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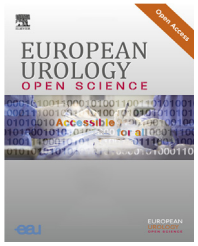

European Association of Urology

Urothelial Cancer

Enfortumab Vedotin in Metastatic Urothelial Carcinoma: Survival and Safety in a European Multicenter Real-world Patient Cohort

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Abstract

Background: Treatment options for patients with urothelial cancer (UC) refractory to platinum and immunotherapy are limited and survival is short. Enfortumab vedotin (EV) is a monoclonal anti-NECTIN4 antibody conjugated to monomethyl auristatin. It was recently approved because of superior survival in comparison to standard-of-care (SOC) chemotherapy. Real-world patients, however, often have worse characteristics than patients included in clinical trials.
Objective: To analyze the efficacy and safety of EV in a cohort of real-world patients.
Design, setting, and participants: Retrospective data were collected from 23 hospitals and private practices for patients with metastatic and previously treated UC who received EV either when reimbursed by their insurance company before European Medicines Agency (EMA) approval, within a compassionate use program,

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or as SOC treatment after EMA approval. Imaging and therapy management were in accordance with local standards.

Outcome measurements and statistical analysis: Adverse events (AEs) were reported according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria. Objective responses were evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results and limitations: The median age for the 125 eligible patients was 66 yr (range 31–89). The Eastern Cooperative Oncology Group performance status (ECOG PS) was 0–1 for 76.0%, 2–4 for 13.6%, and unknown for 10.4% of patients. EV was administered in the fourth or later line for 44.8% of patients. The overall response rate was 41.6% (partial response 39.2%, complete response 2.4%). Median OS was 10.0 months (mo) (95% confidence interval 7.20–12.80) and median PFS was 5.0 mo (95% confidence interval 4.34–5.67). For patients with ECOG PS of 0–1, median OS was 14 mo. Any-grade AEs were observed in 67.2% and CTCAE grade $\geq$3 AEs in 30.4%. The most common AEs were peripheral sensory neuropathy and skin toxicity. Three fatal events (pneumonia, pneumonitis) occurred. Limitations include the retrospective design and short follow-up.

Conclusions: Administration of EV for real-world patients was feasible with an acceptable toxicity profile. No new safety signals were reported. Antitumor activity in our cohort was comparable to data previously reported for trials. In summary, our results support the use of EV in patients with metastatic UC.

Patient summary: Enfortumab vedotin is a medication that improved the survival of patients with bladder cancer in comparison to standard chemotherapy in clinical trials. However, patients included in clinical trials are highly selected and results for toxicities and improvements in survival do not always transfer to the real-world setting. We analyzed data for 125 patients who were treated with enfortumab vedotin. Our results are comparable to the outcomes from clinical trials regarding the safety and efficacy of this treatment.

1. Introduction

The prognosis for patients with metastatic urothelial cancer (mUC) refractory to platinum and immune checkpoint inhibitor (ICI) therapy is dismal. Until 2020, the standard of care (SOC) consisted of chemotherapy with docetaxel, paclitaxel, and vinflunine. In 2019, the US Food and Drug Administration approved enfortumab vedotin (EV) as third-line therapy (after platinum-based chemotherapy and ICI), followed in 2022 by approval from the European Medicines Agency (EMA).

NECTIN4 is—aside from embryogenesis—almost exclusively found in malignant cells [1,2]. It has been reported that expression of NECTIN4 in UC is as high as 97% for noninvasive papillary tumors and 87% for invasive carcinoma [3–5]. In variant UC, expression levels vary widely. While up to 70% of squamous cell carcinomas and 66% of adenocarcinomas showed NECTIN4-positive tumor cells, NECTIN4 staining was low or absent in sarcomatoid variant (10%) and in small cell carcinoma (0%) [6–8].

EV is an antibody-drug conjugate (ADC) comprising an anti-NECTIN4 antibody linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE). In the phase 1 dose escalation/expansion trial EV-101 (NCT02091999), 201 patients with NECTIN4-positive tumors were treated with EV. Of these, 155 patients with heavily pretreated mUC showed an overall response rate (ORR) of 43% [9]. In the phase 2 single-arm EV-201 trial (NCT03219333) 125 patients received EV. The ORR was 44% (n = 55), with complete remission (CR) in 15 and partial remission (PR) in 40 patients.

In EV-301 (NCT03474107), an open-label, phase 3 trial, 608 patients were 1:1 randomized to either chemotherapy (paclitaxel, docetaxel, or vinflunine) or EV until progression or intolerable toxicity [10]. Median overall survival (mOS) was 12.88 months (mo) (95% confidence interval [CI] 10.58–15.21) versus 8.97 mo (95% CI 8.05–10.74) in favor of EV (hazard ratio [HR] 0.70, 95% CI 0.56–0.89; p = 0.001). Median progression-free survival (mPFS) was 5.55 mo (95% CI 5.32–5.82) with EV and 3.71 mo (95% CI 3.52–3.94) with SOC (HR 0.62, 95% CI 0.51–0.75; p < 0.001). Interestingly, subgroup analysis suggested a larger advantage for male versus female trial participants regarding mOS (HR 0.61, 95% CI 0.47–0.79 vs HR 1.17, 95% CI 0.72–1.89) and mPFS (HR 0.58, 95% CI 0.47–0.72 vs HR 0.99, 95% CI 0.67–1.49). The ORR was 40.6% (95% CI 34.9–46.5%) for patients treated with EV versus 17.9% (95% CI 13.7–22.8%) for patients treated with SOC chemotherapy. The median time for treatment response was 7.39 mo (95% CI 5.59–9.46) in the EV arm. The results from EV-301 led to EMA approval of the drug.

Regarding toxicity, comparable rates of adverse events were noted for chemotherapy versus EV in the EV-301 trial (any grade: 91.8% vs 93.9%; grade ≥3: 49.8% vs 51.4%). However, adverse events of special interest were noted: 13% of patients had skin reactions of grade ≥3, including Stevens-Johnson syndrome and acute toxic epidermolysis of grade 5. The median time to occurrence of skin reactions was 0.6 mo (range 0.1–6.4). Hyperglycemia was detected in 14% of patients. Risk factors were pre-existing hyperglycemia and body mass index ≥30 kg/m^2. Patients with hemoglobin A1c ≥8% were excluded from clinical trials and the compassionate use program. Pooled data from trials revealed that peripheral neuropathy occurred in 52% of patients, of whom 19% experienced a complete and 39% a partial improvement in symptoms after discontinuation of EV [11].

In this retrospective study, we investigated the safety and efficacy of EV in a multicenter real-world mUC cohort.

2. Patients and methods

2.1. Patient cohort and EV treatment

Clinical data for patients with mUC treated with EV were collected from 23 hospitals and private practices (in alphabetical order: Berlin, *n* = 3; Bochum; Bonn; Chur; Cologne; Düsseldorf; Essen; Hamburg; Hannover; Heidelberg, *n* = 2; Koblenz; Lübeck; Marburg; Munich, *n* = 4; Münster; Stuttgart; and Ulm). Data were retrieved retrospectively from patient charts. Imaging and therapy management followed the SOC at each institution. A dose of 1.25 mg/kg on days 1 and 8, 15 qd22 was considered the routine regimen. EV was approved in May 2022 and drug supply was established by June 1, 2022 in Germany. However, the majority of patients in this cohort received treatment before EV approval either on a compassionate use basis (EV-902, program number 257871, enrolment August 2021–May 2022) or after import from international pharmacies if reimbursement was secured on an individual basis. Adverse events were reported according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria. Objective responses were evaluated by local investigators according to Response Evaluation Criteria in Solid Tumors version 1.1.

All procedures performed were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients provided written informed consent for medical treatment. In cases of EV use before EMA approval, separate informed consent to off-label drug use was signed. Any information connected to the identity of individual subjects was removed before study entry. The study was approved by the ethics committee of the University of Heidelberg (S-568/2022).

2.2. Statistical analysis

PFS and OS were censored in the absence of disease progression and death at the last follow-up date. Kaplan-Meier survival times were estimated. Follow-up duration was calculated from the date of treatment initiation to either date of death or last known follow-up. SPSS version 28.0 (IBM, Armonk, NY, USA) was used for statistical assessment. A two-sided *p* value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 125 patients who received at least one dose of EV were identified. Baseline characteristics are listed in Table 1.

Table 1 – Characteristics of the 125 patients

Parameter	Result[a]
Median age at diagnosis, yr (range)	62.0 (29–87)
Median age at EV initiation, yr (range)	66.0 (31–89)
Age ≥75 yr at EV initiation, *n* (%)	24 (19.2)
Sex, *n* (%)	
Male	87 (69.6)
Female	38 (30.4)
Comorbidities, *n* (%)	
Vascular disease	10 (8.0)
Cerebrovascular disease	10 (8.0)
Pulmonary disease	14 (11.2)
Cardiac disease	26 (20.8)
Diabetes mellitus	23 (18.4)
Moderate CKD (GFR ≥30 ml/min)	39 (31.2)
Severe CKD (GFR <30 ml/min)	9 (7.2)
Primary tumor location, *n* (%)	
Bladder	81 (64.8)
Upper urinary tract	28 (22.4)
Unknown	16 (12.8)
Histology, *n* (%)	
Urothelial carcinoma	123 (98.4)
Squamous cell carcinoma	1 (0.8)
Unknown	1 (0.8)
Prior definitive local treatment, *n* (%)	
Yes	89 (71.2)
No	36 (28.8)
ECOG PS, *n* (%)	
0	45 (36.0)
1	50 (40.0)
2	13 (10.4)
3	3 (2.4)
4	1 (0.8)
Unknown	13 (10.4)
Sites of metastases, *n* (%)	
Lymph nodes	101 (80.8)
Lung	61 (48.8)
Bone	62 (49.6)
Liver	46 (36.8)
Adrenal glands	10 (8.0)
Peritoneal	11 (8.8)
Brain	7 (5.6)
Other	44 (35.2)
Prior treatment lines, *n* (%)[b]	
1	1 (0.8)
2	68 (54.4)
3	29 (23.2)
4	22 (17.6)
5	5 (4.0)
Prior treatment, *n* (%)	
Chemotherapy	125 (100.0)
Cisplatin	99 (79.2)
Carboplatin	30 (24.0)
Vinflunine	47 (37.6)
Taxane	29 (23.2)
Immune checkpoint inhibitor	121 (96.8)
Pembrolizumab	67 (53.6)
Avelumab	33 (26.4)
Nivolumab	16 (12.8)
Atezolizumab	9 (7.2)
Ipilimumab	4 (3.2)
FGFR inhibitor	7 (5.6)
Sacituzumab govitecan	2 (1.6)
Other investigational agent	3 (2.4)

CKD = chronic kidney disease; ECOG PS = Eastern Cooperative Oncology Group performance status; EV = enfortumab vedotin; GFR – glomerular filtration rate.
[a] Percentages may not total 100 because of rounding.
[b] Maintenance therapy with avelumab was counted as a separate treatment line.

The median age at diagnosis was 62 years (yr) (range 29–87 yr) and the median age at EV initiation was 66 yr (range 31–89 yr). At the start of EV treatment, 19.2% of patients were

aged ≥75 yr. Further, 70% of the patients were male, and 38.4%, 18.4%, and 11.2% had pre-existing chronic kidney disease, diabetes mellitus, and pulmonary disease, respectively. The bladder was the primary tumor location in 64.8% of patients. Eastern Cooperative Oncology Group performance status (ECOG PS) was 0, 1, 2, 3, 4, and unknown for 36.0%, 40.0%, 10.4%, 2.4%, 0.8%, and 10.4%, respectively.

The most prevalent histology was UC (98.4%). The majority of patients (71.2%) had received prior local treatment with curative intent. Sites of metastases included lymph nodes (80.8%), lung (48.8%), bone (49.6%), liver (36.0%), adrenal glands (8.0%), peritoneum (8.8%), brain (5.6%), and other, such as local recurrence (35.2%).

The median number of prior treatment lines was 2 (range 1–5), which mostly consisted of cisplatin/carboplatin plus gemcitabine and ICI (Table 1). Avelumab maintenance was defined as separate treatment line.

3.2. *Efficacy and OS*

Median follow-up was 8.0 mo (95% CI 6.11–9.89). At the time of last follow-up, 73 patients (58.4%) were alive and 52 (41.6%) had died. Median OS was 10.0 mo (95% CI 7.20–12.80, Fig. 1A). Median OS was 14.0 mo (95%CI:8.78-19.22) for patients with ECOG PS 0–1 at EV initiation, compared to 3.0 mo (95% CI 1.26–4.74) for patients with ECOG PS 2–4 ($p < 0.001$).

Median PFS was 5.0 mo (95% CI 4.34–5.67; Fig. 1B). Median PFS was 5.0 mo (95%CI 3.12–6.88) for patients with ECOG PS 0–1 at EV initiation, compared to 1.0 mo (95% CI 0.01–1.99, $p < 0.001$) for patients with ECOG PS 2–4. With regard to sex, comparable results were seen for mOS (females 10 mo, 95% CI 3.54–16.46; males 10 mo, 95% CI 6.58–13.42) and mPFS (females 4 mo, 95% CI 1.49–6.51; males 5 mo, 95% CI 4.36–5.64). Application in the second or third line versus later lines was not associated with better mPFS (5.0 mo, 95% CI 3.54–6.35 vs 4.0 mo, 95%CI 2.49–5.51; $p = 0.217$) or mOS (12.0 mo, 95% CI 6.98–17.03 vs 10.0 mo, 95% CI 6.43–13.57; $p = 0.507$). There were no significant differences in mPFS by liver metastasis (yes vs no), bone metastasis (yes vs no), brain metastasis (yes vs no), or upper tract carcinoma (vs bladder primary vs unknown location) status (data not shown).

Thirty patients (24.0%) had received ≥6 mo of EV. The ORR was 41.6% (52/125) and the disease control rate (DCR) was 52.0% (65/125, Table 2). The best response to treatment was CR in three patients. The best response in the group with ECOG PS 2–4 at baseline was PR in four of 17 patients, stable disease in one of 17, and progressive disease (PD) in 12/17 (ORR 23.5%; DCR 29.4%).

Of note, in the group of patients with PD as the best response, ten (8.0%) had a mixed response or oligoprogressive disease, and some of these patients received EV beyond progression in combination with local treatment. Treatment was discontinued because of PD or death in 49.6% of patients.

3.3. *Safety*

In total, 67.2% of patients experienced any-grade treatment-related toxicities and 30.4% experienced grade 3–5 toxicities (Tables 3 and 4). In 10.4% of patients, EV treatment was permanently discontinued because of intolerable toxicity. The most common side effect was peripheral sensory neuropathy (any grade, 25.6%; grade 3–4, 9.6%), followed by skin toxicity (any grade, 24.8%; grade 3–4, 3.2%), including a case of Stevens-Johnson syndrome. Eye disorders (dry eye, conjunctivitis, abducens paresis) were noted in 5.6% of patients (all grade 1–2). Although 18.4% of patients had diabetes, disturbed glucose control was described as a side effect of any grade in only 2.4% and of grade 3–4 in 1.6 % of patients ($n = 2$ with known diabetes mellitus). Respiratory toxicity was recorded in 6.4% of patients, of which one case was grade 4 and three cases were grade 5 toxicity. All three patients whose death was attributed to EV treatment died from pneumonia or pneumonitis.

4. Discussion

To the best of our knowledge, this is the first retrospective international multicenter study exploring both efficacy and safety outcomes for real-world patients treated with

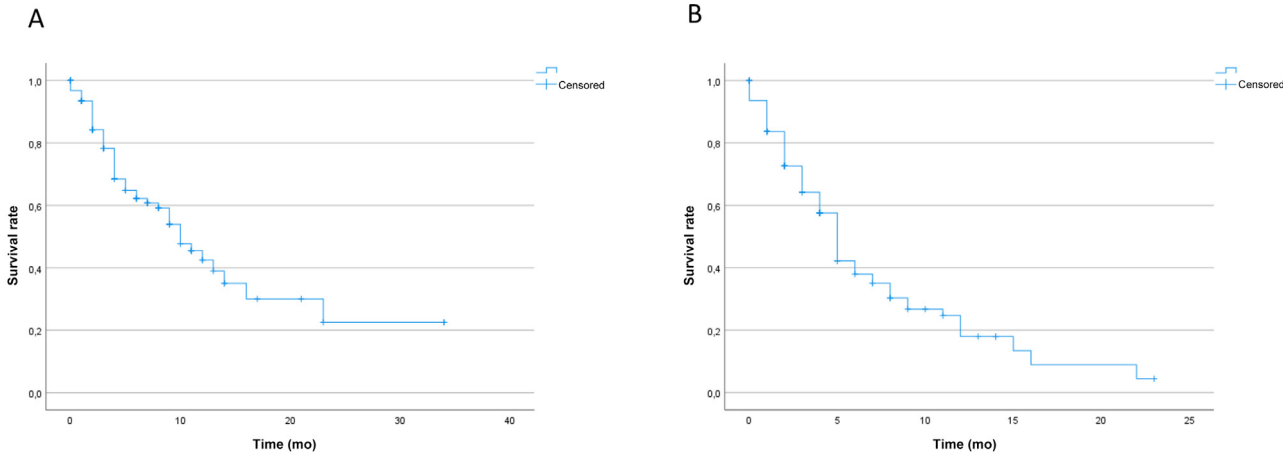

Fig. 1 – Survival of patients treated with enfortumab vedotin. (A) Median overall survival was 10.0 mo (95% confidence interval 7.201–12.799). (B) Median progression-free survival was 5.0 mo (95% confidence interval 4.335–5.665).

Table 2 – Efficacy of enfortumab vedotin treatment among the 125 patients

Response	Patients, *n* (%)
Overall response rate	52 (41.6)
Disease control rate	65 (52.0)
Complete remission	3 (2.4)
Partial remission	49 (39.2)
Stable disease	13 (10.4)
Progressive disease	51 (40.8)
Not evaluable	9 (7.2)

Table 3 – Summary of TRAEs among 125 patients

Adverse events	Patients, *n* (%)
TRAE	80 (69.6)
Grade ≥3 TRAE	36 (31.3)
TRAE resulting in treatment discontinuation	13 (10.4)
TRAE leading to death	3 (2.6)

TRAE = treatment-related adverse event.

Table 4 – Summary of treatment-related adverse events

Adverse event type	Patients, *n* (%)	
	All grades	Grade 3–5
Peripheral sensory neuropathy	32 (25.6)	12 (9.6)
Skin (rash)	31 (24.8)	4 (3.2)
Fatigue	22 (17.6)	4 (3.2)
Hematotoxicity	15 (12.0)	9 (7.2)
General deterioration	15 (12.0)	5 (4.0)
Infection	12 (9.6)	6 (4.8)
Diarrhea	11 (8.8)	2 (1.6)
Respiratory	8 (6.4)	4 (3.2)
Dysgeusia	8 (6.4)	0
Nausea	7 (5.6)	1 (0.8)
Eye disorder	7 (5.6)	0
Pruritus	6 (4.8)	0
Loss of appetite	4 (3.2)	1 (0.8)
Hyperglycaemia	3 (2.4)	2 (1.6)
Constipation	3 (2.4)	1 (0.8)
Liver toxicity	1 (0.8)	1 (0.8)

EV outside of clinical trials and not exclusively in academic centers. To date, only one retrospective register (UNITE) has been published, which recruited 260 patients from 16 academic centers in the USA [12]. UNITE has reported efficacy data, but no safety data so far.

We report data for 125 patients from 15 academic hospitals, three community hospitals, and five private practices. With a median age of 66 yr and only 19.2% of patients aged ≥75 yr at EV initiation, our cohort is younger than those in EV-201, EV-301, and UNITE. mOS in our study was 10.0 mo, which is shorter than in UNITE (14.4 mo), EV-201 (11.7 mo), and EV-301 (12.88 mo). A number of factors may have contributed to this difference. The proportion of patients treated in the third or later lines was 44.8% in our study, which is higher than in the pivotal EV-301 trial (13.0%) and in the UNITE cohort (22%). In EV-301, most patients had received one or two prior treatment lines and the HR for OS was 0.69 (95% CI 0.54–0.88) in this group of patients. However, the treatment effect seemed to be less robust for patients who received EV in third or later lines, with a HR of 0.88 (95% CI 0.47–1.64).

ECOG PS is another factor that contributes to prognosis and treatment efficacy. While prospective trials testing EV were limited to patients with ECOG PS of 0–1, real-world practice consists of a broader range of patients. Similar to the UNITE cohort, we identified 17 patients (13.6%) with ECOG PS of 2–4 on starting EV. Treatment outcomes remained poor in this group of patients (PFS 1.0 mo, 95% CI 0.006–1.994; OS:3.0 mo, 95% CI 1.260–4.740). This is not surprising and indicates that a decision on treatment initiation in patients with poor performance status should be carefully weighed against possible adverse effects and that patients should be well informed about the limited efficacy of treatment. Conversely, mOS for patients with ECOG PS 0–1 in our cohort was 14.0 mo (95% CI 8.783–19.217), which is comparable to prospective trial data and reiterates the role of ECOG PS as a selector for clinical decision-making. In contrast to previous studies, our retrospective data revealed comparable results for female and male patients for both mOS and mPFS, and the sex distribution was as expected and comparable to other trials, with a higher proportion of male patients. Nevertheless, we support further research on the sex disparities for mUC outcomes that have been seen in many trials in the past.

In our real-world cohort, rates of treatment-related adverse events (any grade: 67.2%; grade 3–5: 30.4%) were lower than in the prospective EV-201 and EV-301 trials (any grade: 94%; grade 3–5: 51–54%). This is possibly because of the retrospective nature of our study. All our study sites regularly participate in clinical trials and are familiar with CTCAE reporting. However, documentation of adverse events in daily clinical practice seems to be limited to those that most severely affect a patient's quality of life. Reporting bias as a reason for these differences is also likely, as the rate of treatment discontinuation because of side effects in our cohort (10.4%) is comparable to that in the pivotal study (13.5%). For instance, alopecia was reported in at least 45% of patients in prospective EV trials (the most common adverse event in EV-201 and the second most common in EV-301), but it was documented for only four patients (3.2%, grade 1–2) in our cohort. By contrast, the rate of grade 3–5 peripheral sensory neuropathy was higher than in the prospective trials (9.6% vs 2% in EV-201 and 3.0% in EV-301). A possible explanation for this finding is the higher previous chemotherapy exposure in our cohort, which includes agents known to induce neurotoxicity, such as cisplatin, taxanes, and vinflunine. Our real-world data also show that patients may experience ophthalmologic adverse events, affecting 5.6% of our patients, but this did not limit treatment continuation. This observation is of particular interest because pre-emptive ophthalmologic visits were not mandatory for real-world patients, in contrast to clinical EV trials, which may explain the difference in xerophthalmy incidence (30%). More importantly, this finding indicates that ophthalmologic examinations can be restricted to patients with pre-existing conditions or a higher risk of ocular toxicities in real-world practice. The incidence of hyperglycemia among patients treated with EV has been reported as 14.0%. However, the incidence in our cohort was low (2.4%) and the clinical relevance of this adverse event seems limited. EV skin toxicity affected

24.8% of our patients. Four (3.2%) experienced grade 3–4 skin toxicity, including one case of Stevens-Johnson syndrome. NECTIN4 is physiologically expressed in keratinocytes and skin, which explains this observation. Preventive measures such as barrier-protective agents and sunscreen are therefore recommended [13]. During our study observation period, a series of severe skin toxicities was described and included rare events such as Stevens-Johnson syndrome and toxic epidermal necrolysis, which may have affected recognition and therapeutic management of skin toxicities [14]. We observed three fatal cases (2.4%) of pneumonia/pneumonitis possibly related to EV use, which is in contrast to its occurrence in the pivotal EV trials. All patients were pretreated with ICI and delayed immune-related adverse events may have occurred. However, pneumonia/pneumonitis onset may indicate a connection to EV treatment. Yoon et al [15] analyzed the Korean patient population enrolled in EV-201 and EV-301. Of 64 patients, 18 (28.1%) developed any-grade pneumonia that was fatal in two cases. Limitations of our study include its retrospective design and the short follow-up.

Ongoing clinical trials are currently evaluating combination strategies (eg, with PD-1 inhibitors in the perioperative setting [NCT05239624 and NCT03924895] and in first-line mUC treatment [EV-302 and NCT03474107], with FGFR inhibitors [NCT04963153], and with other ADCs such as sacituzumab govitecan [NCT04724018]) and efficacy in the neoadjuvant setting. Other agents targeting NECTIN4 are also being investigated, such as second-generation bicyclic peptides (Bicycle) that bind to NECTIN4, MMAE (NCT04561362), CD 137 (NCT05163041), and NECTIN4-targeted chimeric antigen receptor-T cells (NCT03932565), among others.

5. Conclusions

In summary, our real-world data confirm the promising efficacy in pivotal trials of EV in patients with good performance status at the start of treatment. Outside of a clinical trial, the toxicity of EV was manageable. Adverse events of special interest remain for neuropathy and skin and respiratory toxicities.

Author contributions: Stefanie Zschäbitz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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