



Baseline Disease Characteristics and Platinum Sensitivity as Predictors of Outcomes in Sequential Therapy with Platinum-Based Chemotherapy, Avelumab Maintenance, and Enfortumab Vedotin in Advanced Urothelial Carcinoma (ARON-2EV Study)

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Abstract

Background Numerous case series have corroborated the efficacy of the first-line approach of platinum-based chemotherapy and avelumab maintenance followed by enfortumab vedotin monotherapy (PBC-AM-EV) in real-world patients with advanced urothelial carcinoma.

Objective The present investigation aimed to characterize the baseline clinical and pathological characteristics and outcomes of the PBC-AM-EV treatment sequence in the advanced urothelial carcinoma population.

Methods ARON-2^{EV} is a global retrospective study investigating the real-world use of EV in patients with advanced urothelial carcinoma. Two hundred and three patients receiving PBC-AM-EV were analyzed. Primary endpoints were disease response, therapy sequence duration, and overall survival. Secondary objectives included the evaluation of clinical factors associated with outcomes. Patient characteristics were analyzed using descriptive statistics; overall survival and therapy sequence duration were estimated using the Kaplan–Meier method and assessed with log-rank tests and Cox proportional hazards models.

Results Following a median follow-up of 23.1 months, the median overall survival from PBC initiation was 31.6 months, with a 2-year overall survival rate of 68%. Survival outcomes were consistent across most clinicopathologic subgroups, but were significantly influenced by Eastern Cooperative Oncology Group performance status, prior response to PBC, and cisplatin-based regimens. Median therapy sequence duration was 26.5 months and was prolonged in patients with exclusive nodal metastases and cisplatin exposure. A 43% objective response rate was achieved by EV, including durable disease control, particularly among patients who benefited from prior PBC and avelumab maintenance.

Conclusions The PBC-AM-EV sequence demonstrates sustained real-world efficacy, with outcomes driven by baseline characteristics, platinum responsiveness, and preserved EV activity irrespective of prior immunotherapy response.

1 Introduction

For more than two decades, the therapeutic strategy for advanced urothelial carcinoma (aUC) consisted of first-line platinum-based chemotherapy (PBC) and subsequent chemotherapeutic agents with limited efficacy, without exceeding a median overall survival of 12–16 months [1–4]. However, recent therapeutic advances have emerged, offering a

substantially renewed therapeutic landscape for patients with aUC.

Current first-line treatment guidelines [5–7] recommend three therapeutic options: the combination of enfortumab vedotin (EV) and pembrolizumab [8], PBC followed by avelumab as maintenance (AM) treatment in patients without disease progression [9–11], and the combination of cisplatin-based chemotherapy with nivolumab in cisplatin-eligible patients [12]. Presently, PBC followed by AM is the most common first-line treatment strategy for patients with aUC worldwide [13–15]. The clinical outcomes reported in numerous recently published case series [16–22] evaluating

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Key Points

In real-world patients with advanced urothelial carcinoma, the platinum chemotherapy-avelumab maintenance-enfortumab vedotin sequence was associated with sustained clinical efficacy and durable outcomes.

Clinical benefit was influenced by baseline patient characteristics and prior responsiveness to platinum-based chemotherapy, underscoring the importance of patient selection when sequencing therapy.

Enfortumab vedotin retained meaningful efficacy irrespective of prior immunotherapy response, supporting the robustness of this treatment sequence for long-term disease management in routine clinical practice.

this first-line sequence in the real-world population are consistent with the JAVELIN Bladder 100 [9–11]. Therapeutic options of first choice for patients progressing after PBC and programmed cell death protein 1/programmed death-ligand 1 checkpoint inhibitors are enfortumab vedotin (EV) [23] and erdafitinib for patients with fibroblast growth factor receptor 2/3 alterations [24]. Currently, EV monotherapy is the most widely used second-line treatment worldwide after PBC and AM [15]. This treatment scenario has been evaluated in several recent real-world case series [25–27], confirming the clinical results of the EV-301 pivotal trial [23].

Given the clinical and pathological heterogeneity of patients with aUC, which is not well represented in pivotal trials, it is essential to gain a comprehensive real-world perspective of this patient population. The ARON-2^{EV} study (ClinicalTrials.gov identifier NCT05290038) collected worldwide real-world data on patients with aUC receiving EV monotherapy after PBC and immunotherapy (AM or second-line pembrolizumab). The current investigation aimed to characterize the baseline clinical and pathological features and treatment outcomes of patients with aUC included in the international ARON-2^{EV} study, focusing on those who received the therapeutic sequence of PBC-AM-EV.

2 Patients and Methods

2.1 Study Population

The ARON-2^{EV} study population included patients aged ≥ 18 years with a cytological and/or histological confirmed diagnosis of aUC treated with EV between 1 January, 2022 and 30 September, 2025 at 46 institutes in 17 countries worldwide (Fig. S1 of the Electronic Supplementary Material [ESM]). This sub-analysis of the ARON-2^{EV} study

included patients who received the therapeutic sequence consisting of first-line PBC followed by AM and then EV. All patients included in this sub-analysis of the ARON2^{EV} had available data on: age, sex, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), ethnicity, history of smoking, primary tumor location (upper vs lower tract), tumor histology, surgery on primary tumor and/or metastases, previous neoadjuvant or adjuvant chemotherapy, regimen and duration of first-line PBC, best response to first-line PBC, AM and EV, time of metastatic disease (synchronous vs metachronous disease), metastatic sites, and date of last follow-up or death.

The clinical data were extracted retrospectively from the patients' medical records at each participating center. The pathological information was obtained from pathology reports for clinical use. Tumor response to anticancer therapies was assessed by local investigators at each participating institution as part of routine clinical practice, according to the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1). No retrospective central review or re-measurement of imaging studies was performed. Seventy-eight patients were excluded from the analysis because of missing information (31), treatment with ICI in combination (11), targeted therapy (19), or other drugs (17) during the therapeutic sequence.

2.2 Study Endpoints

Objective response was assessed according to RECIST 1.1 as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate was calculated as the sum of CR and PR. Therapy sequence duration (TSD) was calculated from the first dose of PBC until documented disease progression or death from any cause during treatment with EV monotherapy. Overall survival (OS) was calculated from the start of first-line PBC until death from any cause or lost to follow-up. Patients without disease progression or death or lost to follow-up at the time of analysis were censored at the last follow-up visit.

2.3 Statistical Analysis

Patient characteristics were summarized using descriptive statistical methods, including measures of central tendency and dispersion for continuous variables and frequency distributions for categorical variables. The Kaplan–Meier method with Rothman's 95% confidence intervals (CIs) was used to estimate survival curves for OS and TSD. Comparisons between survival curves were performed using the log-rank test. Cox proportional hazards models were adopted to estimate the effects on survival and to estimate hazard ratios (HRs) and 95% CIs. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

MedCalc Version 19.6.4 (MedCalc Software, Mariakerke, Belgium) was used for the statistical analyses.

3 Results

3.1 Patient Population

Two hundred and three patients with aUC who received the therapeutic PBC-AM-EV sequence were included in this sub-analysis of the ARON-2^{EV} study. The median follow-up time was 23.1 months (95% CI 21.1–60.2) and 66 (33%) patients had died at the time of analysis. Median age at PBC initiation was 71 years (range 37–88); 158 (78%) patients were male (Table 1). Pure UC histology was observed in 183 patients (90%). Ninety-eight patients (48%) received cisplatin-based chemotherapy as first-line treatment while 105 (52%) were treated with the carboplatin-based regimen (Table 1). One hundred patients (50%) progressed during EV therapy; of them, 35 (17%) received further therapies (Table 2).

3.2 Survival Outcomes

The median OS from the start of PBC was 31.6 months (95% CI 28.0–36.5), with a 2-year OS rate of 68% (Fig. 1). The analysis of OS across various patient subgroups revealed broadly similar outcomes, regardless of sex, tumor histology, primary tumor location, timing of metastatic disease, or specific metastatic sites. The median OS was not reached, 30.4 months (95% CI 27.3–33.7) and 20.4 months (95% CI 16.1–30.2) in patients with ECOG-PS 0, 1, and 2, respectively ($p = 0.006$, Fig. S2 of the ESM).

Although differences were not statistically significant, patients with metastases limited to distant lymph nodes appeared to experience a longer median OS (32.3 months, 95% CI 28.1–33.7 vs 30.4 months, 95% CI 26.3–40.3, HR 0.63, 95% CI 0.39–1.05, $p = 0.075$). The univariable analysis stratifying patients based on their response to PBC showed a median OS that was not reached in those achieving CR, and 35.7 and 27.6 months (95% CI 29.5–40.3 and 21.1–31.6) in patients with PR and SD, respectively ($p = 0.015$, Fig. S3 of the ESM). In the same univariable framework, a statistically significant difference in OS was observed between patients treated with cisplatin-based versus carboplatin-based chemotherapy (median OS 36.5 vs 28.1 months; HR 0.54, 95% CI 0.33–0.90; $p = 0.018$; Fig. S3 of the ESM).

3.3 Therapy Sequence Duration (TSD)

The median TSD from the start of PBC was 26.5 months (95% CI 23.9–60.2, Fig. 1), with a 2-year TSD rate of 61%.

Table 1 Patient characteristics before platinum-based chemotherapy

Characteristics	203 (%)
Age (years)	
Median	71
Range	(37–88)
Sex	
Male	159 (78)
Female	44 (22)
ECOG Performance Status at platinum baseline	
0–1	179 (88)
≥ 2	24 (12)
Ethnicity	
White	194 (96)
Asian	7 (3)
Hispanic or Latino	2 (1)
Smoking	
Current or former	131 (65)
No	72 (35)
Tumor histology	
Urothelial carcinoma	183 (90)
Squamous cell carcinoma	10 (5)
Other histological variant	10 (5)
Site of primary tumor	
Upper urinary tract	61 (30)
Lower urinary tract	142 (70)
De novo metastatic disease	
Yes	82 (40)
No	121 (60)
Prior surgery on primary tumor	
Yes	114 (56)
No	89 (44)
Metastatic sites	
Lymph nodes (non-regional)	140 (69)
Lung	75 (37)
Liver	37 (18)
Bone	30 (15)
Brain	0 (0)

ECOG Eastern Cooperative Oncology Group

The median TSD was 29.4 months (95% CI 24.0–35.7), 26.1 months (95% CI 23.1–60.2), and 19.7 months (95% CI 16.1–28.3) in patients with ECOG-PS 0, 1, or 2, respectively ($p = 0.019$, Fig. S2 of the ESM).

At univariable analysis, TSD was similar across subgroups defined by sex, histology, tumor location, and timing of metastatic disease, as well as according to metastatic sites including lung, bone, and liver. When stratified by prior response to PBC, median TSD was slightly longer in patients achieving CR than in those with PR or SD, although the differences were not statistically significant (p

Table 2 Previous treatments and response to therapy

Characteristics	203 (%)
Previous neoadjuvant PBC	
Yes	12 (6)
No	191 (94)
Previous adjuvant PBC	
Yes	15 (7)
No	188 (93)
First-line PBC: scheme	
Cisplatin based	98 (48)
Carboplatin based	105 (52)
Best response to first-line PBC	
Complete response	9 (4)
Partial response	125 (62)
Stable disease	69 (34)
Best response to AM	
Complete response	9 (4)
Partial response	42 (21)
Stable disease	69 (34)
Progressive disease	83 (41)
Best response to EV	
Complete response	12 (6)
Partial response	75 (37)
Stable disease	73 (36)
Progressive disease	42 (21)
Subsequent therapy lines after progression to EV	
Paclitaxel	13 (6)
Vinflunine	6 (3)
Clinical trials	6 (3)
Carboplatin + paclitaxel	4 (2)
Docetaxel	2 (1)
Gemcitabine + paclitaxel	2 (1)
Erdafitinib	1 (<1)
Epirubicin	1 (<1)

AM avelumab maintenance, EV enfortumab vedotin, PBC platinum-based chemotherapy

= 0.139). Median TSD was 31.3 months (95% CI 20.0–60.2) in patients achieving CR, 26.1 months (95% CI 23.1–30.2) in those with PR, and 26.3 months (95% CI 18.9–28.0) in patients with SD.

Metastatic spread limited to distant lymph nodes was associated with a significantly longer median TSD (28.1 months, 95% CI 24.6–60.2 vs 24.3 months, 95% CI 21.1–40.3, HR 0.63, 95% CI 0.42–0.94, $p = 0.025$, Fig. S4 of the ESM). Moreover, the difference in terms of median TSD was statistically significant between patients treated with cisplatin-based versus carboplatin-based chemotherapy (28.7 months, 95% CI 24.6–60.2 vs 23.9 months, 95% CI 21.1–28.0, HR 0.56, 95% CI 0.37–0.84, $p = 0.005$, Fig. S4 of the ESM).

3.4 Response to Enfortumab Vedotin

We observed 6% CR, 37% PR, 36% SD, and 21% PD as best response to EV (Table 2). We further stratified the responses to EV by the response to PBC and AM therapy. Figure 2 shows the response to EV in patients who achieved CR or PR with PBC (134 patients, 9 with CR and 125 with PR, 66% of the overall study population), showing that 56% achieved CR/PR/SD with EV, with 10% having primary refractory disease. Figure 3 shows the response to EV obtained in subjects who experienced SD with PBC (69 patients, 34% of the overall study population), showing that 23% achieved CR/PR/SD with EV, with 11% having primary refractory disease.

We further stratified patients based on tumor sites. In patients with lower tract UC, the best response to EV was CR/PR in 49% of patients who achieved CR/PR with PBC, 32% in patients who achieved SD, and 45% in patients who achieved PD as best response to PBC. Rates of primary refractory disease were 16%, 21%, and 20%, respectively, in patients who achieved CR/PR, SD, or PD with PBC. Among patients with upper tract UC, the likelihood of achieving a CR/PR with EV varied according to the best response obtained with prior PBC. Complete response/partial response with EV was observed in 58% of patients who had previously achieved CR/PR with PBC, in 50% of those whose best prior response was SD, and in 27% of those who had experienced PD during PBC. Rates of primary refractory disease to EV were 17%, 13%, and 33% among patients with prior CR/PR, SD, and PD to PBC, respectively.

4 Discussion

The present sub-analysis of the ARON-2EV study provided real-world evidence on outcomes with the sequential strategy of PBC followed by AM and subsequent EV in patients with aUC. The survival outcomes observed in this cohort are consistent with those reported in previous real-world analyses [26–29] and add granularity to how clinical characteristics and early treatment responses shape outcomes across three consecutive therapeutic steps.

A key finding of the present analysis is the persistent prognostic gradient, both in terms of OS and TSD, observed across subgroups defined by metastatic burden, first-line exposure to cisplatin versus carboplatin, and depth of response to PBC. These patterns partially mirror historical observations dating back to the seminal work by Bajorin et al. [30], in which good ECOG PS and the presence of lymph node-only metastases were established as key favorable prognostic factors. Moreover, our findings are in line with literature evidence suggesting that patients eligible for

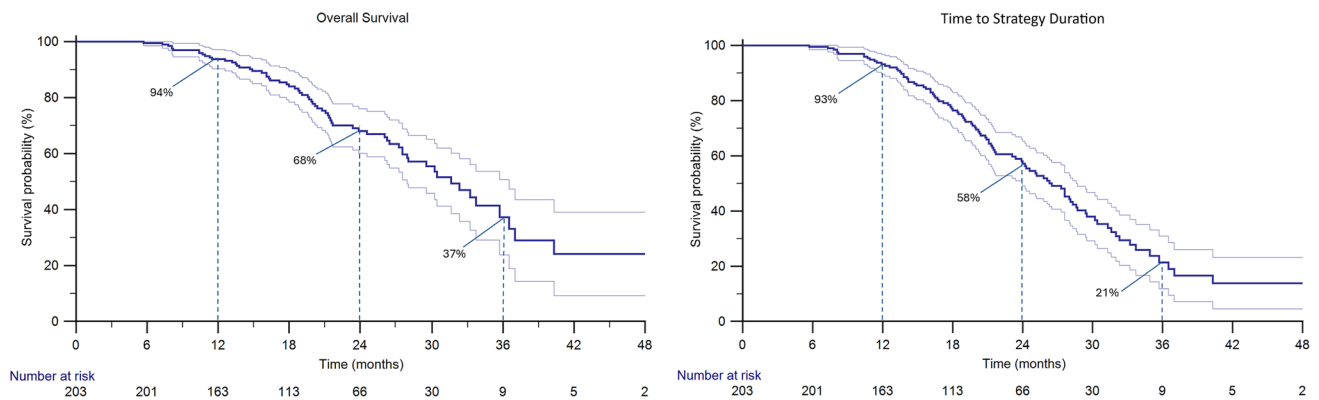


Fig. 1 Overall survival and time to strategy failure in patients receiving platinum-based chemotherapy followed by avelumab and enfortumab vedotin

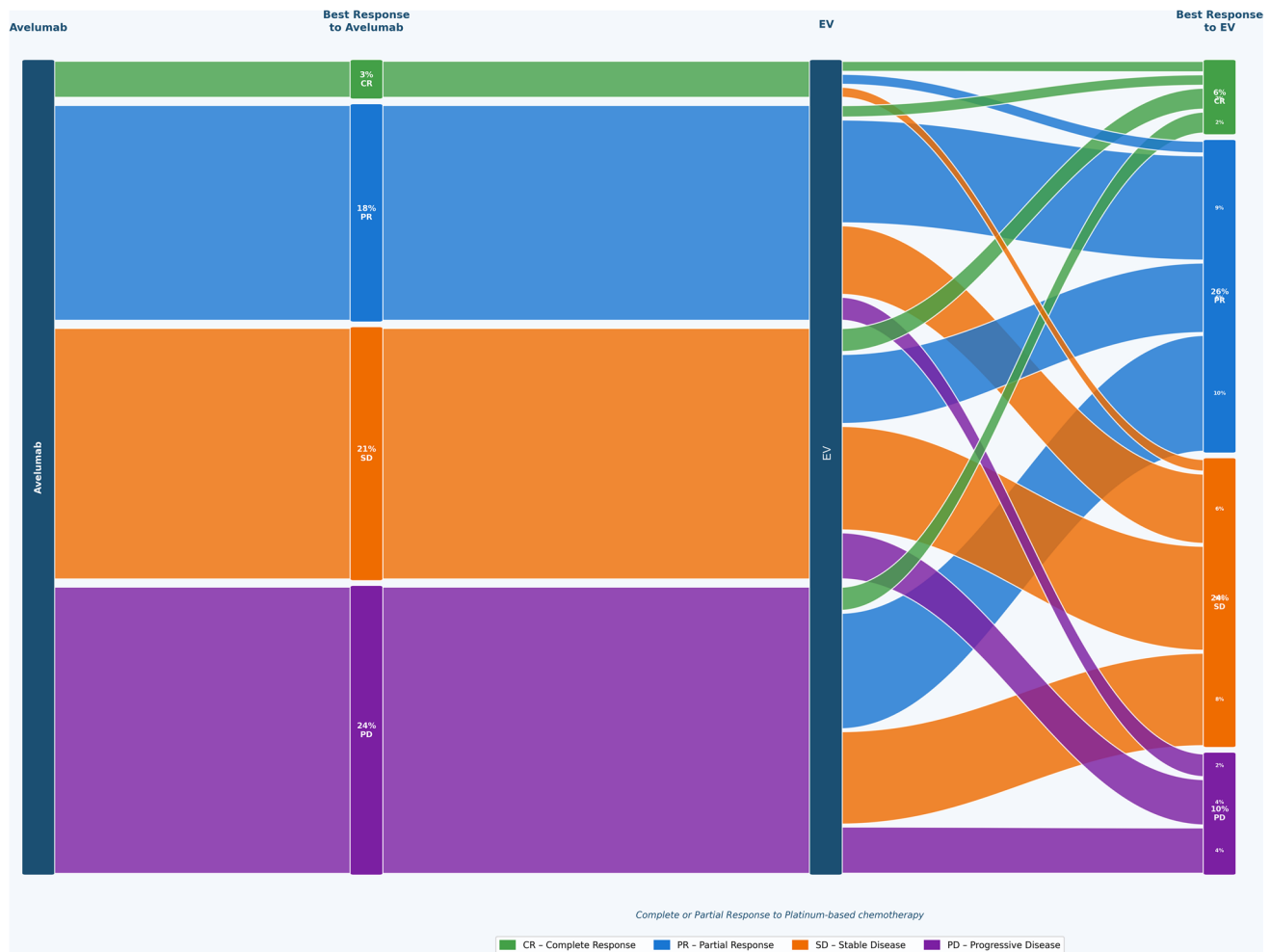


Fig. 2 Sankey diagram illustrating responses to maintenance avelumab and subsequent enfortumab vedotin (EV) in patients who achieved complete response (CR) or partial response (PR) with platinum-based chemotherapy. Percentages refer to the overall study population

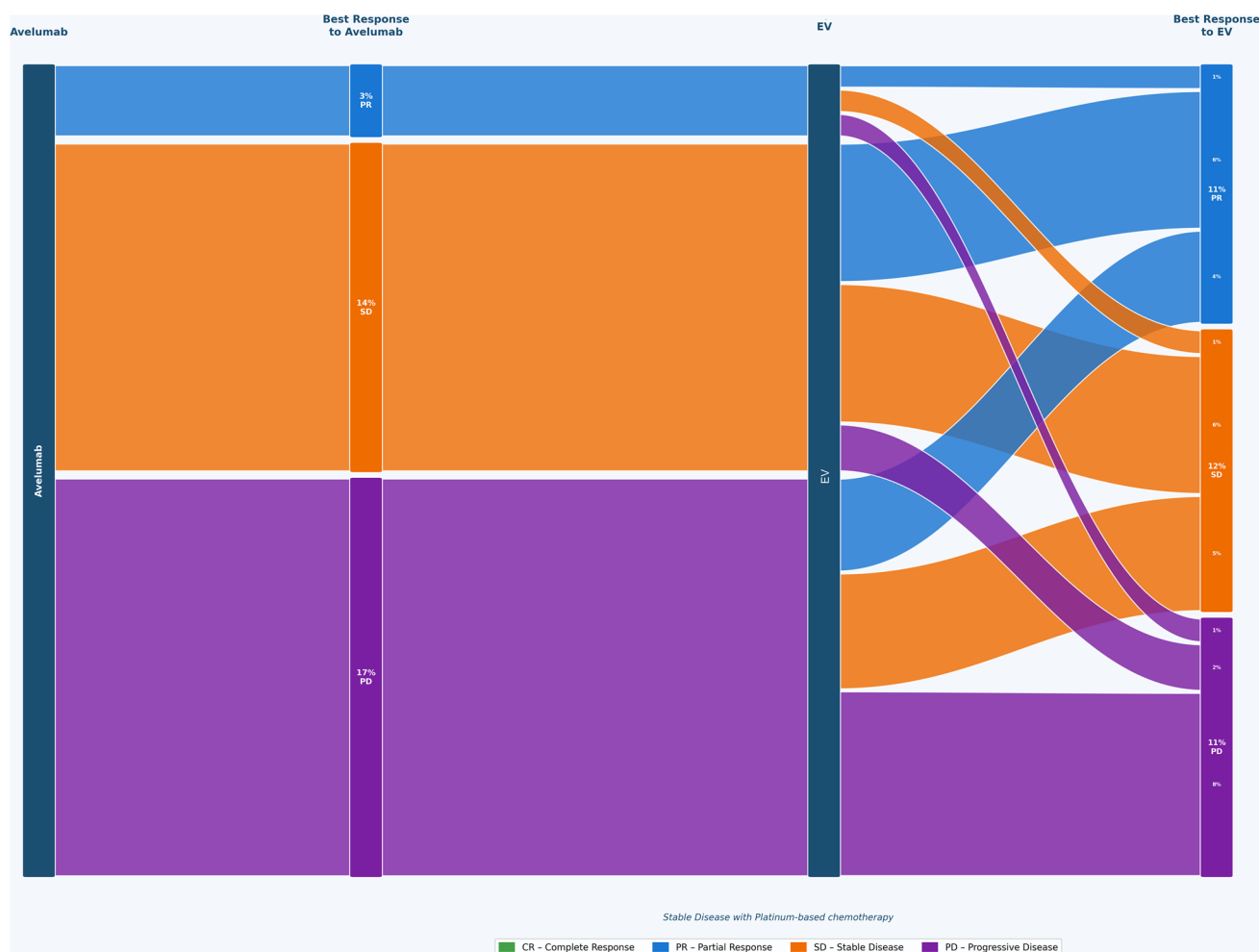


Fig. 3 Sankey diagram illustrating responses to maintenance avelumab and subsequent enfortumab vedotin in patients who achieved stable disease (SD) with platinum-based chemotherapy. Percentages refer to the overall study population

cisplatin, typically reflecting better baseline PS and organ function, tend to exhibit improved outcomes over subsequent therapy lines in aUC [31]. The depth of response to PBC emerged as an additional determinant of downstream outcomes. Patients achieving CR or PR demonstrated longer OS and TSD and a higher probability of benefiting from EV, supporting the hypothesis that platinum chemosensitivity may reflect a more favorable underlying tumor biology, potentially translating into broader therapeutic susceptibility. Conversely, SD with PBC appeared to mark a biologically less sensitive disease, associated with reduced probability of response to EV. Importantly, the key factor may not be how a complete response is achieved, but rather the probability of attaining it, which could depend on disease burden (e.g., nodal-only metastases) and patient-related factors such as PS.

Importantly, only 21% of patients were primarily refractory to EV, slightly lower than previously reported in real-world series evaluating the PBC-pembrolizumab-EV

sequence [26, 29] and similar to that reported in the EV-301 trial [23]. Notably, approximately half of the EV-refractory patients had achieved an objective response to PBC, suggesting that platinum sensitivity does not universally translate into EV sensitivity. Possible biological explanations include heterogeneous or dynamic nectin-4 expression, impaired internalization of the antibody-drug conjugate, alterations in intracellular trafficking of monomethyl auristatin E (MMAE), activation of compensatory signaling pathways, and changes in the tumor microenvironment following prior treatments [32–36].

Although such mechanisms have been described in pre-clinical models and in correlative clinical analyses, the potential contribution of prior platinum exposure to these mechanisms remains plausible but has not been firmly demonstrated. Nevertheless, EV demonstrated consistent activity across nearly all analyzed subgroups, including patients who experienced PD during AM, indicating that immunotherapy failure does not preclude benefit from EV: indeed, as

shown in Fig. 2, responses to EV were observed not only in patients who had achieved CR/PR/SD but also in those with PD as the best response to AM. This finding aligns with the recently reported results from the ARON-2EV cohort treated with the PBC-pembrolizumab-EV sequence, where EV outcomes appeared largely independent of previous immunotherapy responses [26]. Overall, these observations support the robustness of EV activity in later lines and reinforce its role as a key component of sequential treatment strategies.

Our study has several limitations inherent to its retrospective multi-institutional nature and real-world context. Tumor response assessments were performed in routine clinical practice by local investigators rather than through a centralized radiological review, which may introduce variability in the objective response evaluations. Differences across centers in follow-up schedules, imaging frequency, and supportive care may also have influenced outcomes. Moreover, the study lacks biomarker analyses, including nectin-4 expression or genomic profiling, which could further clarify mechanisms underlying sensitivity or resistance to EV. Furthermore, the exclusion of patients with missing data, rather than the application of multiple imputation or other missing data methods, represents a methodological limitation of this study.

The current first-line therapeutic landscape has evolved substantially, and the findings of this study should therefore be interpreted within an appropriately updated context. These results remain applicable primarily to the subset of patients who are still considered candidates for first-line PBC followed by avelumab maintenance, rather than for upfront EV plus pembrolizumab. Notably, this treatment option continues to be included in major international guidelines in selected patients [6, 7].

5 Conclusions

The present analysis underscores the prognostic relevance of initial disease characteristics and platinum responsiveness across the therapeutic continuum and confirms the maintained activity of EV irrespective of prior avelumab response. Although the treatment paradigm is evolving, we believe that the PBC-AM-EV sequence may retain a possible role for selected patients in current clinical practice.

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Declarations

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Ethics approval The study protocol was approved on 28 September, 2023 by the ethical committee of the coordinating center (Marche Region, Italy, no. 2022 39/7875) and by the institutional review boards of the participating centers. The study was conducted in accordance with Good Clinical Practice and the International Ethical Guidelines for Biomedical Research.

Consent to participate Informed consent with a subsequent analysis of the follow-up data was obtained from all participants.

Consent for publication Not applicable.

Availability of data and material The data and materials supporting the findings of this study are available from the last author upon reasonable request.

Code availability Not applicable.

Authors' contributions Conceptualization: MR, SB, EG, MS. Methodology: MR, MS. Formal analysis: MS. Data curation: MS. Writing

(original draft): MR, SB, EG, MS. Writing (review and editing): all authors. Supervision: MR, SB, EG, MS.

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