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ORIGINAL RESEARCH ARTICLE

Enfortumab Vedotin Following Platinum Chemotherapy and Avelumab Maintenance in Patients with Metastatic Urothelial Carcinoma: A Retrospective Data from the ARON-2^{EV} Study

Ondřej Fiala[1,2] · Francesco Massari[3,4] · Umberto Basso[5] · Patrizia Giannatempo[6] · Enrique Grande[7] · Sebastiano Buti[8,9] · Zin W. Myint[10] · Ugo De Giorgi[11] · Renate Pichler[12] · Francesco Grillone[13] · Yüksel Ürün[14] · Fabio Calabrò[15] · Maria T. Bourlon[16,17] · Luca Galli[18] · Ravindran Kanesvaran[19] · Giandomenico Roviello[20] · Jakub Kucharz[21] · Mimma Rizzo[22] · Se Hoon Park[23] · Linda Cerbone[24] · Emmanuel Seront[25] · Carlo Messina[26] · Javier Molina-Cerrillo[27] · Daniele Santini[28] · Akihiro Yano[29] · Lorena Incorvaia[30] · Martina Catalano[19] · Alvaro Pinto[31] · Luigi Formisano[32] · Andrey Soares[33,34] · Gaetano Facchini[35] · Giuseppe Fornarini[36] · Alexandr Poprach[37,38] · Sara Elena Rebuzzi[39,40] · Cecilia Nasso[41] · Gian Paolo Spinelli[42] · Martin Angel[43] · Marco Stellato[6] · Deniz Tural[44] · Gaetano Aurilio[45] · Ilana Epstein[46] · Francesco Carrozza[47] · Fernando Sabino Marques Monteiro[48,49] · Giovanni Benedetti[50] · Tomáš Büchler[51] · Cinzia Ortega[52] · Roubini Zakopoulou[53] · Nicola Battelli[54] · Camillo Porta[55] · Joaquin Bellmunt[56,57] · Shilpa Gupta[58] · Matteo Santoni[54]

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Abstract

Background Enfortumab vedotin (EV) has been approved for the treatment of patients with locally advanced/metastatic urothelial carcinoma (la/mUC) who previously received platinum-based chemotherapy followed by immune checkpoint inhibitors. However, the pivotal clinical trials did not include patients previously treated with avelumab maintenance therapy.

Objective The aim of the present retrospective analysis was to assess the effectiveness of EV following avelumab in patients with mUC enrolled in the ARON-2^{EV} study.

Patients and Methods The study included 182 patients with mUC treated with EV following avelumab maintenance. The primary objective was to assess clinical outcomes, including progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and duration of response (DoR). Statistical analysis involved Fisher exact test, Kaplan–Meier method, log-rank test, and univariate/multivariate Cox proportional hazard regression models.

Results Median OS and PFS were 12.7 (95% CI 10.2–14.1) and 7.9 (95% CI 6.4–9.9) months, respectively. Complete response (CR) was achieved in 5% and partial response (PR) in 34% of patients, with an ORR of 39%. The DoR in patients who achieved CR/PR was 10.9 months (95% CI 8.1–11.4). The incidence of grade ≥ 3 peripheral neuropathy and skin rash was 9%, followed by 8% of grade ≥ 3 diarrhea and 4% of grade ≥ 3 hyperglycemia.

Conclusions The results of our large international retrospective study confirm the effectiveness of EV and endorse its use in the population of patients with mUC treated with EV following the frontline platinum-based chemotherapy and subsequent maintenance treatment with avelumab.

Key Points

The results confirm the effectiveness of enfortumab vedotin in patients with metastatic urothelial carcinoma following frontline chemotherapy and subsequent maintenance treatment with avelumab who were not included in the pivotal clinical trials.

The results confirm the safety profile of enfortumab vedotin.

Ondřej Fiala and Francesco Massari are co-first authors.

Shilpa Gupta and Matteo Santoni are co-senior authors.

Extended author information available on the last page of the article

1 Introduction

Frontline platinum-based chemotherapy has been used to treat patients with locally advanced/metastatic urothelial carcinoma (la/mUC) for decades. Although the treatment scenario is evolving, the most commonly used first-line treatment regimens are currently the combination of gemcitabine with cisplatin or carboplatin and the combination of methotrexate, vinblastine, adriamycin with cisplatin (M-VAC) [1, 2]. Patients without disease progression on platinum-based chemotherapy are candidates for the switch maintenance with avelumab, an immune checkpoint inhibitor (ICI) targeting the programmed cell death protein-ligand-1 (PD-L1) [3]. In the second-line setting, following progression on platinum-based chemotherapy, three ICIs targeting the PD-1/PD-L1 pathway are available, though with geographical differences, including pembrolizumab, nivolumab, and atezolizumab [4–6]. Enfortumab vedotin (EV) is an antibody targeting nectin-4 linked to a microtubule disrupting agent monomethyl auristatin E (MMAE), which has been approved for the treatment of patients with la/mUC who previously received platinum-based chemotherapy followed by PD-1/PD-L1 inhibitors. EV exhibited efficacy in a phase II and phase III clinical trials, which demonstrated significant improvement of both progression-free survival (PFS) and overall survival (OS), with higher response rates as compared with single-agent chemotherapy [3, 7]. However, EV has been approved for patients refractory to previous platinum-based chemotherapy and ICIs [8], it should be noted that the pivotal clinical trials did not include patients previously treated with avelumab maintenance therapy [3, 7]. Recently, the combination of EV plus pembrolizumab has emerged with positive results compared with chemotherapy in a randomized phase III trial, EV-302 [9]. This combination regimen has recently become the preferred first-line treatment for la/mUC. While the combination of EV plus pembrolizumab is beginning to be available in real-world clinical practice, the majority of patients continue to receive platinum-based chemotherapy in the frontline setting, which is still the current standard of care for many patients in many countries. Therefore, the real-world experience with EV after ICI, especially after avelumab, is of great interest.

The aim of the present retrospective analysis was to assess the effectiveness of EV following avelumab in patients with mUC enrolled in the ARON-2^{EV} study.

2 Patients and Methods

2.1 Study Design

We retrospectively analyzed clinical data from mUC patients enrolled in ARON-2^{EV} (NCT05290038), an international multicenter observational study designed to collect data on EV in patients progressing after platinum-based chemotherapy and ICIs. The ARON-2^{EV} involved 50 oncological centers from 15 countries (Table S1). Patients selected for the present analysis were treated with EV after frontline platinum-based chemotherapy and avelumab switch maintenance. The clinical data were collected between 1 January 2022 and 30 April 2024 and were extracted at each participating center from the patients' medical reports. Patients with missing clinical or outcome data were excluded from the analysis. Patients previously treated with adjuvant immunotherapy were not included. EV was administered intravenously as a single agent in the standard approved schedule (1.25 mg/kg given on days 1, 8, and 15 of each 28-day cycle). The treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Physical examination and laboratory tests and computed tomography (CT) scans were performed following standard local procedures.

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 participating centers. The study was conducted according to Good Clinical Practice (GCP) and International Ethical Guidelines for Biomedical Research, and the protocol has been designed with the ethical principles laid out in the Declaration of Helsinki on human experimentation.

2.2 Study Objectives

The primary objective was to assess the outcome of patients with mUC treated with EV following avelumab maintenance. OS was calculated from the initiation of EV therapy until death for any cause. PFS was defined as the time from the EV initiation until progression or death from any cause. The objective response [progressive disease (PD), stable disease (SD), partial response (PR), complete response (CR)] was evaluated using the RECIST version 1.1.; iRECIST were not used for evaluation of response to avelumab [10]. Duration of response (DoR) was defined as the time from first imaging to assess the achievement of CR or PR with EV until disease progression or death from any cause. ORR was calculated as the sum of CR+PR. For the analysis of EV toxicity, only selected grade ≥ 3 adverse events (AEs) were reported, including overall incidence, peripheral neuropathy, skin rash, diarrhea, and hyperglycemia. The grade of AEs was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) [11].

2.3 Statistics

The comparison of PFS and OS between the groups was performed using the Kaplan–Meier method and log-rank test. The median follow-up was calculated with the Kaplan–Meier method. Patients without progression or death at their last follow-up were censored. Hazard ratios (HRs)

were estimated using Cox proportional hazards regression models, 95% confidence intervals (CIs) were calculated for medians and HRs. To identify prognostic factors for PFS and OS, univariate and multivariate Cox proportional hazard regression models were performed. The comparison between subgroups was performed with the Fisher exact test. *p*-values < 0.05 were considered statistically significant. Statistical analyses were conducted using MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

3 Results

3.1 Study Population

A total of 182 patients with mUC treated with EV were studied from the ARON-2^{EV} dataset (Fig. S1). The median follow-up time was 12.0 months (95% CI 5.9–21.6); 125 (69%) patients were dead at the time of analysis. The clinical characteristics of the patients are summarized in Table 1.

Table 1 Baseline clinical characteristics of patients

	Patients ($n = 182$)
Sex, *n* (%)	
Male	141 (77)
Female	41 (23)
Age, years	
Median	70
Range	46–88
ECOG Performance Status, *n* (%)	
0	62 (34)
1	100 (55)
2	20 (11)
Current or former smokers, *n* (%)	120 (66)
Primary tumor location, *n* (%)	
Upper urinary tract	56 (31)
Lower urinary tract	126 (69)
Tumor histology, *n* (%)	
Pure urothelial carcinoma	162 (89)
Variants	20 (11)
Metastatic disease, *n* (%)	
Synchronous	72 (40)
Metachronous	110 (60)
Common sites of metastasis, *n* (%)	
Non-regional lymph nodes	141 (77)
Lung	79 (43)
Liver	57 (31)
Bone	48 (26)
Brain	7 (4)
Response to avelumab maintenance therapy, *n* (%)	
CR/PR	43 (24)
SD	62 (34)
PD	77 (42)

ECOG-PS Eastern Cooperative Oncology Group-Performance Status, *UC* urothelial carcinoma, *CI* confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

3.2 Survival

The median OS in the overall study population was 12.7 months (95% CI 10.2–14.1, Fig. 1). No significant differences were found stratifying patients by sex ($p = 0.759$), age at EV initiation ($p = 0.529$), or body mass index (BMI) ($p = 0.771$), primary tumor localization ($p = 0.245$), histology ($p = 0.120$), response to avelumab maintenance therapy ($p = 0.557$), and metastatic sites. A statistically significant difference in OS was found according to ECOG PS 0 (median OS 14.7 months, 95% CI 13.4–20.1), 1 (11.3 months, 95% CI 9.2–14.1), and 2 (4.8 months, 95% CI 2.4–7.9, $p < 0.001$, Fig. 2). The OS data are summarized in Table 2. The median PFS for EV was 7.9 months (95% CI 6.4–9.9, Fig. 1), with 83 patients (46%) progressing on EV and 99 patients ongoing treatment (54%). The median PFS for avelumab maintenance therapy was 4.0 months (95% CI 3.5–26.1). The median PFS for patients who had reached > 4 months PFS on avelumab (group A) was 10.0 months (95% CI 6.7–11.3) versus 6.3 months (95% CI 5.7–17.7, $p = 0.019$) for those who had reached ≤ 4 months PFS on avelumab (group B) (Fig. 3).

3.3 Univariate and Multivariate Survival Analyses

In the univariate Cox model, ECOG PS (2 versus 0–1) was the only factor significantly associated with OS (HR 4.45, 95% CI 2.77−7.17, $p < 0.001$), while ECOG PS (2 versus 0–1) and duration of avelumab therapy (> 4 versus ≤ 4 months) were significantly associated with PFS [HR 2.38 (95% CI 1.67−3.38), $p < 0.001$ and HR 0.59 (95% CI 0.38−0.92), $p = 0.021$, respectively]. Subsequently, both ECOG PS and duration of avelumab therapy remained significant predictors of PFS in the multivariate Cox regression analyses [2.46 (95% CI 1.71−3.52), $p < 0.001$ and HR 0.56 (95% CI 0.36−0.89), $p = 0.014$, respectively] (Table 3).

3.4 Objective Response

We further analyzed the best objective response to EV, showing 5% CR, 34% PR, 40% SD, and 21% PD, with an ORR of 39%. The median OS was not reached (NR) (95% CI NR–NR) for patients who achieved CR, 15.6

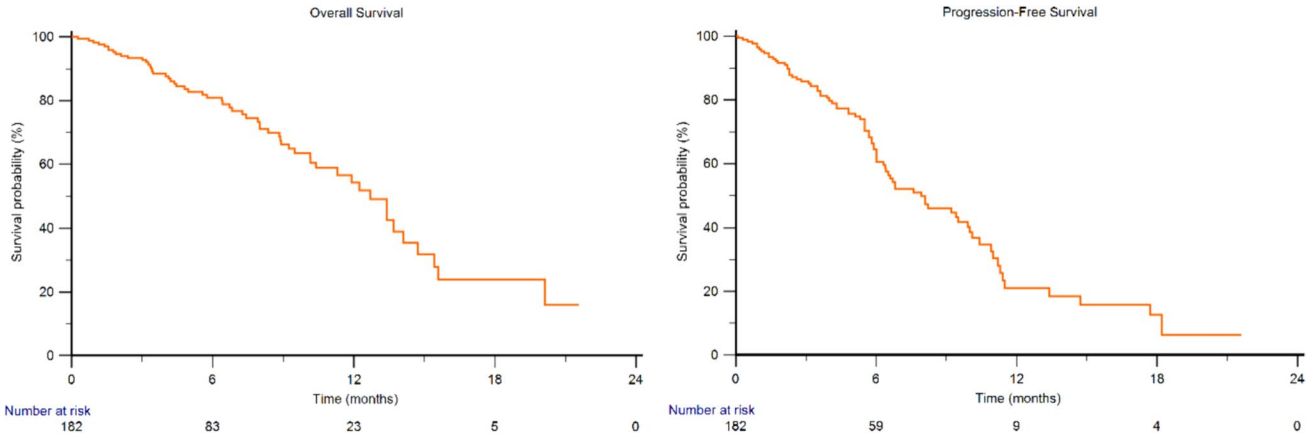

Fig. 1 Overall survival and progression-free survival for patients treated with enfortumab vedotin for metastatic urothelial carcinoma following avelumab maintenance therapy

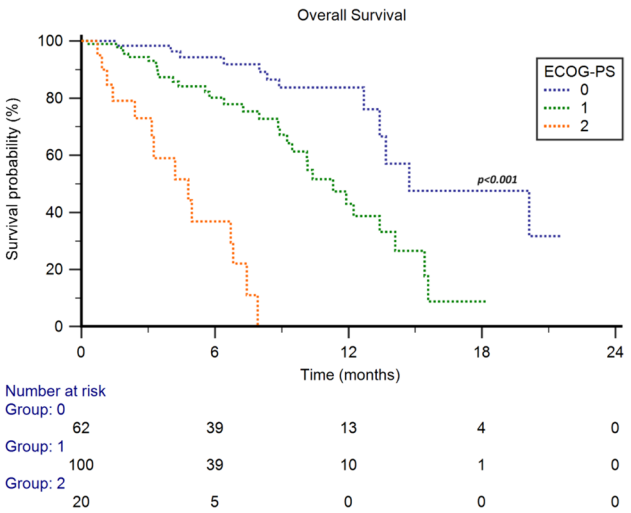

Fig. 2 Overall survival for patients treated with enfortumab vedotin for metastatic urothelial carcinoma following avelumab maintenance therapy stratified by Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

months (95% CI 12.2–20.1) for those who achieved PR, 11.3 months (95% CI 8.9–14.7) for those with SD, and 4.4 months (95% CI 3.4–13.7) for those with PD ($p < 0.001$). Disease patterns for patients who achieved CR are available in Table S2. The DoR in the 70 patients who achieved CR/PR was 10.9 months (95% CI 8.1–11.4). Patients who achieved CR/PR with avelumab maintenance therapy showed 9% CR, 42% PR, 30% SD, and 19% PD with EV; those who achieved SD reported 2% CR, 30% PR, 46% SD, and 22% PD with EV; and those with PD showed 5% CR, 33% PR, 39% SD, and 23% PD (Fig. 4). The ORR were 51%, 32%, and 38%, respectively ($p = 0.020$). Similarly to PFS, we further investigated the objective response to EV obtained in group A versus group B. Group A showed 8% of CR, 32% of PR, 43% of SD, and 17% of PD, while in group B we observed 2% of CR, 35% of PR, 36% of SD, and 27% of PD (ORR 40% versus 37%, $p = 0.771$).

3.5 Safety

A total of 37 patients (30%) experienced grade ≥ 3 AEs. The incidence of grade ≥ 3 peripheral neuropathy and skin rash was 9%, followed by 8% of grade ≥ 3 diarrhea and 4% of grade ≥ 3 hyperglycemia. The incidence of grade ≥ 3 AEs was higher in the group A compared with group B (30% versus 13%, $p = 0.006$).

4 Discussion

Data from the present retrospective study including 182 patients with mUC treated with EV following avelumab maintenance therapy confirm the efficacy of EV and support its use in this patient population. We observed an ORR of 39%, with DoR of 10.9 months. The median PFS and OS were 7.9 and 12.7 months, respectively.

The treatment landscape for la/mUC beyond front-line platinum containing chemotherapy regimens has been rapidly expanding in the recent years. The efficacy and safety of EV have been demonstrated in clinical trials as well as in real-world retrospective studies, and three prospective clinical trials have been of pivotal importance. A phase I trial, EV-101 (NCT02091999), focused on patients with various nectin-4-expressing tumors, including 155 patients with mUC [12, 13]. EV demonstrated impressive ORR of 43% in heavily pretreated patients with mUC, suggesting its high effectiveness. The median OS was 12.3 months. EV-201 (NCT03219333), a phase II non-randomized two-cohort clinical trial, investigated EV in patients with mUC who

Table 2 Subgroup data for overall survival (OS)

	Median OS (95% CI), months	*p*-value
Whole cohort	12.7 (10.2–14.1)	
Gender		
Male	12.7 (10.1–15.4)	$p = 0.759$
Female	11.3 (8.8–14.7)	
Age		
< 70 years	12.7 (8.9–13.7)	$p = 0.529$
≥ 70 years	14.1 (10.1–20.1)	
Body mass index (BMI)		
≥ 25 kg/m^2	12.7 (10.1–13.7)	$p = 0.771$
< 25 kg/m^2	7.4 (10.1–13.7)	
Histology		
Pure UC	12.2 (9.5–14.1)	$p = 0.120$
Other variants	20.1 (10.4–20.1)	
ECOG-PS		
0	14.7 (13.4–20.1)	**$p < 0.001$**
1	11.3 (9.2–14,1)	
2	4.8 (2.4–7.9)	
Primary tumor site		
Bladder UC	12.7 (10.2–13.7)	$p = 0.245$
Upper tract UC	14.7 (9.5–20.1)	
Site of distant metastases		
Lymph node (non-regional)		
Yes	12.7 (10.2–14.7)	$p = 0.788$
No	14.1 (6.8–14.1)	
Bone		
Yes	13.7 (6.7–13.7)	$p = 0.748$
No	12.7 (10.2–14.7)	
Lung		
Yes	12.7 (8.9–15.6)	$p = 0.759$
No	12.2 (10.1–14.1)	
Liver		
Yes	9.2 (7.4–12.2)	$p = 0.188$
No	13.4 (11.9–15.4)	
Respose to avelumab maintenance		
CR/PR	13.7 (11.3–15.4)	$p = 0.557$
SD	13.4 (8.9–14.7)	
PD	10.4 (8.9–14.7)	

ECOG-PS Eastern Cooperative Oncology Group-Performance Status, *UC* urothelial carcinoma, *CI* confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Note: Statistically significant *p*-values are in bold

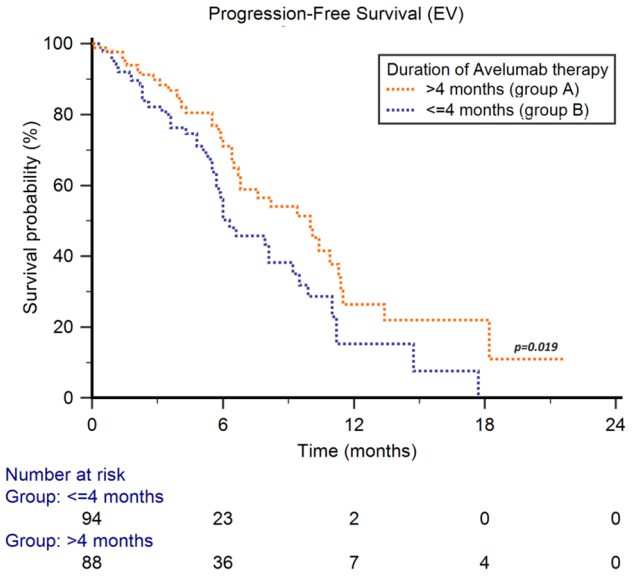

Fig. 3 Progression-free survival (PFS) for enfortumab vedotin according to the median PFS of previous avelumab maintenance therapy

had received prior platinum-based chemotherapy (cohort 1) or those who were platinum-ineligible (cohort 2) and subsequently ICI [7]. EV reached an ORR of 44.0% with a DoR of 7.6 months, and an ORR of 52% was shown in cisplatin-ineligible patients who had received ICI [14]. The positive results led to a subsequent phase III study, EV-301 (NCT03474107). This randomized phase III clinical trial enrolled 608 patients and compared EV with chemotherapy in patients refractory to platinum-based chemotherapy and following ICIs [3, 15]. The median PFS and OS were 5.55 and 12.88 months for patients receiving EV versus 3.71 and 8.97 months for those treated with chemotherapy (PFS: HR 0.62, $p < 0.001$; OS: HR 0.70, $p = 0.00142$). This study proved superiority of EV over standard chemotherapy, leading to its approval for this patient population [8]. Treatment-related grade ≥ 3 AEs occurred in 52.4% of patients in the EV arm. The most common grade ≥ 3 AEs were neutrophil count decrease (6.1%), anemia (2.7%), rash (7.4%), fatigue (6.8%), diarrhea (3.4%), and peripheral neuropathy (5.1%). AEs of special interest (any grade) included 47.3% rash, 48.0% peripheral neuropathy, and 6.8% hyperglycemia. Data from a real-world clinical practice have been reported in four retrospective studies. A large retrospective study on EV administration after ICI has been conducted by Kawahara et al. [16]. They analyzed 6007 patients with mUC treated with pembrolizumab; 563 among them subsequently received EV. The results demonstrated extended OS for patients treated with EV as compared with those treated with chemotherapy (HR 0.71, $p = 0.013$). Of note, this study did not include patients treated with avelumab maintenance prior to EV. The UNITE is a real-world registry-based study focused on patients with la/mUC who received EV. The initial analysis included 260 patients treated with EV and demonstrated an ORR of 52% and median PFS and OS of 6.8 and 14.4 months, respectively [17]. In terms of treatment prior to EV, the majority of patients (67%) had received two or more

Table 3 Univariate and multivariate survival analyses

Overall survival	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex (female versus male)	1.11 (0.58−2.11)	0.760		
Age ≥ 70 years (yes versus no)	0.85 (0.50−1.42)	0.530		
BMI (> 25 versus ≤ 25)	0.93 (0.55−1.56)	0.771		
ECOG-PS 2 versus 0–1	4.45 (2.77−7.17)	**< 0.001**		
Histology (mixed versus pure UC)	0.50 (0.21−1.22)	0.127		
Lower versus upper urinary tract	0.70 (0.39−1.27)	0.237		
Synchronous metastatic disease (yes versus no)	0.94 (0.54−1.62)	0.815		
Distant lymph node (yes versus no)	1.10 (0.55−2.18)	0.789		
Lung metastases (yes versus no)	0.92 (0.54−1.56)	0.760		
Liver metastases (yes versus no)	1.46 (0.83-2.76)	0.191		
Bone metastases (yes versus no)	1.11 (0.59−2.07)	0.749		
Duration of avelumab therapy (> 4 months versus ≤ 4 months)	0.70 (0.41−1.20)	0.191		
Progression-free survival	**Univariate Cox regression**		**Multivariate Cox regression**	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex (female versus male)	1.28 (0.76−2.11)	0.358		
Age ≥ 70 years (yes versus no)	0.99 (0.65−1.54)	0.997		
BMI (> 25 versus ≤ 25)	0.81 (0.53−1.25)	0.346		
ECOG-PS 2 versus 0–1	2.38 (1.67−3.38)	**< 0.001**	2.46 (1.71−3.52)	**< 0.001**
Histology (mixed versus pure UC)	1.07 (0.58−1.99)	0.822		
Lower versus upper urinary tract	0.74 (0.45−1.20)	0.221		
Synchronous metastatic disease (yes versus no)	0.99 (0.63−1.55)	0.964		
Distant lymph node (yes versus no)	0.84 (0.51−1.39)	0.184		
Lung metastases (yes versus no)	0.96 (0.62−1.48)	0.847		
Liver metastases (yes versus no)	1.25 (0.79-1.98)	0.343		
Bone metastases (yes versus no)	1.17 (0.70−1.96)	0.555		
Duration of avelumab therapy (> 4 months versus ≤ 4 months)	0.59 (0.38−0.92)	**0.021**	0.56 (0.36−0.89)	**0.014**

BMI body mass index, *ECOG-PS* Eastern Cooperative Oncology Group-Performance Status, *UC* urothelial carcinoma, *HR* hazard ratio, *CI* confidence interval

Note: Statistically significant *p*-values are in bold

lines of systemic therapy, including 128 (49.2%) patients who had been previously treated with platinum-based chemotherapy and ICI. In the UNITE study, prior ICI therapy was not specified and the outcomes according to the previous systemic therapy were not assessed in the initial analysis. Outcomes of 49 patients who received EV after avelumab maintenance were recently reported and showed an ORR of 54% and median PFS and OS of 7.0 and 13.3 months, respectively [18]. Another retrospective study exploring the efficacy of EV has been conducted by Fukuokaya et al. [19]. This study including 103 patients reported an ORR of 50.5%, median PFS and OS were 6.0 and 14.5 months, respectively. Regarding the treatment prior to EV, 79.0% of patients had received pembrolizumab and only 21% had been treated with avelumab. The outcomes according to the type of ICI prior to EV were not reported in detail. A retrospective analysis aiming to compare the efficacy of EV according to the prior treatment with avelumab or pembrolizumab in a cohort of 100 patients with mUC has recently been reported by Hirasawa et al. [20]. The study observed an ORR of 66.6% in EV after avelumab versus 46.8% in EV after pembrolizumab groups, respectively ($p = 0.14$). The median PFS and OS for EV following avelumab versus pembrolizumab were 10.4 versus 5.2 months ($p = 0.039$) and NR versus 14.7 months ($p = 0.17$), respectively. Thus, the results suggested superior PFS for patients treated with EV after avelumab, while OS showed no significant difference between the two groups. The analysis of subsequent treatment after avelumab from an ambispective study, AVENANCE, has been reported by Barthelemy et al. Their results confirm the effectiveness

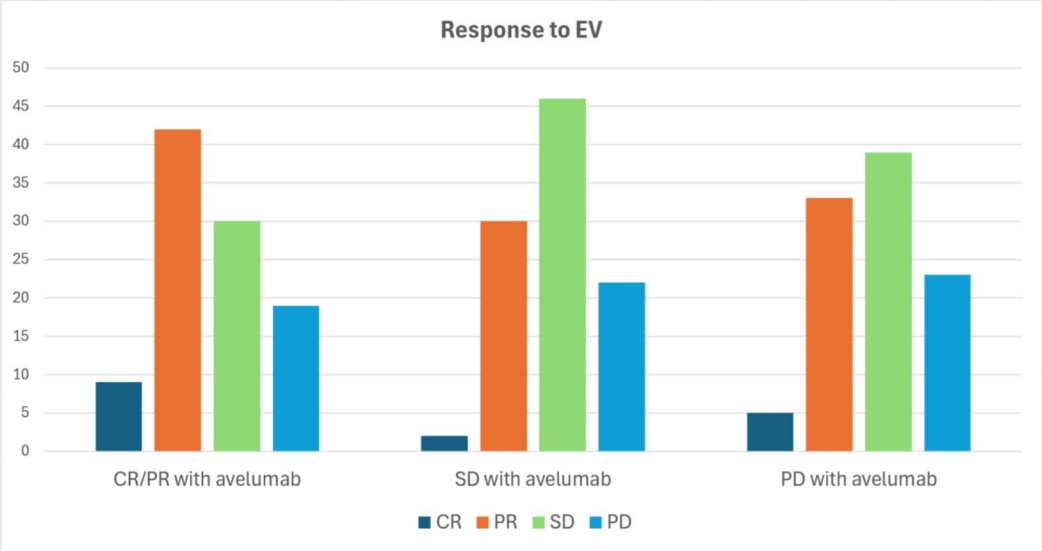

Fig. 4 Objective response to enfortumab vedotin (EV) according to the objective response to avelumab maintenance therapy prior to EV. *EV* enfortumab vedotin, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

of avelumab maintenance and showed encouraging OS in a cohort of 52 patients receiving EV following avelumab. Median OS from the initiation of avelumab was 31.3 months for the subsequent EV cohort, while the survival for EV separately was not shown [21].

Data on outcomes with EV in patients treated with frontline platinum-based chemotherapy followed by avelumab switch maintenance prior to EV are very limited due to the fact that those were not included in the prospective clinical trials, and the three retrospective studies to date included only small numbers of patients. Compared with the survival data from the EV-301 phase III trial, we observed slightly shorter PFS and similar OS, despite the different patient population with respect to the prior ICI treatment strategy [3, 15]. The results of Cox multivariate survival analyses in our study revealed inferior PFS for patients with ECOG PS 2 and those with duration of previous avelumab therapy $\leq$ 4 months, which is in line with data reported by Nizam et al. [18]. We found that patients who had achieved CR or PR with avelumab had significantly higher ORR compared with those with SD or PD with avelumab. However, such an effect was not seen for OS, suggesting that EV appears to have a survival benefit regardless of prior response to avelumab. Regarding toxicity, in comparison with EV 301 trial, we observed lower overall incidence of grade $\geq$ 3 AEs (30% versus 52.4%), while we found higher rate of grade $\geq$ 3 diarrhea (8% versus 3.4%), skin rash (9% versus 7.4%), and peripheral neuropathy (9% versus 5.1%) [3].

The role of predictive biomarkers in the frame of personalized oncology has been developing. The potential predictive role of several easily accessible biomarkers derived from peripheral blood has been of interest also in patients with mUC treated with EV. Uchimoto et al. have recently reported that C-reactive protein–albumin ratio predicts ORR to EV [22]. In our study, we focused strictly on basic clinical aspects of the treatment with EV following avelumab maintenance in patients with mUC. However, to find effective and easily accessible predictive and prognostic biomarkers for EV is an important issue in the current research.

Major limitations of the present study include retrospective design, lack of a central radiology review board, lack of detailed data on premature discontinuation of treatment, and relatively limited sample size. Furthermore, the evaluation of safety profile was limited due to the retrospective design and only selected grade $\geq$ 3 AEs were taken into account. Nevertheless, our study included the largest cohort of patients with mUC treated with platinum-based chemotherapy following avelumab maintenance prior to EV. In addition, our study included patients from various countries and represents a truly global patient dataset.

5 Conclusions

The results of our large international retrospective study confirm the effectiveness of EV and endorse its use in the population of patients with mUC treated with EV following the frontline platinum-based chemotherapy and subsequent maintenance treatment with avelumab.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-024-01099-0.

Declarations

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Conflicts of Interest Ondřej Fiala received honoraria from Roche, Janssen, GSK, and Pfizer for consultations and lectures unrelated to this project. Francesco Massari has received research support and/or honoraria from Advanced Accelerator Applications, Astellas, Astra Zeneca, Bayer, BMS, Janssen, Ipsen, MSD, and Pfizer outside the submitted work. Umberto Basso received honoraria for Bristol-Myers Squibb, Novartis, and Astra Zeneca; research funding from Ipsen; and travel grants from Bristol-Myers Squibb, Janssen Oncology, Astellas Pharma, MSD Oncology, Merck/Pfizer, and Bayer, all unrelated to this project. Sebastiano Buti received honoraria as speaker at scientific events and advisory role by BMS, Pfizer, MSD, Ipsen, Roche, Eli Lilly, AstraZeneca, Pierre-Fabre, Novartis, Merck, Gentili, and Astellas, all unrelated to the present paper. Yüksel Ürün has served on advisory board for Abdi-İbrahim, Astellas, AstraZeneca, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen ilaç, Gilead, GSK, Janssen, Merck, MSD, Novartis, Pfizer, and Roche and received travel grants, honoraria, or consultation fees from Abdi-İbrahim, Astellas, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen İlaç, Gilead, GSK, Janssen, Merck, Novartis, Pfizer, and Roche, all unrelated to the present paper. Maria T. Bourlon is a consultant of Bristol Myers Squibb, Merck, MSD, Gilead, Astellas, and Asofarma and a speaker for Janssen Pharmaceuticasl, MSD, Merck, and Astellas, all unrelated to the present paper. Mimma Rizzo has received honoraria as a speaker/consultant by MSD, Merck Serono, Astrazeneca, Bristol Myers Squibb, Eisai, and Gilead, all unrelated to the present paper. Linda Cerbone has received honoraria for advisory boards, speaker engagements, and scientific consultancy for educational purposes from AstraZeneca, EISAI, MSD, Ipsen, BMS, and A.A.A.; and is a past MSD employee in Medical Affairs. Javier Molina-Cerrillo reports research funding from Roche, Ipsen, Pfizer, and Janssen; travel support from Pfizer, Janssen, Ipsen, and BMS; and a consulting or advisory role with Ipsen, Roche, BMS, Pfizer, Sanofi, Janssen, Astellas, Eisai, Adium, and MSD, all unrelated to the present paper. Álvaro Pinto is a member of advisory boards of Pfizer, Novartis, Ipsen, BMS, Janssen, Astellas, Sanofi, Bayer, Clovis, Roche, MSD, Pierre Fabre, and Merck; has received research support from Pfizer and BMS; clinical trial payments from Pfizer, Bayer, Janssen, MSD, Clovis, Pharmacyclics, BMS, Sanofi, Astra Zeneca, Roche, Eisai, and Aveo; and travel arrangements from Janssen, Roche, Pfizer, BMS, and Ipsen, all unrelated to the present paper. Andrey Soares reports honoraria from Janssen, Pfizer, Bayer, AstraZeneca, Astellas Pharma, Merck Serono, Sanofi, Ipsen, and Adium; consulting or advisory role from Astellas Pharma, Janssen, Roche, Bayer, AstraZeneca, MSD, Bristol-Myers Squibb, Adium, Ipsen, Pfizer, and Novartis; research funding from Bristol-Myers Squibb (Inst), Astellas (Inst), and AstraZeneca (Inst); travel, accommodations, and expenses from Bayer, Janssen, Ipsen, Adium, MSD, and Merck Serono; and ownership in BIO, Brazilian Information Oncology; all unrelated to this study. Alexandr Poprach has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from BMS, Ipsen, Roche, Astellas, Merck, Eisai, MSD, Novartis, and Pfizer, unrelated to this project. Gian Paolo Spinelli has received payment or honoraria for advidory boards from Novartis, Roche, and Bayer, unrelated to this project. 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Tomáš Büchler and Camillo Porta were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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, Study Protocol "ARON 2 Study" NCT05290038) and by the Institutional Review Boards of participating centers.

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

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated and/or analyzed during the current study are not publicly available due to patient data security but are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Author Contributions Study concept and design: all authors; acquisition of data: all authors; analysis and interpretation of data: all authors; drafting of the manuscript: Fiala, Massari, Gupta, and Santoni; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: Santoni; obtaining funding: none; administrative, technical, or material support: none; and supervision: Gupta and Santoni.

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Authors and Affiliations

Ondřej Fiala[1,2] · Francesco Massari[3,4] · Umberto Basso[5] · Patrizia Giannatempo[6] · Enrique Grande[7] · Sebastiano Buti[8,9] · Zin W. Myint[10] · Ugo De Giorgi[11] · Renate Pichler[12] · Francesco Grillone[13] · Yüksel Ürün[14] · Fabio Calabrò[15] · Maria T. Bourlon[16,17] · Luca Galli[18] · Ravindran Kanesvaran[19] · Giandomenico Roviello[20] · Jakub Kucharz[21] · Mimma Rizzo[22] · Se Hoon Park[23] · Linda Cerbone[24] · Emmanuel Seront[25] · Carlo Messina[26] · Javier Molina-Cerrillo[27] · Daniele Santini[28] · Akihiro Yano[29] · Lorena Incorvaia[30] · Martina Catalano[19] · Alvaro Pinto[31] · Luigi Formisano[32] · Andrey Soares[33,34] · Gaetano Facchini[35] · Giuseppe Fornarini[36] · Alexandr Poprach[37,38] · Sara Elena Rebuzzi[39,40] · Cecilia Nasso[41] · Gian Paolo Spinelli[42] · Martin Angel[43] · Marco Stellato[6] · Deniz Tural[44] · Gaetano Aurilio[45] · Ilana Epstein[46] · Francesco Carrozza[47] · Fernando Sabino Marques Monteiro[48,49] · Giovanni Benedetti[50] · Tomáš Büchler[51] · Cinzia Ortega[52] · Roubini Zakopoulou[53] · Nicola Battelli[54] · Camillo Porta[55] · Joaquin Bellmunt[56,57] · Shilpa Gupta[58] · Matteo Santoni[54]

✉ Ondřej Fiala
fialao@fnplzen.cz

[1] Department of Oncology and Radiotherapeutics, Faculty of Medicine, University Hospital in Pilsen, Charles University, alej Svobody 80, 30460 Pilsen, Czech Republic

[2] Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic

[3] Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[4] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

[5] Medical Oncology 1 Unit, Department of Oncology, Istituto Oncologico Veneto IOV IRCCS, 35128 Padova, Italy

[6] Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian 1, Milan, Italy

[7] Department of Medical Oncology, MD Anderson Cancer Center Madrid, Madrid, Spain

[8] Department of Medicine and Surgery, University of Parma, Parma, Italy

[9] Medical Oncology Unit, University Hospital of Parma, Parma, Italy

[10] Division of Medical Oncology, Department of Internal Medicine, Markey Cancer Center, University of Kentucky, Lexington, KY, USA

[11] Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

[12] Department of Urology, Medical University of Innsbruck, Innsbruck, Austria

[13] Unità Operativa di Oncologia Presidio Pugliese-Ciaccio Azienda Ospedaliera Universitaria Renato Dulbecco, Catanzaro, Italy

[14] Department of Medical Oncology, Faculty of Medicine, Ankara University, Ankara, Turkey

[15] Medical Oncology, 1-IRCCS Regina Elena National Cancer Institute, Rome, Italy

[16] Department of Hemato-Oncology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

[17] Escuela de Medicina, Universidad Panamericana, Mexico City, Mexico

[18] Medical Oncology Unit 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

[19] Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

[20] Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Viale Pieraccini, 6, Florence, Italy

[21] Department of Uro-Oncology, Maria Sklodowska-Curie National Research Institute of Oncology Warsaw, Warsaw, Poland

[22] Medical Oncology Unit, Azienda Ospedaliera Universitaria Consorziale Policlinico di Bari, Bari, Italy

[23] Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[24] Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy

[25] Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

[26] Oncology Unit, A.R.N.A.S. Civico, Palermo, Italy

[27] Department of Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain

[28] Oncologia, Dip, Scienze e Biotecnologie Medico-chirurgiche, Policlinico Umberto 1, Rome, Italy

[29] Department of Urology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

[30] Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.), Section of Medical Oncology, University of Palermo, Palermo, Italy

[31] Servicio de Oncología, Hospital Universitario La Paz, Madrid, Spain

[32] Department of Medicine and Surgery, Federico II University, Naples, Italy

[33] Hospital Israelita Albert Einstein, São Paulo, SP, Brazil

[34] Centro Paulista de Oncologia/Oncoclínicas, São Paulo, SP, Brazil

[35] Oncology Unit, "S. Maria Delle Grazie" Hospital, ASL NA2 NORD, Pozzuoli, Naples, Italy

[36] IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[37] Masaryk Memorial Cancer Institute, Brno, Czech Republic

[38] Faculty of Medicine, Masaryk University, Brno, Czech Republic

[39] Medical Oncology Unit, Ospedale San Paolo, Savona, Italy

[40] Department of Internal Medicine and Medical Specialties (Di.M.I.), University of Genoa, Genoa, Italy

[41] Medical Oncology, Ospedale Santa Corona, Pietra Ligure, Italy

[42] UOC Oncologia Territoriale Ausl Latina, Aprilia, Italy

[43] Clinical Oncology, Genitourinary Oncology Unit, Alexander Fleming Institute, Buenos Aires, Argentina

[44] Department of Medical Oncology, Bakirköy Dr. SadiKonuk Training and Research Hospital, Tevfik, Bakirkoy, Istanbul, Turkey

[45] Division of Cancer Prevention and Genetics, IEO European Institute of Oncology IRCCS, Milan, Italy

[46] Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[47] Oncology Unit, Department of Oncology and Hematology, Santa Maria delle Croci Hospital, AUSL Romagna, Ravenna, Italy

[48] Hospital Sírio-Libanês, Brasília, DF, Brazil

[49] Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Brazil

[50] U.O. Oncologia, Ospedale di Civitanova Marche, Civitanova Marche, Italy

[51] Department of Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

[52] Dipartimento di Oncologia, Ospedale San Lazzaro, Azienda sanitaria locale CN2, Alba, Cuneo, Italy

[53] 2nd Propaedeutic Department of Internal Medicine, School of Medicine, ATTIKON University Hospital, National and Kapodistrian University of Athens, Athens, Greece

[54] Medical Oncology Unit, Macerata Hospital, Macerata, Italy

[55] Interdisciplinary Department of Medicina, Division of Medical Oncology, University of Bari "Aldo Moro", A.O.U. Consorziale Policlinico di Bari, Bari, Italy

[56] Harvard Medical School, Boston, MA, USA

[57] Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[58] Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA