing – review and editing. **Francesco Massari:** Conceptualization; writing – review and editing. **Fernando Sabino Marques Monteiro:** Conceptualization; writing – review and editing. **Matteo Santoni:** Conceptualization; writing – review and editing.

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. 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.

Javier Molina-Cerrillo[1,2]
Giandomenico Roviello[2,3]
Ondrej Fiala[2,4,5]
Tarek Taha[2,6]
Sebastiano Buti[2,7,8]
Mimma Rizzo[2,9]
Francesco Massari[2,10,11]
Fernando Sabino Marques Monteiro[2,12]
Matteo Santoni[2,13]

[1]*Department of Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain*
[2]*ARON Research Foundation ETS, Macerata, Italy*
[3]*Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Florence, Italy*
[4]*Department of Oncology and Radiotherapeutics, Faculty of Medicine and University Hospital in Pilsen, Charles University, Pilsen, Czech Republic*
[5]*Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic*
[6]*Royal Marsden NHS Foundation Trust, London, UK*
[7]*Medical Oncology Unit, University Hospital of Parma, Parma, Italy*
[8]*Department of Medicine and Surgery, University of Parma, Parma, Italy*
[9]*Medical Oncology Unit, Azienda Ospedaliera Universitaria Consorziale Policlinico di Bari, Bari, Italy*
[10]*Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*
[11]*Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy*
[12]*Oncology and Hematology Department, Hospital Sírio Libanês, Brasília, Brazil*
[13]*Medical Oncology Unit, Macerata Hospital, Macerata, Italy*

Correspondence
Javier Molina-Cerrillo, Department of Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain.
Email: jmolinac@salud.madrid.org; javier.molinace@gmail.com

ORCID

Giandomenico Roviello https://orcid.org/0000-0001-5504-8237
Sebastiano Buti https://orcid.org/0000-0003-0876-0226
Fernando Sabino Marques Monteiro https://orcid.org/0000-0002-6621-8251

REFERENCES

1. Molina-Cerrillo J, Roviello G, Bourlon MT, et al. Toxicity-related immunotherapy discontinuation and outcome in patients with advanced renal cell carcinoma treated with immune-based combinations (ARON-1 study). *Int J Cancer*. 2026;158(5):1396-1405. doi:10.1002/ijc.70228
2. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival in patients with melanoma treated with ipilimumab. *J Clin Oncol*. 2015;33(28):3193-3198. doi:10.1200/JCO.2015.60.8448
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158-168. doi:10.1056/NEJMra1703481
4. Cook S, Samuel V, Meyers DE, et al. Immune-related adverse events and survival among patients with metastatic non-small cell lung cancer treated with immune checkpoint inhibitors. *JAMA Netw Open*. 2024;7(1):e2352302. doi:10.1001/jamanetworkopen.2023.52302
5. Teraoka S, Fujimoto D, Morimoto T, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: a prospective cohort study. *J Thorac Oncol*. 2017;12(12):1798-1805. doi:10.1016/j.jtho.2017.08.022
6. Stellato M, Procopio G, De Giorgi U, et al. Clinical outcome of renal cancer patients who early interrupted immunotherapy due to serious immune-related adverse events (Meet-Uro 13 trial). *J Transl Med*. 2021;19(1):328. doi:10.1186/s12967-021-03003-2
7. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16(9):563-580. doi:10.1038/s41571-019-0218-0
8. Taha T, Hall E, de Bono JS. Mind the gap: the disconnect between clinical trials and real-world oncology patients. *Eur Urol*. 2025;87(5):501-503. doi:10.1016/j.eururo.2025.02.003
9. Karim S, Xu Y, Kong S, Abdel-Rahman O, Quan ML, Cheung WY. generalisability of common oncology clinical trial eligibility criteria in the real world. *Clin Oncol (R Coll Radiol)*. 2019;31(9):e160-e166. doi:10.1016/j.clon.2019.05.003
10. Khozin S, Carson KR, Zhi J, et al. Real-world outcomes of patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors in the year following U.S. regulatory approval. *Oncologist*. 2019;24(5):648-656. doi:10.1634/theoncologist.2018-0307