Oncol Ther (2025) 13:1155–1167
https://doi.org/10.1007/s40487-025-00387-7

ORIGINAL RESEARCH

Overlapping Extremes: An Analysis of Avelumab Maintenance and Pembrolizumab in Advanced Urothelial Carcinoma

Martina Catalano · Irene de Gennaro Aquino · Ismaela Anna Vascotto · Adriana Guarino · Silvia Mancini · Laura Doni · Alexandra Paulet · Virginia Rossi · Roberta Giorgione · Gabriella Nesi · Lorenzo Antonuzzo · Giandomenico Roviello

Received: August 29, 2025 / Accepted: September 29, 2025 / Published online: October 15, 2025

ABSTRACT

***Introduction*:** Avelumab and pembrolizumab are approved immune checkpoint inhibitors (ICIs) for advanced urothelial carcinoma (UC) that are used as maintenance and salvage therapies, respectively. The aim of this study was to highlight patterns of extreme response and support the development of biomarker-driven strategies to optimise patient selection and treatment sequencing.

***Methods*:** This was a prospective study that included 79 patients with advanced UC treated with avelumab ($n = 32$) or pembrolizumab ($n = 47$) following platinum-based chemotherapy. Outcomes included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS).

***Results*:** Avelumab was associated with a DCR of 84.4% and a complete response (CR) rate of 34.4%, while pembrolizumab was associated with a DCR of 55.3% and a CR rate of 12.8%. Progressive disease (PD) occurred in 15.6% and 44.7% of patients, respectively. Despite differences in treatment indications and timing, median PFS and OS in patients with CR and PD were surprisingly comparable across the two agents.

***Conclusions*:** These findings suggest that extreme responses to ICIs in advanced UC—ranging from complete response to primary progression—may occur irrespective of treatment setting, underscoring the pivotal role of tumour–immune biology. Biomarker-driven strategies are needed to optimise patient selection.

***Trial Registration*:** OBSERVE-UC study; registration ID: CEAVC 25351.

Lorenzo Antonuzzo and Giandomenico Roviello have contributed equally to this study.

This work has not been previously published or presented.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40487-025-00387-7.

M. Catalano · G. Roviello (✉)
Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy
e-mail: giandomenico.roviello@unifi.it

I. de Gennaro Aquino · I. A. Vascotto · A. Guarino · S. Mancini · A. Paulet · L. Antonuzzo
Department of Experimental and Clinical Medicine, University of Florence, 50134 Florence, Italy

L. Doni · V. Rossi · R. Giorgione
Clinical Oncology Unit, Careggi University Hospital, 50234 Florence, Italy
e-mail: roberta.giorgione@unifi.it

G. Nesi
Section of Anatomic Pathology, Department of Health Sciences, University of Florence, 50139 Florence, Italy
e-mail: gabriella.nesi@unifi.it

Keywords: Avelumab; Pembrolizumab; Immunotherapy; Biomarkers

Key Points
Why carry out this study?
Advanced urothelial carcinoma (UC) remains associated with poor long-term survival despite platinum-based chemotherapy, and real-world data on immune checkpoint inhibitors (ICIs) are limited
In patients with advanced UC, avelumab is approved as maintenance therapy and pembrolizumab as salvage therapy
We prospectively reported outcomes of avelumab maintenance versus pembrolizumab salvage therapy in patients with advanced UC previously treated with platinum-based chemotherapy
What was learned from the study?
In patients treated with avelumab, the disease control rate (DCR) was 84.4% and the complete response (CR) rate was 34.4%, whereas in those treated with pembrolizumab, the DCR was 55.3% and the CR rate was 12.8%. PD was observed in 15.6% and 44.7% of patients, respectively
Median progression-free survival and overall survival in extreme responders—either complete response or primary progression—appeared across both treatment settings, suggesting that these outcomes may be driven more by tumour–immune biology than by treatment timing. These results underscore the urgent need for biomarker-driven strategies to optimise patient selection

INTRODUCTION

Urothelial carcinoma (UC) represents the most common form of genitourinary malignancy in Europe, second only to prostate cancer [1]. While early-stage disease can often be managed effectively with surgery and intravesical therapies, advanced and metastatic UC continues to be associated with poor long-term survival [2]. First-line treatment typically consists of platinum-based chemotherapy, but despite initial responses, the majority of patients eventually develop resistance or disease progression, with limited treatment options available thereafter [3].

In recent years, immune checkpoint inhibitors (ICIs) targeting the programmed cell death-1 (PD-1) receptor or its ligand PD-L1 have significantly altered the therapeutic landscape for advanced UC [3]. Pembrolizumab, a monoclonal antibody against PD-1, was the first ICI to demonstrate an overall survival (OS) benefit in platinum-pretreated UC in the phase III KEYNOTE-045 trial, leading to its approval for use in the second-line setting [4]. Avelumab, an anti-PD-L1 monoclonal antibody, gained approval for use as switch maintenance therapy following response or stable disease with first-line platinum-based chemotherapy, based on the landmark JAVELIN Bladder 100 study [5]. These approvals represent two distinct indications and timing of ICI therapy—post chemotherapy progression versus maintenance strategy—which may influence patient selection, treatment efficacy and outcomes.

Although clinical trial data support the efficacy of both pembrolizumab and avelumab, their performance in the real-world setting, particularly outside of strict trial eligibility criteria, remains less well characterised. Real-world evidence is essential to understand how these therapies perform in broader [6], more heterogeneous patient populations, including older individuals, those with comorbidities and/or patients with variant histologies and multiple metastatic sites. Furthermore, the direct comparison of pembrolizumab and avelumab in clinical practice has not been systematically explored, and no head-to-head randomised trials currently exist.

In this context, the aim of this prospective observational study was to assess the clinical characteristics, treatment outcomes, progression-free survival (PFS) and OS of patients with advanced UC treated with avelumab as maintenance therapy or pembrolizumab after

progression at our institution. By providing real-world evidence on the contrasting roles of these two ICIs, we also aimed to highlight patterns of extreme response and support the development of biomarker-driven strategies to optimise patient selection and treatment sequencing.

METHODS

This was a single-centre, prospective cohort study conducted to evaluate the clinical efficacy of ICIs in patients with advanced or metastatic UC. The study included consecutive patients treated with either avelumab or pembrolizumab between January 2019 and December 2024 at the Careggi University Hospital (Florence, Italy).

Eligible patients were adults (≥ 18 years) with histologically confirmed advanced or metastatic UC who had received treatment with either avelumab or pembrolizumab. All patients had previously received platinum-based chemotherapy (gemcitabine + cisplatin, or gemcitabine + carboplatin). All participants were of white European descent (Italian origin). No additional disaggregated data on race/ethnicity were collected. Exclusion criteria included the presence of another concurrent malignancy requiring systemic therapy and lack of available clinical or radiological follow-up data. All patients receiving avelumab did so as maintenance therapy after achieving at least stable disease with first-line platinum-based chemotherapy, whereas all pembrolizumab-treated patients received the drug as second-line therapy after documented progression on platinum therapy.

Clinical and pathological data were extracted from electronic medical records. Baseline characteristics collected included age, sex, Eastern Cooperative Oncology Group (ECOG) Performance Status Scale, primary tumour site, histology, presence of metastasis at diagnosis, prior chemotherapy regimen and metastatic sites at the time of ICI initiation. Type of immunotherapy (avelumab or pembrolizumab) and treatment indication (maintenance or salvage) were also recorded.

Tumour response was assessed according to RECIST 1.1 [7] criteria through serial imaging and clinical evaluation. The best overall response was classified as complete response (CR), partial response (PR), stable disease (SD, or progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients achieving CR or PR, while the disease control rate (DCR) included patients with CR, PR or SD. Response was assessed by comparing tumour burden at the start of immunotherapy with the immediate pre-immunotherapy imaging assessment—and not with the pre-chemotherapy baseline. PFS was defined as the time from initiation of immunotherapy to radiologic or clinical progression or death from any cause, whichever occurred first. OS was defined as the time from immunotherapy initiation to death from any cause. Patients who were alive or without progression at the time of data cut-off were censored at the date of last follow-up. Median PFS and OS were estimated using the Kaplan–Meier method, and 95% confidence intervals (CIs) were calculated.

Descriptive statistics were used to summarise baseline characteristics and clinical outcomes. Categorical variables were expressed as counts and percentages, while continuous variables were presented as the median and range. Comparative analyses between treatment groups were exploratory and based on univariate descriptive comparisons.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (trial registration number: OBSERVE-UC study; CEAVC 25351; Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana: Sezione: AREA VASTA CENTRO; Careggi University of Florence Hospital ethical committee).

RESULTS

A total of 79 patients with advanced UC were included in this retrospective analysis (Table 1). Of these, 32 patients (40.5%) received avelumab and 47 (59.5%) were treated with

Table 1 Patient baseline characteristics

Variables	Total patient population *N* =79
Age	
Median (range), years	74 (47–88)
≥ 75 years, *n* (%)	39 (49.7)
Sex, n (%)	
Male	198 (81.48)
Female	45 (18.52))
ECOG performance status, n (%)	
0	37 (46.84)
1	37 (46.84)
2	5 (6.33)
Primary tumor site, n (%)	
Bladder	61 (77.22)
Upper urinary tract	18 (22.78)
Histology	
Urothelial	74 (93.67)
Variant	5 (6.33)
Metastatic at diagnosis, n (%)	
Yes	25 (31.65)
No	54 (68.35)
Prior chemotherapy regimen, n (%)	
Gemcitabine + cisplatin	24 (30.77)
Gemcitabine + carboplatin	54 (69.23)
Site of metastasis, n (%)	
Lung	40 (50.63)
Bone	28 (35.44)
Liver	19 (24.05)
Mediastinal lymph node	19 (24.05)
Abdominal lymph node	58 (73.42)
Other (soft tissue; peritoneum)	41 (51.9)
Brain	3 (3.80)
Type of immunotherapy, n (%)	
Avelumab	32 (40.51)
Pembrolizumab	47 (59.49)

ECOG Eastern Cooperative Oncology Group (Performance Status Scale)

pembrolizumab. The median age of the study population was 74 (range 47–88) years, and nearly half of the patients (49.7%) were aged 75 years or older. The cohort was predominantly male (81.5%), and most patients had a preserved performance status, with an ECOG score of 0 or 1 in 93.7% of cases. The primary tumour site was the bladder in 61 patients (77.2%), while 18 patients (22.8%) had upper urinary tract tumours. Histologically, the majority had pure urothelial carcinoma (93.7%), with only 6.3% showing variant differentiation. Metastatic disease at initial diagnosis was reported in 31.7% of patients.

All patients had received prior platinum-based chemotherapy, with gemcitabine + carboplatin being the most frequently used regimen (69.2%). The most common sites of metastasis included abdominal lymph nodes (73.4%), lung (50.6%) and soft tissues or peritoneum (51.9%).

Across the entire cohort, the ORR was 38.0%, with 17 patients (21.5%) achieving CR and 13 patients (16.5%) achieving PR. SD was observed in 23 patients (29.1%), resulting in a DCR of 67.1%. PD occurred in 26 patients (32.9%) (Table 2; Fig. 1; Electronic Supplementary Material Fig. S1).

When stratified by immunotherapy type, the CR rate was 34.4% in the avelumab subgroup and 12.8% in the pembrolizumab subgroup. PR occurred in 12.5% of avelumab-treated patients and in 19.1% of pembrolizumab-treated patients. The DCR was 84.4% in the avelumab group and 55.3% in the pembrolizumab group. PD was observed in 15.6% of patients in the avelumab group and 44.7% of patients in the pembrolizumab group (Fig. 1).

Table 2 Tumour response in all patients and according to type of immunotherapy

Tumour response	All patients ($N=79$)	Avelumab ($N=32$)	Pembrolizumab ($N=47$)
CR	17 (21.52)	11 (34.38)	6 (12.77)
PR	13 (16.46)	4 (12.50)	9 (19.15)
SD	23 (29.11)	12 (37.50)	11 (23.40)
RR (CR + PR)	30 (37.97)	15 (46.88)	15 (31.91)
DCR (CR + PR + SD)	53 (67.09)	27 (84.38)	26 (55.32)
PD	26 (32.91)	5 (15.62)	21 (44.68)

Data in table are presented as a number (of patients) with the percentage in parentheses

CR Complete response, *DCR* disease control rate, *PD* progressive disease, *PR* partial response, *RR* response rate, *SD* stable disease

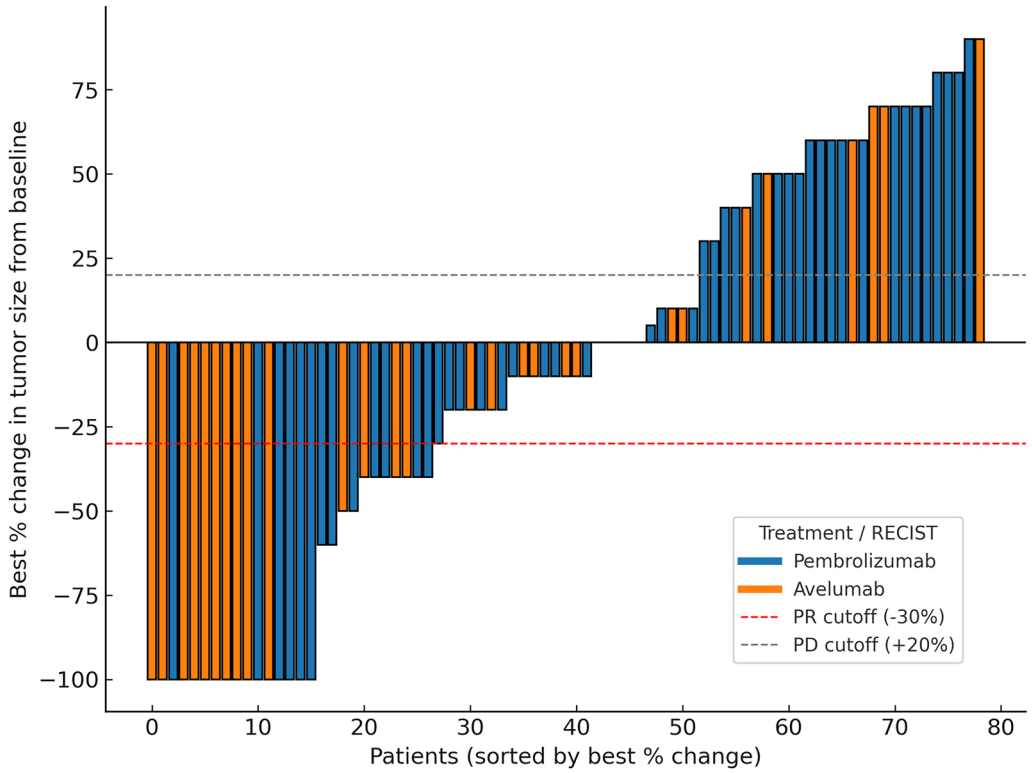

Fig. 1 Waterfall plot of change in tumour size by treatment. *PD* progressive disease, *PR* partial response

Median PFS varied substantially based on tumour response. Among all patients, those achieving CR had a median PFS of 49.7 (95% CI 38–not reached [NR]) months, while those with PR and SD had a median PFS of 26.4 (95% CI 11.4–NR) months and 7.0 (95% CI 4.4–11.7) months, respectively (Table 3; Fig. 2). In patients receiving avelumab, median PFS was

Table 3 Efficacy and survival according to tumour response in all patients and according to type of immunotherapy

Tumour response	All patients ($N=79$)	Avelumab	Pembrolizumab
PFS (months)			
CR	49.7 (38–NR)	49.7 (27.3–NR)	NR (NR–NR)
PR	26.4 (11.4–NR)	15.2 (3.3–NR)	26.5 (4.9–NR)
SD	7 (4.4–11.7)	4.8 (2.3–15.6)	7.7 (4.1–15.0)
RR (CR + PR)	48.5 (27.3–NR)	49.7 (26.4–NR)	48.5 (15.5–NR)
DCR (CR + PR + SD)	25.7 (11.7–33.3)	26.4 (6.5–33.3)	24.7 (9.1–48.5)
PD	2.5 (1.7–3.4)	3 (1.1–NR)	2.5 (1.4–NR)
	All patients ($N=79$)	**Avelumab**	**Pembrolizumab**
OS (months)			
CR	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)
PR	47.1 (20.3–NR)	NR (14–NR)	37.4 (4.9–NR)
SD	20.1 (5.4–35.6)	26.5 (2.7–NR)	9.4 (4.1–27.9)
RR (CR + PR)	NR (47.1–NR)	NR (NR–NR)	NR (25.7–NR)
DCR (CR + PR + SD)	44.2 (27.9–NR)	NR (35.6–NR)	31.9 (17.1–NR)
PD	5.1 (1.9–14.3)	6.8 (1.1–NR)	4.4 (1.7–14.3)

Data in table are presented as the median with the 95% confidence interval given in parentheses

CR Complete response, *DCR* disease control rate, *NR* not reached, *OS* overall survival, *PD* progressive disease, *PFS* progression free survival, *PR* partial response, *RR* response rate, *SD* stable disease

49.7 months for those with CR, 15.2 months for those with PR and 4.8 months for those with SD (Fig. 3). Among pembrolizumab-treated patients, median PFS was not reached in the CR subgroup, was 26.5 months in the PR subgroup and was 7.7 months in the SD subgroup (Fig. 4). Patients with PD had poor prognoses, with median PFS of 3.0 (95% CI 1.1–NR) months in the avelumab group and 2.5 (95% CI 1.4–NR) months in the pembrolizumab group (Table 3).

After a median follow-up of 21.1 months for the entire cohort (range 1–61.5 months), the median OS was not reached (NR) in patients who achieved CR or in those with an objective response (CR + PR) across treatment groups, indicating prolonged survival in responders (Table 3; Fig. 5). Among patients with PR, the median OS was 47.1 months in the overall cohort, with NR in the avelumab group ((Fig. 6) and 37.4 months (95% CI 4.9–NR) in the pembrolizumab group (Fig. 7). Patients who achieved SD had a median OS of 20.1 months (95% CI 5.4–35.6). The median OS was 26.5 months in the avelumab group and 9.4 months in the pembrolizumab group. Patients with PD had a median OS of 6.8 months (95% CI 1.1–NR) in the avelumab group and 4.4 months (95% CI 1.7–14.3) in the pembrolizumab group (Table 3).

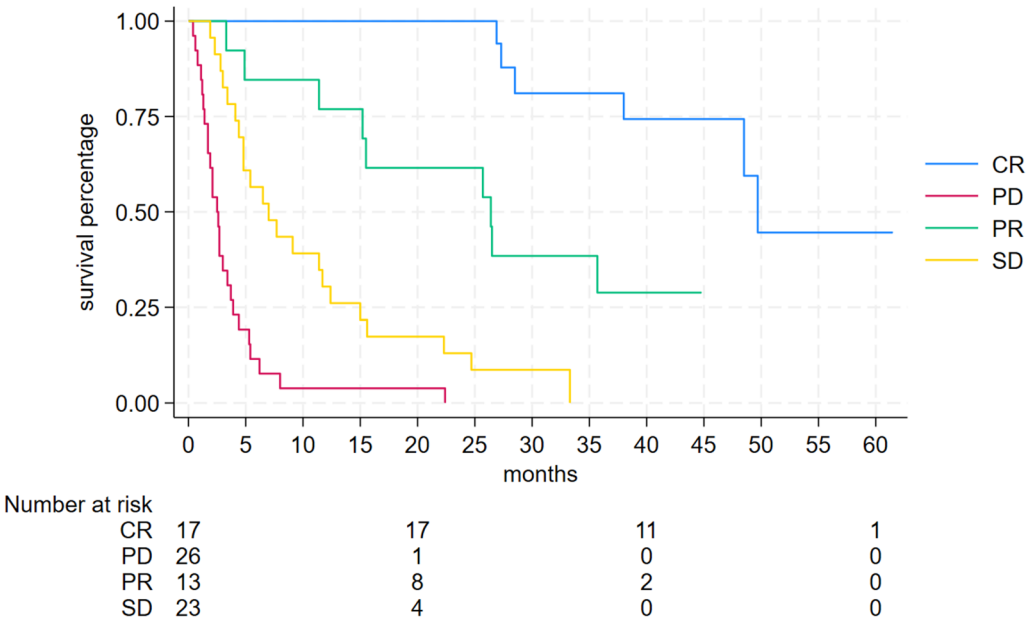

Fig. 2 Progression-free survival according tumor response to immunotherapy. *CR* complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease

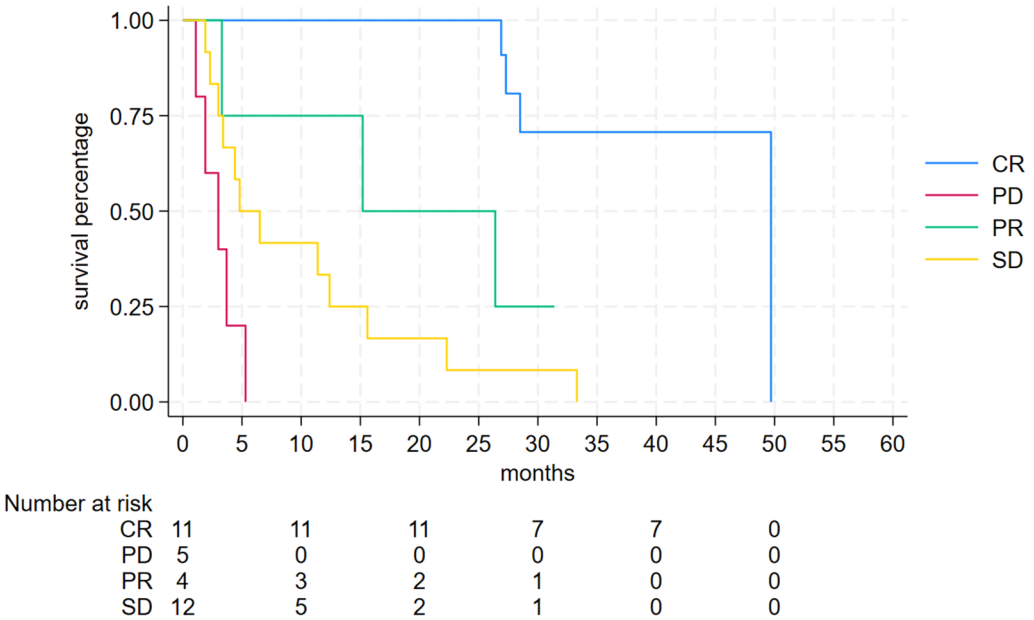

Fig. 3 Progression-free survival according tumor response to avelumab. *CR* Complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease

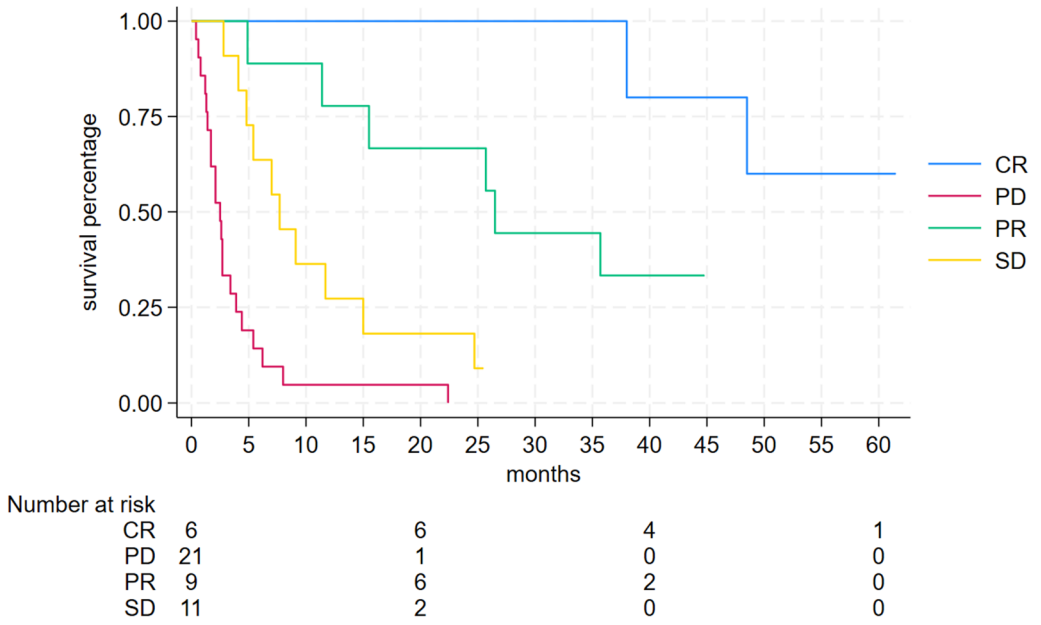

Fig. 4 Progression-free survival according to tumor response to pembrolizumab. *CR* Complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease

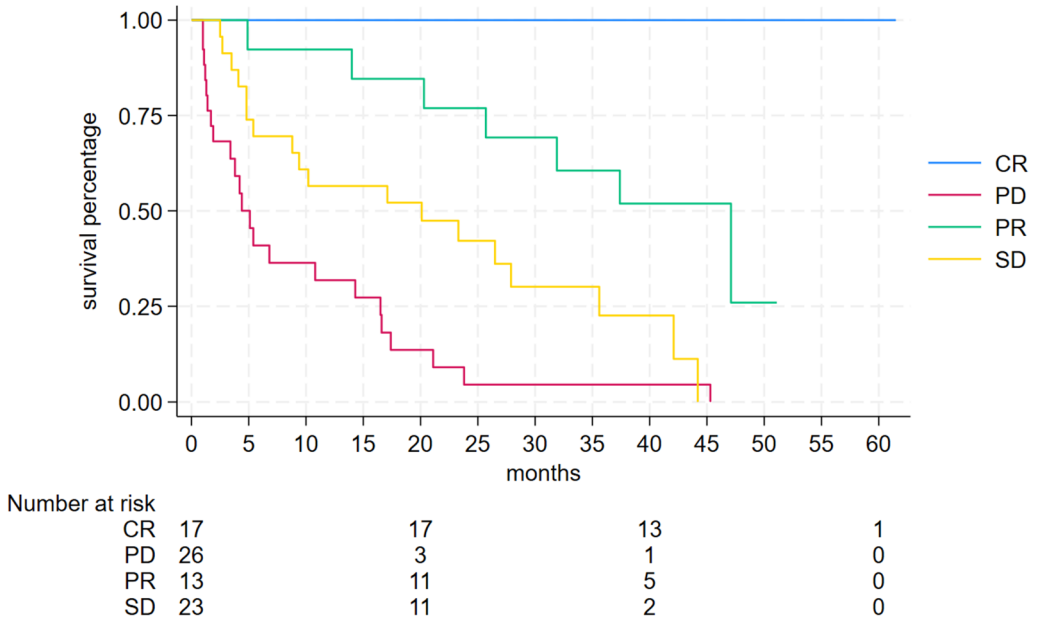

Fig. 5 Overall survival according tumor response to immunotherapy. *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

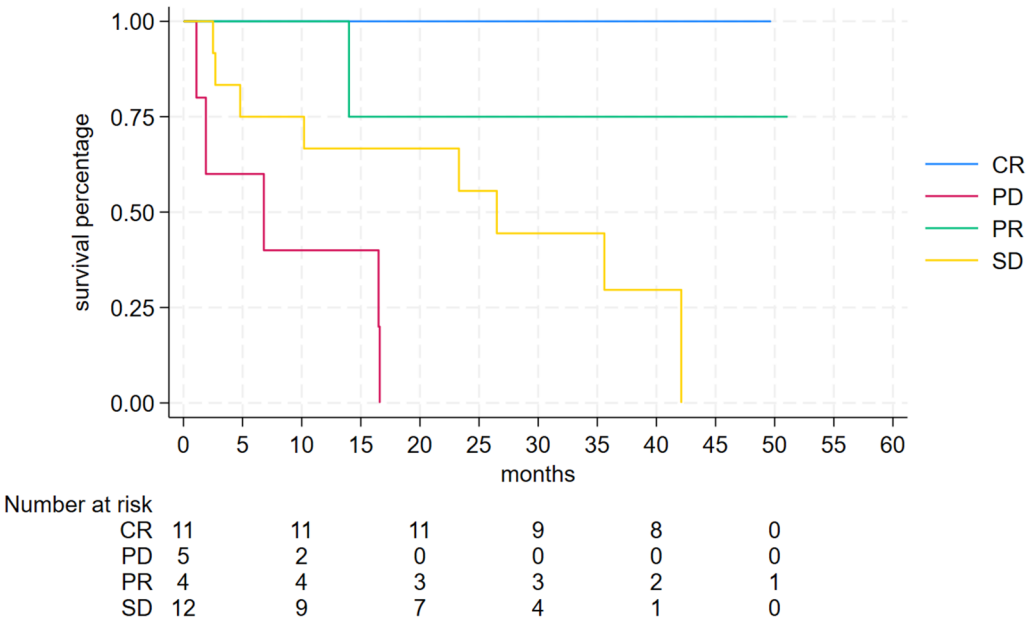

Fig. 6 Progression-free survival according tumor response to avelumab. *CR* complete response, *PR* Partial Response, *SD* stable disease, *PD* progressive disease

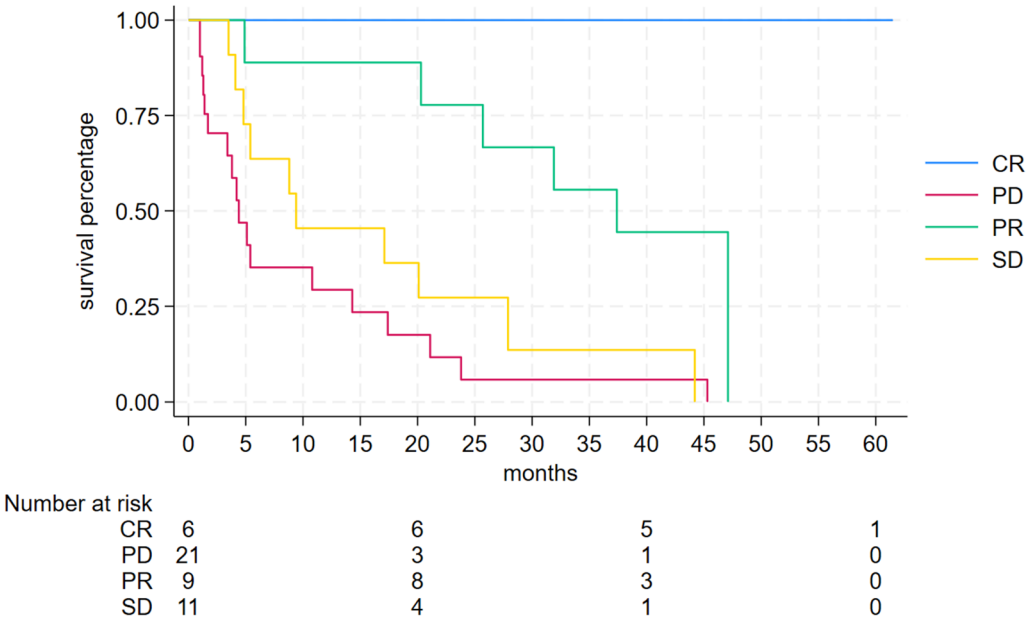

Fig. 7 Progression-free survival according tumor response to pembrolizumab. *CR* Complete Response, *PR* partial response, *SD* stable disease, *PD* progressive disease

DISCUSSION

The results of our prospective analysis offer novel insights into the real-world use of ICIs in patients with advanced UC, with a particular focus on the real-world outcomes of avelumab and pembrolizumab. Notably, our data reveal that, despite differences in treatment indications and timing—maintenance after chemotherapy in the case of avelumab versus second-line therapy post-progression for pembrolizumab—median PFS and OS in patients with CR and PD were surprisingly comparable across the two agents. These findings prompt a series of reflections on the biology of UC, patient selection and the urgent need for predictive biomarkers to personalise immunotherapy [8–10].

In the JAVELIN Bladder 100 trial, avelumab demonstrated a significant improvement in OS when used as maintenance therapy in patients without disease progression following first-line platinum-based chemotherapy. The authors of this study reported a median OS of 21.4 months with avelumab plus best supportive care (BSC), compared to 14.3 months with BSC alone (hazard ratio [HR] 0.69, 95% CI 0.56–0.86) [5]. In contrast, pembrolizumab was evaluated in a distinct clinical context: the phase III KEYNOTE-045 trial enrolled patients with progression during or after platinum-based chemotherapy, and showed a median OS of 10.3 months with pembrolizumab versus 7.4 months with chemotherapy (HR 0.73, 95% CI 0.59–0.91) [4].

In our cohort, in the avelumab group, the DCR was 84.4% and the CR rate was 34.4%, while in the pembrolizumab group, the DCR was 55.3% and the CR rate was 12.8%, consistent with the more favourable clinical status of the former population—namely, patients who had not progressed on prior chemotherapy. However, perhaps the most impressive finding was the similarity in median PFS and OS in patients with CR and PD across both treatment groups. While disease control and partial responses differed as expected based on patient selection, the similarity in median PFS and OS in CR and PD rates raises several important biological and clinical considerations (Table 3).

First, this observation supports the hypothesis that a subset of patients with UC may be intrinsically sensitive or resistant to immune checkpoint inhibition, regardless of prior chemotherapy response [11]. In theory, patients receiving avelumab as maintenance are expected to have more indolent disease and better immune fitness, whereas those receiving pembrolizumab are often in a state of progression and potentially of immune exhaustion. This may suggest that ICI responsiveness is not strictly determined by timing of administration or disease kinetics but rather by underlying tumour biology and immune contexture [11].

Second, our findings underscore the limitations of current clinical criteria in guiding ICI use. Factors such as performance status, prior chemotherapy response and metastatic burden, while useful for treatment decisions, may not adequately predict immunotherapy benefit [12]. Instead, there is a growing consensus that molecular and immunological biomarkers—such as tumour mutational burden (TMB), PD-L1 expression, T-cell inflamed gene signatures and the composition of the tumour microenvironment—are necessary to identify true responders and avoid futile treatment in resistant individuals [13]. The clinical trials that led to the approval of avelumab and pembrolizumab did attempt to explore such biomarkers, but the results were inconclusive. In KEYNOTE-045, PD-L1 expression did not correlate strongly with benefit, while in JAVELIN Bladder 100, PD-L1 positivity was associated with better outcomes, but benefit was still observed across all subgroups [4, 5]. From a translational perspective, these findings highlight the urgent need to develop and validate predictive biomarkers for ICI responsiveness in UC [10, 14–16]. While ongoing studies are exploring circulating tumour DNA (ctDNA), T-cell receptor repertoire analysis and microbiome profiling, none of these tools are as yet ready for clinical implementation. Additionally, the heterogeneity of UC—across anatomical sites, histological variants and molecular subtypes—adds further complexity to biomarker discovery [8–10].

Although the relatively small sample size represents a limitation of our study, the real-world nature of these data provides meaningful

insights into the use of avelumab and pembrolizumab after first-line chemotherapy. Such evidence complements the results of clinical trials by reflecting the outcomes of patients treated in routine clinical practice, where selection criteria and management may differ from controlled study settings. In addition, we acknowledge the relatively small sample size, which also prevented us from performing meaningful analyses of correlations between clinical parameters and treatment response. Such exploratory investigations, although potentially informative, would require larger patient cohorts to provide reliable results. Another limitation of our study is the unbalanced sex distribution, with substantially more males than females. We did not conduct sex-disaggregated efficacy analyses due to the small number of female participants, which would render such comparisons underpowered. Nonetheless, this male predominance is consistent with published epidemiologic data in advanced UC. Future studies should aim for larger and more balanced cohorts are awaited. Finally, there is a lack of disaggregated race/ethnicity data. Since all participants were of white European descent (Italian origin), our findings may not be generalisable to populations with different racial or ethnic backgrounds. Future studies should investigate whether race/ethnicity may influence the observed outcomes.

CONCLUSIONS

In this prospective real-world study of patients with advanced UC, we observed that avelumab maintenance was associated with higher disease control and complete response rates compared with pembrolizumab administered after progression, while median PFS and OS in extreme responders—either complete response or primary progression—appeared across both treatment settings. These findings confirm the feasibility and clinical relevance of ICIs beyond clinical trial populations, and highlight the need for biomarker-driven strategies to optimise patient selection and treatment sequencing.

ACKNOWLEDGEMENTS

We thank the patients who participated in the study.

Medical Writing/Editorial Assistance. The authors received no medical writing or editorial assistance during the preparation of this manuscript.

Author Contributions. Martina Catalano: Conceptualization, data analysis, drafting of the manuscript. Irene de Gennaro Aquino: Data collection. Ismaela Anna Vascotto: Data collection. Adriana Guarino: Data collection. Silvia Mancini: Data collection. Laura Doni: Data collection, manuscript editing. Alexandra Paulet: Data collection. Virginia Rossi: Data collection, manuscript editing. Roberta Giorgione: Data collection, manuscript editing. Gabriella Nesi: Supervision, critical revision of the manuscript for important intellectual content. Lorenzo Antonuzzo: Supervision, critical revision of the manuscript for important intellectual content. Giandomenico Roviello: Conceptualization, supervision, statistical analysis, final approval of the version to be published. All authors read and approved the final manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Data Availability. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Martina Catalano, Irene de Gennaro Aquino, Ismaela Anna Vascotto, Adriana Guarino, Silvia Mancini, Laura Doni, Alexandra Paulet, Virginia Rossi, Roberta Giorgione, Gabriella Nesi, Lorenzo Antonuzzo and Giandomenico Roviello have nothing to disclose.

Ethical Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (trial registration number: OBSERVE-UC study; CEAVC 25351; Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana: Sezione: AREA VASTA CENTRO; Careggi University of Florence Hospital ethical committee).

REFERENCES

1. Enneli D, Baglan T. The many faces of urothelial carcinomas: an update from pathology to clinical approach and challenges in practice. Urol Res Pract. 2023;49(3):147–61. https://doi.org/10.5152/tud.2023.23023.

2. Alvarez-Maestre Y, Gomez-Luna MJ, Cano-Garcia M, et al. A comprehensive review of current approaches in bladder cancer. J Clin Med. 2024;13(2):189.

3. Roviello G, Santoni M, Sonpavde GP, Catalano M. The evolving treatment landscape of metastatic urothelial cancer. Nat Rev Urol. 2024;21(10):580–92. https://doi.org/10.1038/s41585-024-00872-0.

4. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376(11):1015–26. https://doi.org/10.1056/NEJMoa1613683.

5. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218–30. https://doi.org/10.1056/NEJMoa2002788.

6. Costa V, Custodio MG, Gefen E, Fregni F. The relevance of the real-world evidence in research, clinical, and regulatory decision making. Front Public Health. 2025;13:1512429. https://doi.org/10.3389/fpubh.2025.1512429.

7. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-update and clarification: from the RECIST committee. Eur J Cancer. 2016;62:132–7. https://doi.org/10.1016/j.ejca.2016.03.081.

8. Kamoun A, de Reyniès A, Allory Y, et al. A consensus molecular classification of muscle-invasive bladder cancer. Eur Urol. 2020;77(4):420–33. https://doi.org/10.1016/j.eururo.2019.09.006.

9. Faltas BM, Tagawa ST. Molecular profiling and precision medicine in bladder cancer: from promise to practice. Urol Oncol. 2021;39(4):193–202. https://doi.org/10.1016/j.urolonc.2020.10.006.

10. van der Heijden AG, Massard C, Powles T, et al. Biomarkers for immunotherapy in urothelial cancer: a review. Eur Urol. 2022;82(1):20–32. https://doi.org/10.1016/j.eururo.2022.02.025.

11. Usset J, Rosendahl Huber A, Andrianova MA, et al. Five latent factors underlie response to immunotherapy. Nat Genet. 2024;56(10):2112–20. https://doi.org/10.1038/s41588-024-01899-0.

12. Xi K, Jingping L, Yaqing L, et al. Analysis of the factors influencing moderate to poor performance status in patients with cancer after chemotherapy: a cross-sectional study comparing three models. Sci Rep. 2024;14(1):3336. https://doi.org/10.1038/s41598-024-534817.

13. McConkey DJ, Choi W, Dinney CP. Genetic subtypes of bladder cancer: potential implications for immunotherapy. Eur Urol. 2016;69(3):405–7. https://doi.org/10.1016/j.eururo.2015.11.019.

14. Naimi A, Mohammed RN, Raji A, et al. Tumor immunotherapies by immune checkpoint inhibitors (ICIs); the pros and cons. Cell Commun Signal. 2022;20(1):44. https://doi.org/10.1186/s12964-022-00854-y.

15. Roerden M, Spranger S. Cancer immune evasion, immunoediting and intratumour heterogeneity.

Nat Rev Immunol. 2025;25(5):353–69. https://doi.org/10.1038/s41577-024-01111-8.

16. Rossi G, Romano S, De Marco L, et al. Bladder cancer biomarkers: current approaches and future directions. Front Oncol. 2024;13:1210345.