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Enfortumab vedotin in ECOG-PS 2 advanced urothelial carcinoma patients: a real-world study from the ARON-2^{EV} project

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Abstract

Background Enfortumab vedotin (EV) is approved for the treatment of metastatic urothelial carcinoma (mUC), as monotherapy or in combination with immune checkpoint inhibitors (ICIs), following the results of recent practice-changing clinical trials, such as EV-301 and EV-302. However, EV-301 included only patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0 or 1, while ECOG-PS 2 mUC patients were excluded.

Objective In clinical settings, the benefit of EV for this group of vulnerable patients remains a significant and yet unresolved question. The aim of our study was to evaluate the impact of ECOG-PS on survival outcomes in patients treated with EV using the ARON global real-world database.

Patients and methods A total of 483 mUC patients with ECOG-PS 0–1 and 85 with ECOG-PS 2 and treated with EV were included. The coprimary endpoints were Overall Survival (OS) and Progression-Free Survival (PFS) to compare the clinical outcomes of mUC patients with ECOG-PS 2 versus ECOG-PS 0 or 1. The secondary endpoints included the comparison of OS and PFS in these two patient groups according to metastatic sites (liver, bone, lung, lymph nodes, brain, soft tissue).

Results The median OS was 13.63 months (95% CI 11.9-15.57) and 6.34 months (95% CI 4.96–8.48) in mUC patients with ECOG-PS 0–1 and ECOG-PS 2, respectively. Patients with ECOG-PS 2 receiving EV reported statistically significantly shorter OS compared to those with ECOG-PS 0–1 (HR 2.24; 95% CI 1.64–3.06; $p < 0.001$). The median PFS was 7.39 months (95% CI 6.60–8.04) and 3.98 months (95% CI 3.21–5.95) in mUC patients with ECOG-PS 0–1 and ECOG-PS 2, respectively. Patients with ECOG-PS 2 receiving EV reported statistically significantly shorter PFS compared

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to those with ECOG-PS 0–1 (HR 1.71; 95% CI 1.29–2.27; $p < 0.001$). Similarly, shorter OS and PFS was observed in ECOG-PS 2 patients with liver, bone, lung, and lymph nodes metastases, while shorter PFS was associated with lymph nodes and bone metastases.

Conclusions Our analysis showed worse survival outcomes in pretreated mUC with ECOG-PS 2 receiving EV monotherapy; however, given the retrospective design and baseline imbalances between ECOG groups, these findings should not be interpreted as evidence of reduced intrinsic EV efficacy. The outcomes of EV monotherapy in ECOG-PS 2 patients remains uncertain and can only be inferred from non-randomized prospective trials and studies based on real-world evidence. Further studies and multicentric translational collaborations are fundamental to validate these findings.

Highlights

- Our analysis highlighted shorter OS and PFS in pretreated mUC patients with ECOG-PS 2.
- The poorer outcomes observed in ECOG-PS 2 patients may reflect both adverse baseline prognosis and residual confounding, rather than reduced EV efficacy.
- Further studies and multicentric translational collaborations are fundamental to validate these findings.

Keywords Urothelial cancer, Enfortumab vedotin, ECOG-PS, Bladder cancer, Antibody-drug conjugates, Performance status

Introduction

In recent years, the treatment landscape for metastatic urothelial carcinoma (mUC) has significantly evolved, following the development of novel anticancer treatments, such as immunotherapeutics, antibody-drug conjugates (ADCs), and targeted therapies – as monotherapy or as part of combinatorial strategies [1]. Enfortumab vedotin (EV) is an ADC composed of a monoclonal antibody targeting Nectin-4, a cell adhesion molecule highly expressed in urothelial carcinoma, linked to monomethyl auristatin E (MMAE) [2, 3]. The practice-changing phase 3 EV-301 compared EV with standard-of-care chemotherapy (docetaxel, paclitaxel, or vinflunine) in patients with mUC who had progressed after platinum-based chemotherapy and immunotherapy. EV demonstrated a significant survival benefit, with a median Overall Survival (OS) of 12.9 months compared to 8.9 months in the chemotherapy group (HR 0.70 (95% CI 0.58–0.85), $p = 0.00015$) [4, 5]. However, this analysis did not include patients with poor performance status – such as Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 2, leaving a critical gap in knowledge regarding the efficacy of EV in this subgroup [6]. Of note, a significant percentage of patients in poor clinical conditions receive EV in real-world clinical practice, even though there is limited evidence regarding the effectiveness of this new treatment approach for mUC patients with ECOG PS 2 [7]. At the same time, while the ECOG-PS is commonly used, a considerable heterogeneity has traditionally been observed, something that highlights the subjectivity and variability in measuring PS as evaluated by the ECOG scale [8].

The aim of our study was to evaluate the impact of ECOG-PS on survival outcomes in patients treated with EV according to the ARON global real-world retrospective database. This analysis aims to fill a critical gap in knowledge by evaluating the impact of ECOG-PS on outcomes with EV in patients with mUC and ECOG-PS 2.

Patients and methods

Study Population

We retrospectively analyzed clinical data from mUC patients enrolled in ARON-2EV (Clinical Trial Number: NCT05290038), an international multicenter observational study aimed at evaluating data on EV in patients with mUC who had previously progressed on platinum-based chemotherapy and anti-PD-1/PD-L1 inhibitor. Because prior ICI exposure included maintenance avelumab after first-line platinum-based chemotherapy or a later-line PD-1/PD-L1 inhibitors, the exact numerical treatment line of EV could not be assigned uniformly across the cohort. The ARON-2EV involved 56 oncological centers from 15 countries. The clinical data were collected between 1 January 2022 and 30 April 2024 and were extracted at each participating center. Patients with missing outcome data were excluded from the analysis. EV was administered intravenously as a single agent in the standard approved schedule, and EV therapy 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.

Study endpoints

The coprimary endpoints were OS and Progression-Free Survival (PFS) in order to compare the clinical outcomes of mUC patients with ECOG-PS 2 versus ECOG-PS 0 or 1. The secondary endpoints included the comparison of OS and PFS in these two patient groups according to metastatic sites (liver, bone, lung, lymph nodes, brain, soft tissue).

OS was calculated from the start of EV treatment to death from any cause. Patients alive or lost at follow-up at the time of the analysis were censored at the last follow-up visit. PFS was calculated from the first administration of EV to documented disease progression or death from any cause, whichever occurred first. Patients without disease progression or death or lost at follow-up at the time of the analysis were censored at the last follow-up visit. Radiologic assessments were performed according to local practice. Progression was assessed by local investigators using RECIST criteria and recorded in the study database. In absence of blinded independent central review and harmonized assessment intervals across centers, PFS should be interpreted as investigator-assessed PFS based on local RECIST assessments.

Statistical analysis

The Kaplan–Meier method with Rothman's 95% confidence intervals (CI) was used to estimate survival curves of OS and PFS. Comparisons between survival curves were performed using the log-rank test. An initial univariable Cox model including ECOG-PS only was fitted, and hazard ratios (HRs) with 95% confidence intervals (CIs) were provided. A prespecified multivariable Cox proportional hazard model was subsequently constructed in the overall cohort to quantify the independent association between ECOG-PS (2 vs. 0–1) and OS or PFS. Adjustment was performed a priori for sex, age, bone metastases, liver metastases, tumour histology. The proportional hazards assumption was examined using Schoenfeld residuals. When evidence of PH violation was observed, a sensitivity analysis was performed by refitting the Cox model, with a time-varying coefficient for ECOG-PS. As a sensitivity analysis, the same multivariable Cox proportional hazards model was repeated after additional adjustment for prior immune checkpoint inhibitors (ICIs: avelumab, pembrolizumab, atezolizumab/nivolumab). To explore prognostic factors in ECOG-PS 2 patients, univariable and multivariable Cox models for OS and PFS were fitted. The prespecified variables included age, tumor histology, primary tumor site, liver and bone metastases. Given the non-randomized observational design and the expected prognostic differences between ECOG-PS group, adjusted analyses were intended to estimate the independent association between ECOG-PS and outcomes, rather than to infer differential causal efficacy of EV across performance-status categories. Baseline characteristics were summarized using all available data for each variable. Missing data were handled using a complete-case approach for univariable and multivariable regression analyses; no imputation was performed. Safety data were abstracted from medical charts and institutional records. Safety analyses focused on pre-specified EV-related toxicities of interest (cutaneous toxicity, peripheral neuropathy, diarrhea, and diabetes/hyperglycemia). Adverse events (AEs) were collected retrospectively and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. We summarized (i) the proportion of patients experiencing at least one grade 3–4 (G3-4) event among these prespecified toxicities (≥ 1 G3-4 prespecified toxicity) and (ii) toxicity-specific G3-4 rates. Patients could experience more than one prespecified toxicity. Treatment modifications during EV were collected. Any dose reduction after treatment initiation and ≥ 1 skipped administration due to toxicity were recorded. The starting dose for the first administration was classified as standard or reduced. Prespecified key safety endpoints were: (i) ≥ 1 G3-4 prespecified toxicity, (ii) any subsequent dose reduction after EV initiation, and (iii) ≥ 1 skipped EV administration due to toxicity. Comparisons between ECOG-PS groups, and prespecified key safety endpoints, were performed using the χ^2 test or Fisher exact test for categorical variables, as appropriate. The level of significance was set to 0.05. R studio software (version 4.5.1 RStudio, PBC: Boston, MA, USA) was used for the statistical analyses.

Results

Patient population

A total of 575 patients were registered across participating centers; 568 patients were included in the present analysis after exclusion of 7 patients with missing outcome data. Supplementary Table S1 shows the distribution of registred patients by participating center. A total of 483 mUC patients with ECOG-PS 0–1 and 85 with ECOG-PS 2 and treated with EV were included from the ARON-2EV dataset. The median follow-up was 10.3 months (95% CI 9.66–11.3). The clinical characteristics of the patients are summarized in Table 1. Compared with patients with ECOG 0–1, those with ECOG-PS 2 more frequently presented with adverse baseline features, including liver, bone, and brain metastases, suggesting a poorer baseline prognostic profile.

Table 1 Comparison of baseline characteristics between patients with ECOG-PS 0–1 and ECOG-PS 2

Baseline characteristics		**ECOG-PS 0–1**	**ECOG-PS 2**	***p*-value**
	N	***N* = 483**	***N* = 85**	
Tumor histology, n (%)	558			
Pure urothelial carcinoma		376 (79%)	61 (74%)	0.350
Variants		100 (21%)	21 (26%)	
Missing		7	3	
Primary tumor location, n (%)	568			
Lower urinary tract		346 (72%)	65 (76%)	0.358
Upper urinary tract		137 (28%)	20 (24%)	
Age, years	567			
≥ 70		252 (52%)	48 (57%)	0.475
< 70		230 (48%)	37 (43%)	
Missing		1		
Sex, n (%)	565			
Male		362 (75%)	68 (81%)	0.259
Female		119 (25%)	16 (19%)	
Missing		2	1	
BMI	562			
> 25		193 (40%)	23 (27%)	0.019
≤ 25		284 (59%)	62 (73%)	
		6		
Current or former smokers, n (%)	560			
Yes		301 (63%)	59 (70%)	0.217
No		175 (37%)	25 (30%)	
Missing		7	1	
Prior ICI, n(%)	535			
Pembrolizumab		216 (47%)	44 (56%)	0.018*
Avelumab		202 (44%)	23 (29%)	
Atezolizumab /Nivolumab		38 (8.3%)	12 (15%)	
Not available		27	6	
Common sites of metastasis				
Non-regional lymph nodes, n (%)	568			
Yes		350 (72%)	63 (74%)	0.752
No		133 (28%)	22 (26%)	
Lung, n (%)	568			
Yes		227 (47%)	46 (54%)	0.225
No		256 (53%)	39 (46%)	
Brain, n (%)	568			
Yes		13 (2.7%)	7 (8.2%)	0.019
No		470 (97%)	78 (92%)	
Liver, n (%)	568			
Yes		136 (28%)	40 (47%)	< 0.001
No		347 (72%)	45 (53%)	
Bone, n (%)	568			
Yes		152 (31.5%)	42 (49%)	0.001
No		331 (68.5%)	43 (51%)	
Soft tissue, n (%)	555			
Yes		105	22	0.403
No		377	63	
Missing		1		

n (%);Statistical tests were performed excluding missing data; *Pearson's χ^2 test (including 2 × 3 tables)

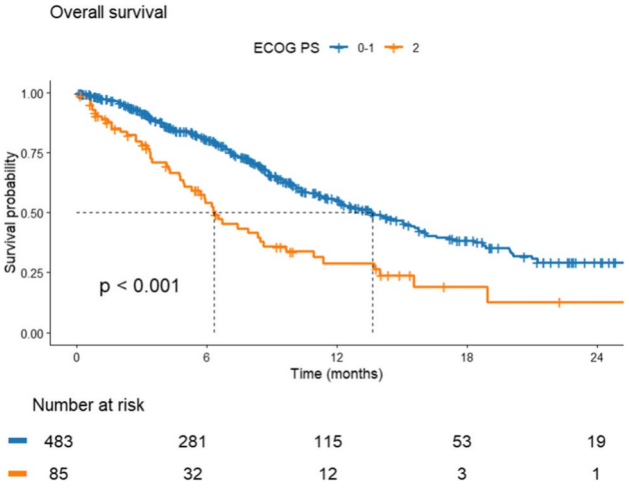


Fig. 1 Overall survival of the included patients

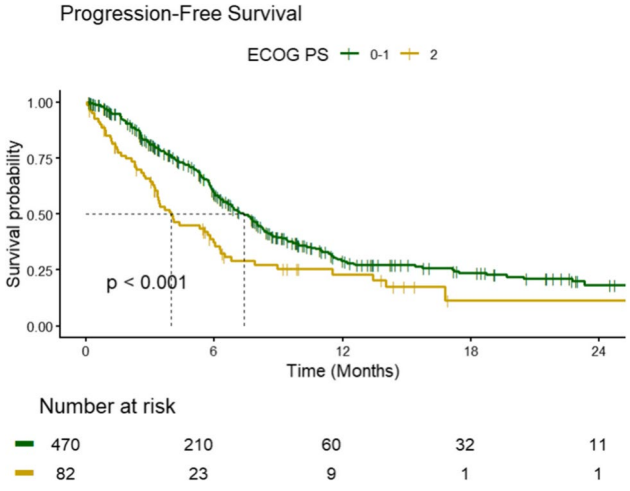


Fig. 2 Progression-free survival of the included patients

Table 2 Multivariable Cox regression analysis for OS

Covariates	Cox regression	
	aHR (95% CI)	*p*-value
ECOG-PS (2 vs. 0–1)	1.94 (1.40–2.69)	< 0.001
Age (≥ 70 vs. <70 years)	0.84 (0.65–1.08)	0.175
Sex (female vs. male)	0.96 (0.71–1.30)	0.804
Histology (mixed vs. pure UC)	1.38 (1.01–1.88)	0.040
Liver metastases (yes vs. no)	1.48 (1.13–1.94)	0.004
Bone metastases (yes vs. no)	1.07 (0.81–1.40)	0.635

aHR Adjusted hazard ratio, *CI* Confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *OS* Overall survival

Table 3 Multivariable Cox regression analysis for PFS

Covariates	Cox regression	
	aHR (95% CI)	*p*-value
ECOG-PS (2 vs. 0–1)	1.51 (1.12–2.03)	0.007
Age (≥ 70 vs. <70 years)	0.93 (0.75–1.16)	0.533
Sex (female vs. male)	1.20 (0.93–1.53)	0.158
Histology (mixed vs. pure UC)	1.61 (1.24–2.09)	< 0.001
Liver metastases (yes vs. no)	1.27 (1.00-1.61)	0.048
Bone metastases (yes vs. no)	1.18 (0.94–1.49)	0.150

aHR Adjusted hazard ratio, *CI* Confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *PFS* Progression free survival

Survival outcomes

OS and PFS according to ECOG-PS 2 and 0–1

The median OS was 13.63 months (95% CI 11.9-15.57) and 6.34 months (95% CI 4.96–8.48) in mUC patients with ECOG-PS 0–1 and ECOG-PS 2, respectively. Patients with ECOG-PS 2 receiving EV reported statistically significantly shorter OS compared to those with ECOG-PS 0–1 (HR 2.24; 95% CI 1.64–3.06; $p < 0.001$) (Fig. 1). In patients with ECOG-PS 2, the 6-months OS rate was 54.3%, the 1-year OS rate 28.9%, and the 2-years OS rate 12.8%; in mUC patients with ECOG-PS 0–1, the 6-months OS rate was 80.7%, the 1-year OS rate 55.4%, and the 2-years OS rate 29.2%. In the primary complete-case multivariable Cox model for OS, 557 patients were included, with 241 OS events. ECOG-PS 2 was independently associated with worse OS (aHR 1.94, 95% CI 1.40–2.69; $p < 0.001$). Mixed tumour histology (aHR 1.38, 95% CI 1.01–1.88; $p = 0.04$) and the presence of liver metastases (aHR 1.48, 95% CI 1.13–1.94; $p = 0.004$) were also associated with shorter OS. (Table 2) The proportional hazard assumption was not violated (global Schoenfeld test $p = 0.06$). In the sensitivity complete-case multivariable Cox model adjusted for ICI agent, 524 patients were included, with 226 OS events. The results were materially unchanged. ECOG 2 remained associated with worse OS (aHR 1.88, 95% CI 1.33–2.65; $p < 0.001$), as did mixed tumor histology (aHR 1.42, 95% CI 1.03–1.95; $p = 0.032$) and liver metastases (aHR 1.47, 95% CI 1.12–1.95; $p = 0.006$) (Supplementary Table S2).

The median PFS was 7.39 months (95% CI 6.60–8.04) and 3.98 months (95% CI 3.21–5.95) in mUC patients with ECOG-PS 0–1 and ECOG-PS 2, respectively. Patients with ECOG-PS 2 receiving EV reported statistically significantly shorter PFS compared to those with ECOG-PS 0–1 (HR 1.71; 95% CI 1.29–2.27; $p < 0.001$) (Fig. 2). In patients with ECOG-PS 2, the 6-months PFS rate was 37.4%, the 1-year PFS rate 22.9%, and the 2-years PFS rate 11.6%; in mUC patients with ECOG-PS 0–1, the 6-months PFS rate was 59.4%, the 1-year PFS rate 29.2%, and the 2-years PFS rate 18.3%. In the primary complete-case multivariable Cox model for PFS, 544 patients were included, with 325 PFS events. ECOG-PS 2 was associated with shorter PFS (aHR 1.51, 95% CI 1.12–2.03; $p = 0.007$). Mixed tumour histology was also associated with shorter PFS (aHR 1.61, 95% CI 1.24–2.09; $p < 0.001$), while the presence of liver metastases showed a weaker association with shorter PFS (aHR 1.27, 95% CI 1.00-1.61; $p = 0.048$). (Table 3). Given evidence of non-proportional hazards, a sensitivity analysis was performed using a Cox model with a time-varying coefficient for ECOG-PS. In

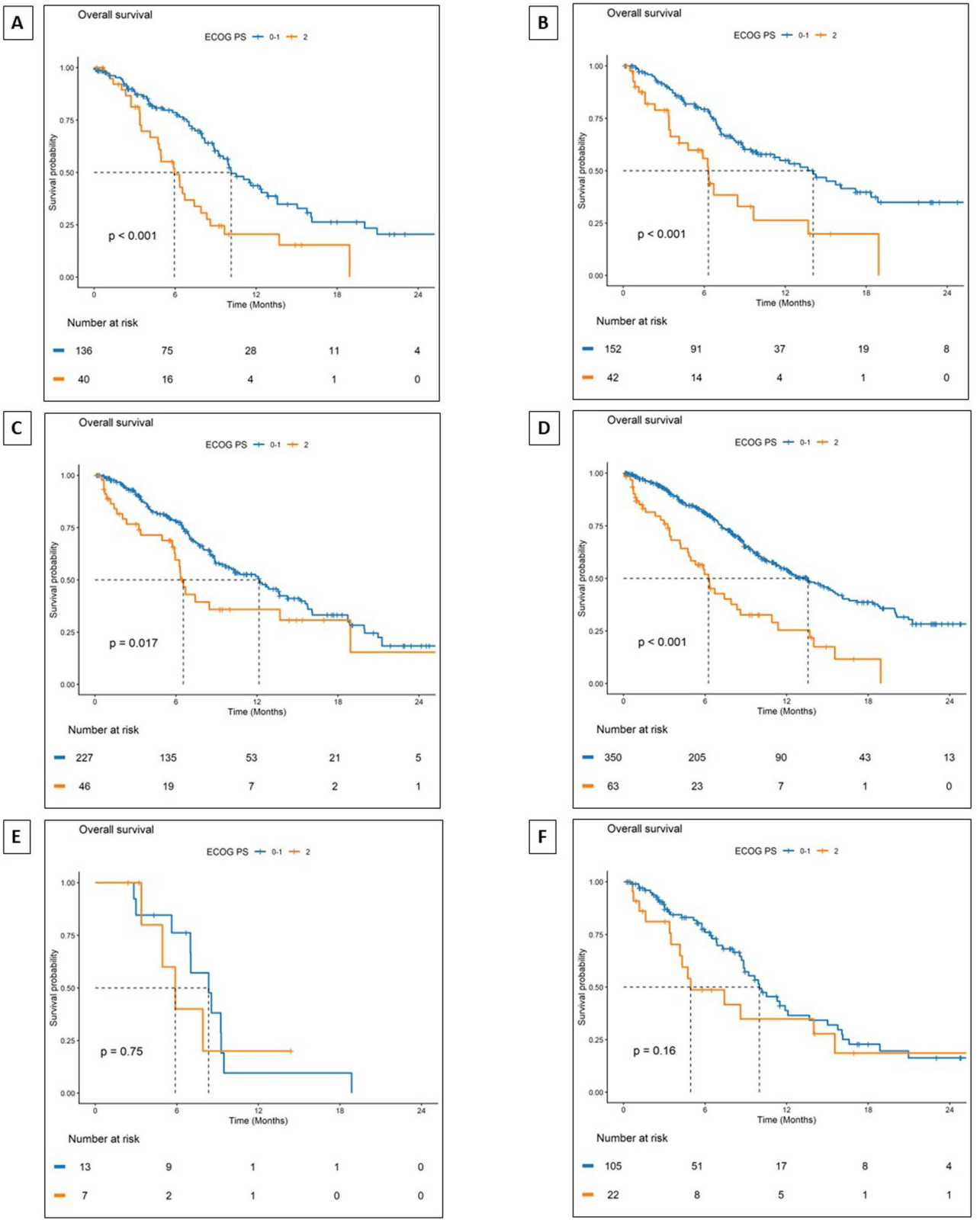


Fig. 3 Overall survival according to metastatic sites (**A**, liver; **B**, bone; **C**, lung; **D**: lymph nodes; **E**: brain; **F**: soft tissue)

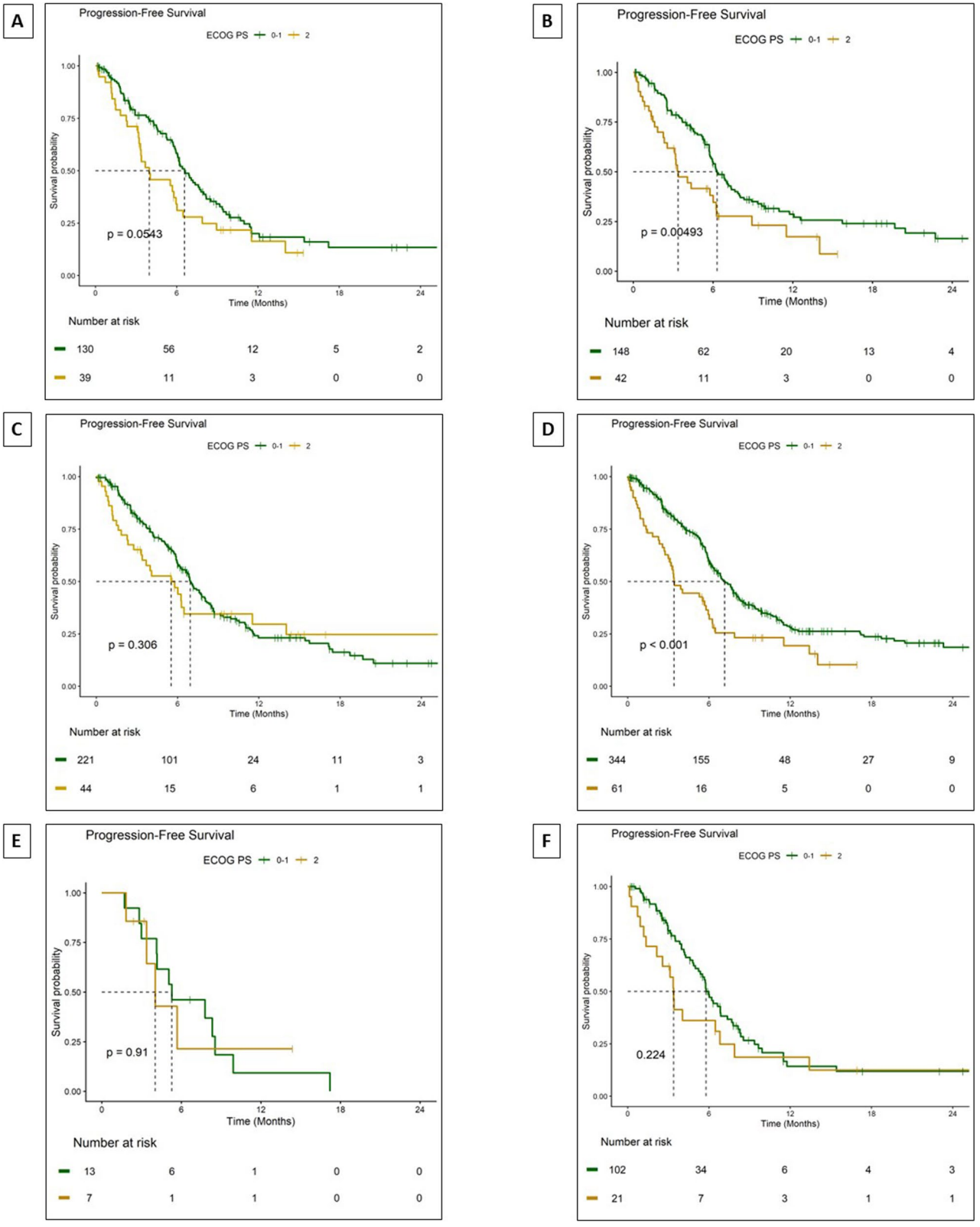


Fig. 4 Progression-free survival according to metastatic sites (**A**, liver; **B**, bone; **C**, lung; **D**: lymph nodes; **E**: brain; **F**: soft tissue)

Table 4 Univariate and multivariate for overall survival among patients with ECOG-PS 2

Overall Survival	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥ 70 years (yes versus no)	0.87 (0.49–1.54)	0.631	1.02 (0.54–1.92)	0.949
Histology (mixed versus pure UC)	1.11 (0.56–2.18)	0.765	1.23 (0.61–2.45)	0.566
Upper versus lower urinary tract	1.15 (0.60–2.19)	0.681	1.11 (0.56–2.18)	0.770
Liver metastases (yes versus no)	1.47 (0.82–2.63)	0.194	1.50 (0.78–2.88)	0.223
Bone metastases (yes versus no)	1.22 (0.68–2.19)	0.499	1.10 (0.58–2.07)	0.779

Table 5 Univariate and multivariate survival analysis for progression-free survival among patients with ECOG-PS 2

Progression Free Survival	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥ 70 years (yes versus no)	0.86 (0.51–1.47)	0.587	0.89 (0.50–1.61)	0.705
Histology (mixed versus pure UC)	1.68 (0.93–3.02)	0.083	1.73 (0.95–3.15)	0.073
Upper versus lower urinary tract	1.23 (0.67–2.23)	0.504	1.24 (0.66–2.31)	0.517
Liver metastases (yes versus no)	1.08 (0.64–1.84)	0.769	1.08 (0.60–1.96)	0.799
Bone metastases (yes versus no)	1.22 (0.72–2.07)	0.3680	1.10 (0.63–1.95)	0.730

this model, the association between ECOG-PS 2 and shorter PFS attenuated over time, with estimated HR of 2.77 at 1 month, 1.56 at 3 months, and 1.08 at 6 months. The time-varying ECOG term was significant ($p < 0.001$). Mixed tumor histology and liver metastases remained associated with shorter PFS. In the sensitivity complete-case multivariable Cox model adjusted for ICI agent, 513 patients were included, with 305 PFS events. The results were materially unchanged. ECOG 2 remained associated with worse PFS (aHR 1.48, 95% CI 1.08–2.01; $p = 0.014$), as did mixed tumor histology (aHR 1.66, 95% CI 1.27–2.17; $p < 0.001$) and liver metastases (aHR 1.29, 95% CI 1.01–1.64; $p = 0.044$) (Supplementary Table S3).

These adjusted analyses support an independent association between ECOG-PS 2 and worse outcomes, although residual confounding related to disease burden and prior treatment trajectory cannot be excluded.

OS according to metastatic sites

Overall, shorter OS in ECOG-PS 2 was observed in those with liver, bone, lymph node, and lung metastases, whereas no statistically significant differences were found in patients with brain or soft tissue metastases (Fig. 3). Detail subgroup-specific median OS estimates, hazard ratios, p-value, and 12-months OS rates are reported in Supplementary Table S4.

PFS according to metastatic sites

By metastatic site, ECOG-PS 2 was associated with shorter PFS in patients with lymph nodes and bone metastases, while no statistically significant differences were detected in patients with liver, lung, brain or soft tissue metastases (Fig. 4). Subgroup-specific median PFS estimates, hazard ratios, p-values, and 12-month PFS rates are summarized in Supplementary Table S5.

Univariate and multivariate survival analysis in patients with ECOG-PS 2

In the complete-case subgroup of patients with ECOG-PS 2, comprising 82 patients and 47 OS events, none of the prespecified variables was significantly associated with OS in univariable analyses, and no independent prognostic association was identified in the multivariable model. (Table 4). A broadly similar pattern was observed for PFS. In the ECOG-PS 2 complete-case subgroup, including 80 patients and 56 PFS events, no prespecified variable was significantly associated with PFS in either univariable or multivariable analyses, (Table 5).

Safety data

No statistically significant differences were observed between the ECOG-PS 0–1 and ECOG-PS 2 groups in the proportion of patients experiencing ≥ 1 grade3-4 prespecified toxicity (19.5% vs. 22.4%, $p = 0.544$), any subsequent dose reduction (38.3% vs. 32.9%, $p = 0.351$), or skipping ≥ 1 EV administration due to toxicity (25.7% vs. 27.4%, $p = 0.751$). Individual grade 3–4 toxicities were compared descriptively and showed numerical differences between groups, with cutaneous toxicity reported in 5.8% versus 3.5%, neuropathy in 6.0% versus 9.4%, diarrhea in 15.2% versus 7.1% and diabetes in 1.2% versus 3.5% of patients in the ECOG-PS 0–1 and ECOG-PS 2 groups, respectively. Most patients received a standard EV starting dose in both groups, although the use of a reduced starting dose appeared more frequent among ECOG-PS 2 (17.6% vs. 7.5%). (Table 6). Data on permanent discontinuation of EV due to toxicity were not systematically available across centers.

Discussion

EV, an ADC targeting Nectin-4, showed considerable clinical benefit compared to systemic chemotherapy in the randomized phase III EV-301 study [9]. In this trial including 608 patients with locally advanced unresectable

Table 6 Grade 3–4 AEs and dose management among ECOG-PS patients

Oncology Center	Number of patients
AMO (Assistência Multidisciplinar em Oncologia) - DASA, Brazil	1
AORN Antonio Cardarelli, Napoli	1
ARNAS Civico Di Cristina Benfratelli, Palermo	12
ASL Latina, Ospedale di Aprilia	2
Ankara University School of Medicine	3
Attikon University Hospital, Athens	10
Azienda Ospedaliera San Camillo-Forlanini, Roma	14
Azienda Ospedaliera Universitaria Federico II, Napoli	12
Azienda Ospedaliera Universitaria Integrata di Verona	6
Azienda Ospedaliero Universitaria Renato Dulbecco, Catanzaro	20
Azienda Ospedaliero-Universitaria Careggi, Firenze	8
Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari	15
Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara	5
Azienda Ospedaliero-Universitaria Pisana	12
Azienda Ospedaliero-Universitaria di Parma	13
Azienda Sanitaria Territoriale Pesaro Urbino, San Salvatore	1
Bakirköy Dr. Sadi Konuk Training and Research Hospital, Istanbul	9
Centre Hospitalier de Jolimont	7
Centro Paulista de Oncologia, Sao Paulo	3
Cliniques Universitaires Saint-Luc, Brussels	8
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano	21
Hospital Universitario Insular de Gran Canaria	8
Hospital Universitario La Paz, Madrid	6
Hospital Universitario Ramón y Cajal, Madrid	26
Hospital de la Santa Creu i Sant Pau, Barcelona	2
Hospital Ángeles del Pedregal, Mexico City	1
IRCCS Azienda Ospedaliero-Universitaria di Bologna - Sant'Orsola	12
IRCCS Istituti Fisioterapici Ospitalieri - Regina Elena, Roma	5
IRCCS Istituto Oncologico Veneto (IOV), Padova	33
IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST), Meldola - Cesena - Forli	20
IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo	6
IRCCS Ospedale Policlinico San Martino, Genova	5
Instituto Alexander Fleming, Buenos Aires	5
Istituto Europeo di Oncologia (IEO), Milano	8
Korea University Anam Hospital	20
MD Anderson Cancer Center Madrid	12
Maria Sklodowska-Curie National Research Institute, Warsaw	15
Markey Cancer Center, University of Kentucky	21
Masaryk Memorial Cancer Institute (MOU), Brno	2
Medical University of Innsbruck	16
National Cancer Centre Singapore	4
Ospedale Santa Corona, Pietra Ligure	7
Ospedale Santa Maria delle Croci, Ravenna	4
Ospedale Santa Maria delle Grazie, Pozzuoli	8
Ospedale di Civitanova Marche (AST Macerata)	2
Policlinico Umberto I, Sapienza University of Rome	6
Saitama Medical Center, Jichi Medical University, Japan	26
The Jikei University Hospital, Tokyo	9
Thomayer University Hospital, Prague	1
University Hospital Bonn	24
University Hospital Motol, Prague	2
University Hospital Olomouc (FNOL)	6
University Hospital Pilsen	13

Table 6 (continued)

Oncology Center	Number of patients
University Medical Center Schleswig-Holstein, Campus Lübeck	1
University of Kansas Cancer Center	48
Winship Cancer Institute of Emory University	8

or metastatic UC who had prior treatments with platinum-based chemotherapy and PD-1/PD-L1 inhibitors, EV showed increased OS and PFS when compared to chemotherapy. Moreover, response rates were greater with enfortumab vedotin compared to chemotherapy (41% versus 19%). However, EV-301 clinical trial included only patients with ECOG-PS 0 or 1, while ECOG-PS 2 mUC patients were excluded [10]. Therefore, in this patient subgroup, the effectiveness of EV monotherapy remains uncertain and can only be inferred from non-randomized prospective trials and studies based on "real world evidence." In clinical settings, the actual benefit of EV for this group of vulnerable patients remains a significant and yet unresolved clinical question [11].

ECOG-PS assesses a patient's capacity for self-care, daily activities, and physical functioning regarding walking and working, or the proportion of waking hours spent restricted to bed or a chair [12, 13]. As a result, this assessment is quite heterogeneous and relies on the personal classification of each individual physician, meaning that various doctors may assess a single patient in different ways, leading to a varied group of patients within the same ECOG-PS level. Notwithstanding this, ECOG-PS continues to be an important and reliable variable, ranking among the most significant independent prognostic indicators in various tumors, including mUC [14, 15].

Based on these premises, our multicenter, real-world analysis provides evidence on the outcomes of EV monotherapy in pretreated mUC patients with ECOG-PS 2, a population that remains underrepresented in prospective trials. First, our study suggests that, as previously suggested for chemotherapy, immunotherapy and targeted agents in this setting – including our previous experience exploring pembrolizumab in ECOG-PS 2 mUC [16, 17], PS at the beginning of the treatment retains prognostic significance in patients treated with EV. Importantly, these findings should not be interpreted as evidence that EV is intrinsically less effective in ECOG-PS 2 patients. Rather, ECOG-PS 2 likely identifies a subgroup with poorer baseline prognosis, greater disease burden, and clinical frailty, all of which may contribute to shorter OS and PFS. In our analysis, we confirmed that ECOG-PS is associated with shorter OS and PFS, in the overall population as well as according to several metastatic sites, such as liver, lung, bone, and lymph nodes metastases. In our cohort, patients with ECOG-PS 2 more frequently had liver and bone metastases, and also showed a higher prevalence of brain metastases, supporting the possibility that worse outcomes partly reflect more aggressive or more clinically advanced disease at EV initiation. At the same time, no prognostic factors were identified considering both univariate and multivariate analysis in ECOG-PS 2 patients. Our study specifically addresses EV monotherapy in a pretreated population and does not inform whether earlier use of EV-based combinations, such as EV plus pembrolizumab, might mitigate the poor outcomes observed in patients who eventually receive EV with ECOG-PS 2.

The major limitations of our study are its retrospective design, which may have influenced our findings. In fact, the retrospective design and lack of data on comorbidities and concomitant medication usage in the study population pose a problem due to potential confounding errors and biases. The lack of an independent radiological central review may also increase the likelihood of incorrectly interpreting treatment response evaluations. Accordingly, PFS was treated as a descriptive time-to-event outcome derived from local clinical practice, and not as a centrally adjudicated efficacy endpoint. Furthermore, we were unable to account for nutritional status beyond baseline BMI. More informative markers such as recent weight loss, albumin, sarcopenia, or inflammation-based nutritional scores were not available, and residual confounding related to cancer-associated malnutrition may have affected outcomes, particularly among ECOG-PS 2 patients. In addition, the lack of genomic evaluation of tumor tissue to detect molecular alterations such as FGFR mutation / fusion, HER2 amplification and/or overexpression, and limited information on patient and treatment characteristics are issues to be considered. In the end, residual confounding remains a major limitation of this analysis, as ECOG-PS 2 may partly reflect cancer-related clinical decline and poorer baseline prognosis rather than performance status alone, while the lack of granular data on prior platinum/ICI benefit and exact EV treatment line may also have contributed to the worse outcomes observed in this group. Although the difference between the full cohort and the complete-case population was relatively small, some degree of bias cannot be excluded if missingness was not random. At the same time, given the overall large sample size and the high number of centers and countries included in the study, our results may represent a topic of reflection for healthcare professionals, especially in countries and geographic areas where novel combinations (such as first-line EV plus pembrolizumab according to EV-302) are

not available yet [18, 19]. Moreover, it appears important to validate alternative measurement instruments for functional performance that may be less subjective and better suited to tackle the diversity of domains influencing PS. Currently, the issue regarding the predictive value of response to EV for ECOG-PS 2 remains unresolved.

Conclusions

Our analysis showed shorter OS and PFS in pretreated mUC patients with ECOG-PS 2 receiving EV monotherapy. The outcomes of EV monotherapy in ECOG-PS 2 patients remains uncertain and can only be inferred from non-randomized prospective studies and real world evidence. Further studies and multicentric translational collaborations are needed to validate these findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-026-16109-9.

Supplementary Material 1: Table S1. List of participating centers and number of patients registred in ARON-2EV. Table S2. Sensitivity analysis: multivariable Cox regression analysis for OS. Table S3. Sensitivity analysis: multivariable Cox regression analysis for PFS. Table S4. Subgroup analyses for OS by metastatic sites. Table S5. Subgroup analyses for PFS by metastatic sites.

Authors' contributions

A.R., F.M. wrote the main manuscript text.S.C.Z., S.B., O.F., K.B., J.A., O.B., D.S., V.M., Y.U. prepared figures.All authors reviewed the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

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.
Informed consent to participate was obtained from all of the participants of the study.

Competing interests

The authors declare no competing interests.

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