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Review – Urothelial Cancer

# Clinical and Molecular Predictors of Response and Survival in Patients with Urothelial Carcinoma Treated with Enfortumab Vedotin: A Systematic Review and Meta-analysis

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## Abstract

***Background and objective:*** Enfortumab vedotin (EV) is emerging as a standard of care for advanced urothelial carcinoma (UC), but identification of which patients might benefit the most or least remains an unmet need. Our aim was to identify clinical and molecular parameters associated with EV sensitivity in patients with advanced UC after failure of previous platinum and immune checkpoint inhibitor (ICI) therapy.

***Methods:*** We queried the PubMed, Embase, and Cochrane Library databases up to January 2024. The review protocol was registered on PROSPERO (CRD42023484339). The outcome measures were the objective response rate (ORR), overall survival (OS), and progression-free survival (PFS).

***Key findings and limitations:*** A total of 23 studies were included. Analyses for 1340 patients revealed a cumulative ORR of 48%, with higher rates in real-world studies (51%) than in clinical trials (44%). EV was similarly effective in bladder and upper-tract UC in terms of OS and PFS, but the ORR was slightly higher in upper-tract UC (odds ratio [OR] 1.29, 95% confidence interval [CI] 1.01–1.63; $p$ = 0.041). The EV ORR was also significantly higher in the subgroups with a response to prior platinum (OR 2.65, 95% CI 1.04–6.72; $p$ = 0.046) or ICI (OR 1.51, 95% CI 1.12–2.04; $p$ = 0.017) therapy. Poor Eastern Cooperative Oncology Group (ECOG) performance status and high Bellmunt risk score were associated with poor ORR, and the presence of histology subtypes was associated with poor PFS (HR 1.62, 95% CI 1.10–2.38; $p$ = 0.015). PD-L1 expression positivity and *FGFR3* alterations were not associated with outcomes.

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***Conclusions and clinical implications:*** EV is an effective therapy in advanced UC. The predictive parameters identified in our analyses, such as ECOG performance status, Bellmunt score, non-UC histology, and response to prior ICI and platinum treatment, can be used to guide optimal patient selection for EV or alternative therapies.
***Patient summary:*** We summarize data from published studies to identify factors that influence outcomes for patients with advanced cancer of the urinary tract treated with a drug called enfortumab vedotin. An understanding of these factors can help in personalizing therapy for patients and improving their care.
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## 1. Introduction

Urothelial carcinoma (UC) is the sixth most common cancer type in developed countries [1]. Patients with metastatic UC (mUC) that is refractory to platinum-based chemotherapy (PBC) and immune checkpoint inhibitor (ICI) therapy have a devastating prognosis, with a 5-yr survival rate of <5% [2]. For more than three decades, PBC has been the standard of care for locally advanced or metastatic UC. However, ICI therapies have remarkably changed the treatment landscape in recent years [3,4]. PBC and ICIs offer survival benefits, but most cases progress and only a few patients experience long-term control, which highlights the need for additional therapies. The FGFR inhibitor erdafitinib has become available for patients with advanced or metastatic UC and an *FGFR3/2* fusion or mutation after progression on PBC and/or ICI therapy [5]. Enfortumab vedotin (EV) has been approved for those progressing on PBC and ICIs, with better overall survival (OS; 12.9 vs 9.0 mo), progression-free survival (PFS; 5.6 vs 3.7 mo), and objective response rate (ORR; 41% vs 18%) over single-agent chemotherapy (paclitaxel, vinflunine, or docetaxel) in the open-label, randomized, phase 3 EV-301 trial [6]. More recently, the EV-302 trial demonstrated that an EV + immune checkpoint inhibitor (ICI) combination outperformed PBC in the first-line setting, which significantly changed the treatment sequence for UC [7]. EV is an antibody-drug conjugate that binds to NECTIN4 on cancer cells and delivers a cytotoxic drug, monomethyl auristatin E, directly to the cells [8,9].

The treatment landscape for advanced UC is rapidly evolving with more therapeutic options, making clinical decisions increasingly complex. Identification of patients with varying therapeutic sensitivities is crucial. In addition, real-world data are essential to assess the true efficacy of new drugs, as the strict inclusion criteria in clinical trials often exclude groups that are later treated in real-world settings.

Therefore, we conducted a systematic review and meta-analysis to comprehensively synthesize and analyze the data available from clinical trials and real-world studies on EV in advanced UC to identify factors influencing therapy efficacy and to help in identifying UC subgroups that benefit most from EV.

## 2. Methods

Our systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the *Cochrane Handbook* [10]. The protocol was registered on PROSPERO (CRD42023484339) and the review fully adhered to this protocol.

### 2.1. Eligibility criteria and parameters assessed

Our question was formulated using the PECO (Population, Exposure, Comparator, Outcome) framework. Eligible studies comprised patients with advanced UC who were treated in third- or later-line EV monotherapy (Population). We compared different statuses of clinical and molecular parameters with each other (Exposure and Comparator) in terms of ORR, OS, and PFS (Outcome). We excluded reviews, meta-analyses, conference abstracts, and case reports. Prospective trials and real-world cohort studies assessing third- or later-line EV monotherapy were eligible. Studies using combination regimens or first-line therapy were excluded.

### 2.2. Information sources

The systematic search was conducted on December 23, 2023 for papers published between 2019 and 2024 using three databases: Embase, MEDLINE (via PubMed), and Cochrane Central Register of Controlled Trials (CENTRAL). After full-text selection, a systematic search of references in the articles included was conducted on 18 January 2024 using the *citationchaser* package [11].

### 2.3. Search strategy

Our search comprised two main elements: the drug and the disease. The detailed search strategy is provided in Supplementary Table 1.

### 2.4. Selection process

Reference manager software (Endnote v9.0; Clarivate Analytics, Philadelphia, PA, USA) was used for the selection process. After removal of duplicates via automated and manual processes, the selection was conducted in parallel by two authors (M.A. and J.V.) at both the title/abstract and full-

text levels. Inter-rater reliability was measured by calculating Cohen's κ coefficient after each step [12]. Conflicts were resolved by a third author (J.H.).

### 2.5. Data collection process

From the eligible articles, data were collected by two authors (M.A. and J.V.) independently and entered into a predefined Excel table (Microsoft Corporation, Redmond, WA, USA). Any conflicts were resolved by a third author (J.H.). For each study, only reported data were used in the meta-analysis. In cases in which essential data (eg, effect estimates or measures of variability) were missing, the study authors were contacted. If data remained unavailable, the study was excluded from the corresponding analysis. No imputation of missing data was performed.

### 2.6. Data items

The following data were extracted: first author, year of publication, study population, period, identification, study type, cohort size, follow-up duration, and ORR, OS, and PFS for different patient characteristics. If data were missing or insufficient, the corresponding author was contacted. To achieve more flexible data extraction from a real-world study, we requested and received aggregate statistical output data instead of using the data in the original article [13].

### 2.7. Assessment of study risk of bias

Two authors (M.A. and J.V.) independently assessed the risk of bias (RoB) using the Quality in Prognostic Studies (QUIPS) tool. The results were summarized using the *robvis* R package [14]. Disagreements were resolved by a third author (J.H.).

### 2.8. Parameters assessed

The following predefined parameters and the corresponding cutoff values reported in the studies were considered for analysis: sex (male vs female), age (<75 vs ≥75 yr), Eastern Cooperative Oncology Group performance status (ECOG PS; 0–1 vs >1), liver metastasis (present vs absent), tumor location (bladder vs upper-tract), UC histology (pure urothelial vs mixed), Bellmunt risk factor (0–1 vs >1), prior lines of therapy (0–2 vs ≥3), response to PBC and ICI therapy (responder vs nonresponder), PD-L1 and NECTIN4 immunostaining status (positive vs negative), *FGFR* mutation status (positive vs negative), neutrophil/lymphocyte ratio (NLR; ≥5 vs <5), hemoglobin (≥10 vs <10 g/dl), and glomerular filtration rate (GFR; ≥60 vs <60 ml/min).

### 2.9. Synthesis methods

Qualitative and quantitative data synthesis was performed using a random-effects model to pool effect sizes via a frequentist approach. Odds ratios (ORs) and proportions with a 95% confidence interval (CI) were used as effect-size measures for dichotomous outcomes and response rates. For time-to-event data, the hazard ratio (HR) was applied for the effect size measure with a 95% CI. To calculate pooled HRs, we calculated the logarithm and standard error of the HR from the available data using the method described by Tierney et al [15]. We used the published HRs and their 95%CIs for these calculations. Individual patient data (IPD) were retrieved from available Kaplan-Meier curves using the algorithm described by Guyot et al [16] to calculate pooled median survival times.

An inverse variance weighting method was used to calculate the pooled OR and the pooled HR. We adjusted the pooled CI using the Hartung-Knapp method. To estimate the heterogeneity variance measure ($\tau^2$) for "raw data" OR calculation, the Paule-Mandel method was used with the Q profile method for the CI. For HRs, the (restricted) maximum-likelihood estimator was used with the Q profile method for the CI. We visualized findings in forest plots. The statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria) with the *meta*, *metafor*, and *metaSurvival* packages.

## 3. Results

### 3.1. Search and selection

Our search identified 1680 articles. After removal of duplicates, 1139 publications remained for further assessment. Title and abstract screening showed good overlap between the two investigators (κ = 0.98), and full-text screening identified 62 candidate publications. Of these, 17 articles met the inclusion criteria (κ = 0.879). After article selection and citation searches, six additional relevant articles were identified, resulting in 23 papers for inclusion in the systematic review and meta-analysis (Fig. 1) [2,8,13,17–37].

### 3.2. Study characteristics

The 23 eligible papers were published between 2019 and 2024, and included 1720 patients with UC treated with EV. Baseline characteristics of the studies are detailed in Table 1. The median age of patients varied between 66 and 76 yr, with two-thirds dominance of males. ORR and disease control rate outcomes were available in 14 and 11 publications, respectively. OS and PFS data were published in 20 studies.

### 3.3. Cumulative survival and response rates

We calculated pooled estimates of median OS and median PFS using a random-effects model for all IPD retrieved from the studies to provide a consolidated measure of survival outcomes (Fig. 2A).

The pooled median OS was 12.3 mo (95% CI 10.4–14.3) for the overall cohort, 13.5 mo (95% CI 10.6–15.2) for clinical trials, and 11.1 mo (95% CI 8.4–13.3) for real-world studies. The pooled median PFS was 5.9 mo (95% CI 5.5–7.0) for the overall cohort, 5.8 mo (95% CI 5.4–6.8) for clinical trials, and 5.9 mo (95% CI 5.0–7.3) for real-world studies. The pooled cumulative ORR was 48% for the overall cohort, with a significantly lower ORR (44%) for clinical trials (with low heterogeneity of 0%) than for real-world studies (51%; Fig. 2B).

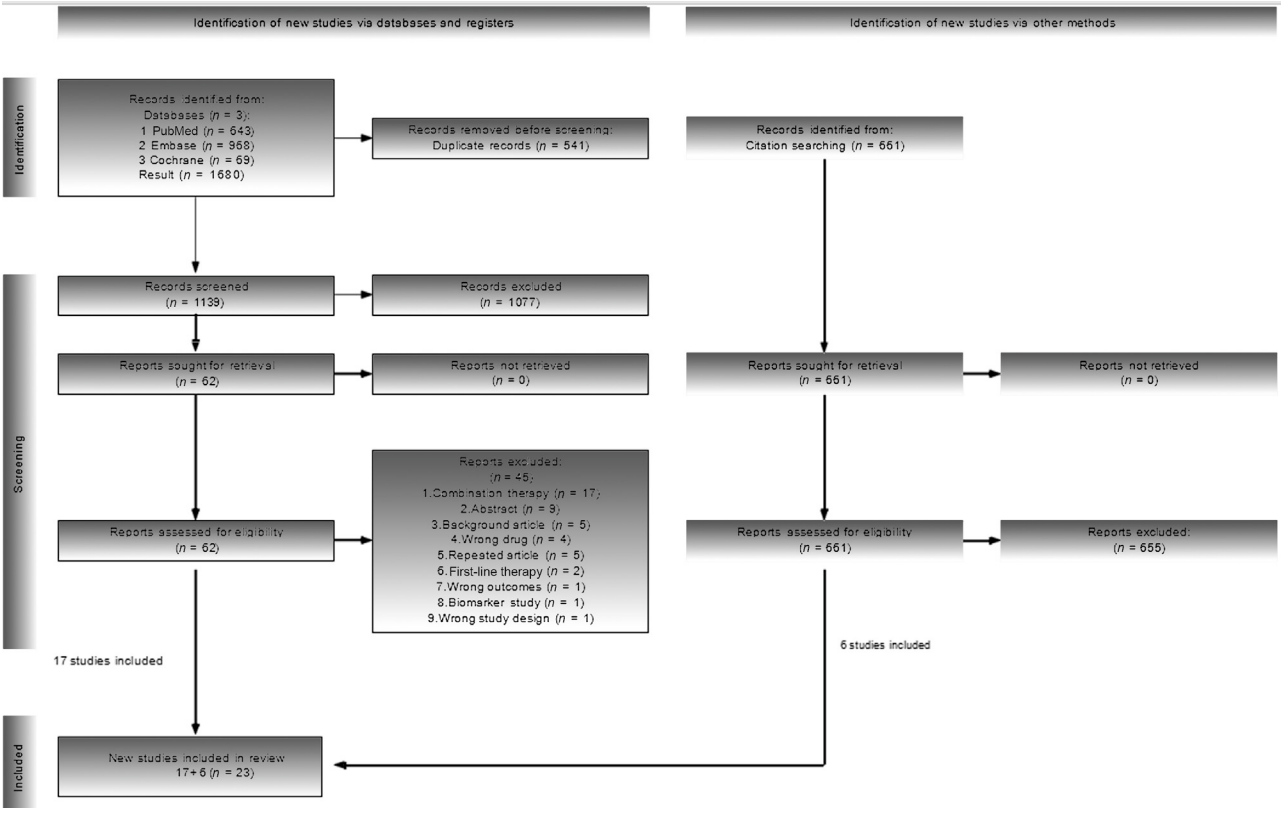



**Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flowchart of the study selection process.**

### 3.4. *Clinicopathological parameters*

Fig. 3 shows a summary of forest plots with pooled ORR, OS, and PFS results for all parameters. Detailed forest plots with all parameters for all studies are provided in Supplementary Figs. 1–16.

We found no significant associations between patient age or sex and the ORR, OS, and PFS outcomes (Supplementary Figs. 1 and 2).

Six articles reported ORRs stratified by ECOG PS (0–1 vs >1). The pooled OR (0.43, 95% CI 0.20–0.95; $p = 0.041$) indicates significantly lower ORR for patients with unfavorable ECOG PS (Supplementary Fig. 3A). Similar results were obtained in the other four studies using a different ECOG PS cutoff (0 vs 1–2; Supplementary Fig. 4). Accordingly, both OS (HR 2.93, 95% CI 1.64–5.22; $p < 0.001$) and PFS (HR 2.14, 95% CI 1.60–2.86; $p < 0.001$) were shorter for patients with unfavorable ECOG PS (Supplementary Fig. 3B,C).

According to data from 11 studies involving 1194 patients, the ORR was significantly higher for upper-tract UC than for bladder UC (OR 1.29, 95% CI 1.01–1.63; $p = 0.041$). OS and PFS were similar between bladder and upper-tract UC, suggesting comparable EV efficacy, with a slightly better ORR for upper-tract UC (Supplementary Fig. 5).

The presence of liver metastasis was associated with significantly shorter OS (HR 1.38, 95% CI 1.10–1.74; $p = 0.005$) whereas ORR and PFS were comparable between the groups with and without liver metastasis, suggesting that liver metastasis is prognostic rather than predictive in EV-treated patients (Supplementary Fig. 6).

We found significantly shorter PFS for tumors harboring secondary non-urothelial histology in comparison to those with pure urothelial histology (HR 1.62, 95% CI 1.10–2.38; $p = 0.015$; Supplementary Fig. 7). The trend was similar for OS and ORR, but the differences did not reach statistical significance. Limited data for each histological variant prevented differentiation between specific non-urothelial subtypes.

Six articles reported ORR data stratified by prior ICI response, and three by prior PBC therapy. The pooled OR for the ORR to EV was significantly higher for the group with a response to prior ICI therapy (OR 1.51, 95% CI 1.12–2.04; $p = 0.017$). An even stronger association was observed for response to PBC therapy, with a more than 2.5-fold higher EV response rate in the group with a radiographic response to prior PBC (OR 2.65, 95% CI 1.04–6.72; $p = 0.046$). These findings suggest that previous responses to PBC and ICI therapies are positive predictive factors for the response to EV in patients with UC (Supplementary Figs. 8 and 9).

### 3.5. *Molecular parameters*

The relationship between molecular parameters and EV response was evaluated for PD-L1 and NECTIN4 immunostaining and *FGFR3* genetic alterations.

**Table 1 – Characteristics of the studies included in the review**

| Study | Country | Study design | Study period | Pts | Median age, yr (range) | F (%) | ORR (%) | mPFS (mo) | mOS (mo) | mFU, mo (IQR) | mNCs (range) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Minato [22] | Japan | RT-RW | 2021–2023 | 26 | 73 65–76) [a] | 15 | 58 | 5.4 | 10.3 | 7.5 (4.9–10.8) | 5 (3–7) [a] |
| Rosenberg [25] EV-201 | USA | PP phase 2 | 2017–2018 | 125 | 69 (40–84) | 30 | 44 | 5.8 | 11.7 | 10.2 (0.5–16.5) [b] | NA |
| Rosenberg [24] EV-101 | USA | PP phase 1 | 2014–2018 | 155 | 67 (24–86) | 28 | 43 | 5.4 | 12.3 | 16.4 (NA) | NA |
| Yu [30] EV-201 | USA | PP phase 2 | 2017–2020 | 89 | 75 (49–90) | 26 | 52 | 5.8 | 14.7 | 13.4 (11.3–18.9) | NA |
| Powles [23] EV-301 | USA | RCT phase 3 | NA | 301 | 68 (34–85) | 21 | 41 | 5.6 | 12.9 | 11.1 (NA) | NA |
| Zschabitz [13] | Germany | RT-RW | 2021–2022 | 188 | 66 (31–89) | 30 | 49 | 7.0 | 12.0 | NA | NA |
| Fukuokaya [33] | Japan | RT-RW | 2022–2023 | 103 | 74 (69–79) | 33 | 51 | 6.0 | 14.5 | 8.9 (0.1–16.4) [b] | NA |
| Taguchi [27] [c] | Japan | RT-RW | 2018–2023 | 39 | 72 (64–77) [a] | 28 | 46 | 5.0 | 11.0 | NA | NA |
| Matsubara [21] [d] | Japan | RCT phase 3 | NA | 86/36 | 70 (58–87) | 22 | 34 | 6.5 | 15.2 | 10.7 (NA) | NA |
| Rosenberg [26] EV-301 | USA | RCT phase 3 | NA | 301 | NA | NA | 41 | 5.6 | 12.9 | 23.6 (NA) | NA |
| Adib [31]; FGFR$^{+}$ | USA | RT-RW | 2017–2021 | 60 | 71 (48–88) | 27 | 45 | 4.1 | 12.9 | NA | NA |
| Adib [31]; FGFR$^{-}$ | USA | RT-RW | 2017–2021 | 60 | 71 (48–88) | 27 | 58 | 5.5 | 12.5 | | NA |
| Miyake [32] | Japan | RT-RW | 2008–2023 | 34 | 76 (64–86) [a] | 26 | 56 | 9.0 | 16.0 | NA | 5 (3–7) [a] |
| Jindal [18] | USA | RT-RW | 2020–2022 | 29 | 70 (NA) | 17 | 41 | 5.1 | 10.2 | 16.3 (NA) | 5 (1–28) |
| Klümper [20] | Germany | RT-RW | NA | 47 | NA | 23 | 37 | NA | NA | NA | NA |
| Minato [35] [e] | Japan | RT-RW | 2021–2023 | 62 | 73 (68–76) | 30/17 | 57/44 | 5.9/4.2 | 16.1/7.3 | 7.1 (4.0–11.8) | 4 (3–7) [a] |
| Endo [34] | Japan | RT-RW | 2021–2023 | 20 | 73 (61–85) | 3 | 55 | 10.5 | 12.9 | 11.2 (2.7–22.5) [b] | 7 (2–18) |
| Takahashi [28] | Japan | RT-RW | NA | 17 | 68 (57–82) | 11 | 35 | 8.1 | NA | NA | 5 |
| Tomiyama [8] | Japan | RT-RW | NA | 99 | 71 (48–87) | 39 | NA | NA | NA | NA | NA |
| Vlachou [29] | USA | RT-RW | 2017–2022 | 56 | 70 (34–90) | 27 | 41 | 6/4.5 | NA | NA | 3-5 |
| Inoue [17] | Japan | RT-RW | 2008–2017 | 11 | NA | NA | NA | NA | NA | 179 [d] (91–611) | NA |
| Jindal [36] PUC | USA | RT-RW | 2014–2022 | 14 [f] | 69.6 | 31 | 50 | 15.8 | 15.8 | NA | NA |
| Jindal [36] UCS | USA | RT-RW | 2014–2022 | 11 [f] | 69.6 | 31 | 18 | 3.9 | 5.5 | NA | NA |
| Kawahara [19] | Japan | RT-RW | 2008–2022 | 563 | 73 (NA) | 33 | NA | NA | NA | NA | NA |
| Koshkin [2] | USA | RT-RW | NA | 260 | 71 | 21 | 52 | 6.8 | 14.4 | 7.2 ( 3.7-11.6) | NA |

Pts = patients; F = female; IQR = interquartile range; ORR = objective response rate; mPFS = median progression-free survival; mOS = median overall survival; mFU = median follow-up; DCR =disease control rate; mNCs = median number of cycles; PUC = pure urothelial carcinoma; PP = prospective study; UCS =urothelial carcinoma with a secondary subtype; RCT =randomized controlled trial; RT-RW = retrospective real-world study, NA = not available.

[a] Interquartile range.

[b] Range.

[c] Before propensity score matching.

[d] Japanese subgroup of EV-301.

[e] Patients were divided into two groups: PUC ($n$ = 44) and SUC ($n$ = 18).

[f] Patients receiving enfortumab vedotin monotherapy.

Four studies involving 338 patients compared the ORR between PD-L1-positive and PD-L1-negative groups. Although the PD-L1-positive group tended to have a lower response rate to EV (OR 0.70, 95% CI 0.43–1.16; $p$ = 0.113), the difference was not statistically significant. Similarly, there was no significant association between PD-L1 status and OS (Supplementary Fig. 10) [2,13].

Three studies involving 346 patients evaluated the association between *FGFR3* alterations and EV treatment outcomes. Our analysis revealed no significant correlation between *FGFR3* mutation status and ORR or OS (Supplementary Fig. 11).

We compiled a data set from three articles [4,5,27] and calculated the standard mean difference (SMD) in NECTIN4 expression. The combined effect size across the studies was substantially null (SMD = −0.00, 95% CI −1.11 to 1.10), indicating no significant overall difference in Nectin-4 expression in this pooled population. This result reflects substantial heterogeneity, indicating considerable variation in results between studies, which may be because of differences in study design, patient populations, or methods for assessing NECTIN4 expression (Supplementary Fig. 12).

### 3.6. *Laboratory parameters*

A high Bellmunt risk score of >1 (OR 0.57, 95% CI 0.37–0.96; $p$ = 0.040) and low GFR of <60 ml/min (OR 0.59, 95% CI 0.47–0.74; $p$ = 0.010) were significantly associated with poor ORR. Similarly, low hemoglobin (<10 g/dl) was associated with significantly shorter OS (HR 0.69, 95% CI 0.55–0.86; $p$ = 0.001) and PFS (HR 0.67, 95% CI 0.56–0.79; $p$ < 0.001; Supplementary Figs. 13–15). By contrast, NLR was not significantly associated with ORR, OS, or PFS (Supplementary Fig. 16).

### 3.7. *RoB assessment*

Results for the RoB assessment are presented in Supplementary Table 2. RoB for participation was low in 13 studies, moderate in six, and high in one study. Study attrition was not applicable because of the retrospective nature. Risk

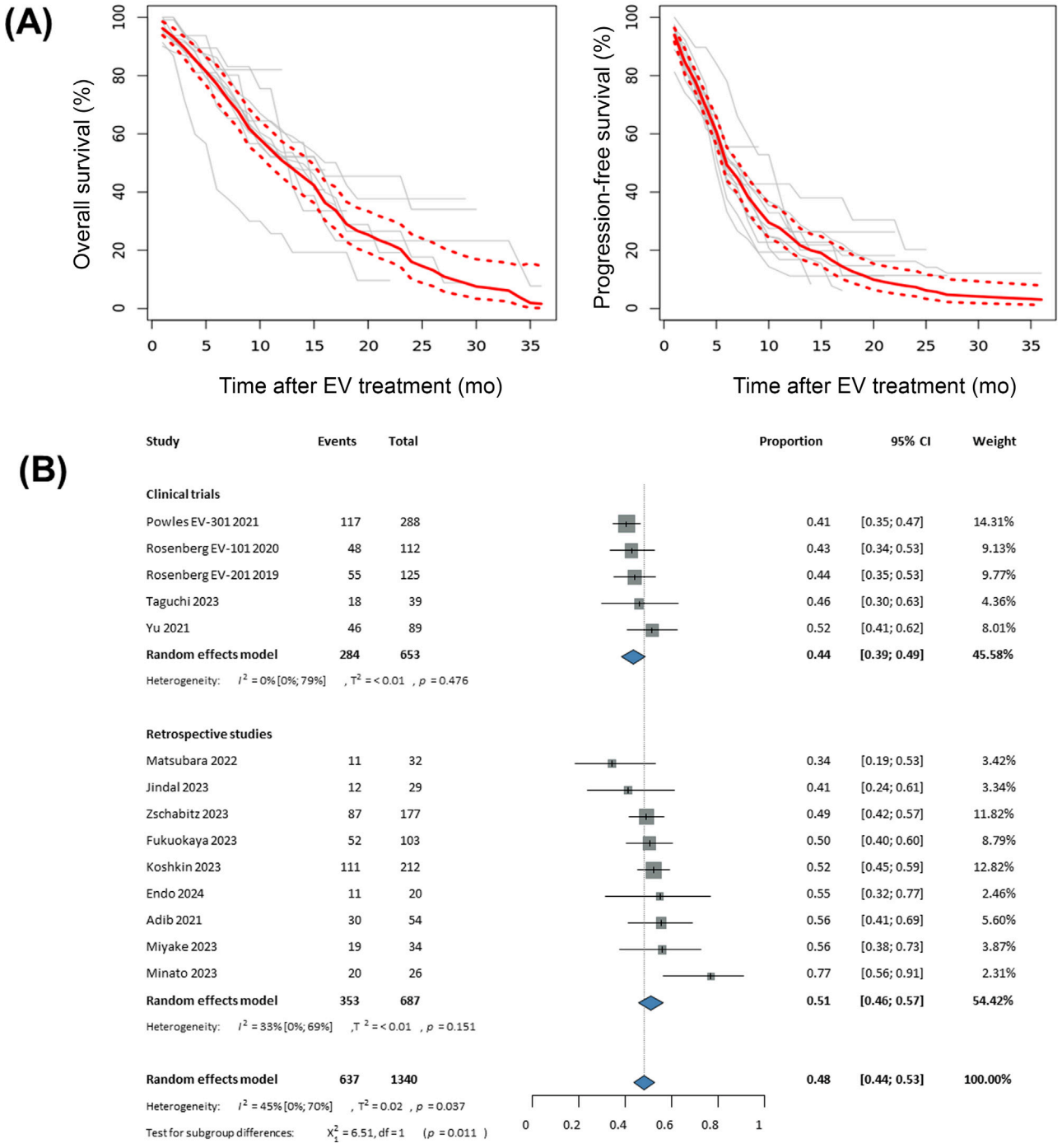



**Fig. 2 – (A) Pooled results for overall survival progression-free survival. Median overall survival was 12.3 mo (95% CI 10.4–14.3) and median progression-free survival was 5.9 mo (95% CI 5.5–7.0). Red solid lines represent pooled survival curves generated using a random-effects model, dashed lines indicate the 95% CI, and grey lines indicate survival probabilities reported in individual studies.(B) Comparison of pooled objective response rates in clinical trials versus real-world studies. CI = confidence interval; EV = enfortumab vedotin.**

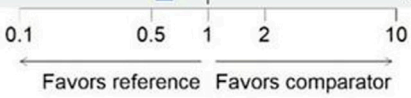
factor and outcome measurement were mainly at low RoB. The highest RoB was for study confounding.

## 4. Discussion

This is the first meta-analysis to assess the association of clinical and molecular factors with treatment response (ORR) and time-to-event outcomes (OS and PFS) for patients with advanced UC who underwent EV monotherapy after chemotherapy and immunotherapy. We identified a favorable EV response for patients who responded to previous PBC and ICI therapy, but high ECOG PS and Bellmunt risk score, and low GFR and hemoglobin levels were associated with poor EV response. By contrast, age, sex, NLR, liver

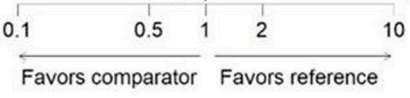
## A) ORR

| Parameters (ref/comparator) | n | Pooled OR (95% CI) | *p* value | $I^2$ |
|---|---|---|---|---|
| Sex (male /female) | 963 | 1.03 (0.82-1.30) | 0.759 | 0% |
| Age (<75 / ≥75 yr) | 1039 | 0.88 (0.54-1.45) | 0.566 | 42% |
| ECOG status (0-1 / >1) | 572 | 0.43 (0.20-0.95) | 0.041 | 24% |
| Bellmunt risk factor (0-1 / >1) | 438 | 0.57 (0.37-0.96) | 0.040 | 7% |
| Liver metastasis (absent /present) | 1052 | 1.02 (0.65-1.59) | 0.921 | 45% |
| Tumor location (bladder /upper tract) | 1194 | 1.29 (1.01-1.63) | 0.041 | 0% |
| Histology (pure urothelial /mixed histology) | 526 | 0.72 (0.37-1.41) | 0.265 | 27% |
| Response to platinum (non-resp /resp) | 106 | 2.65 (1.04-6.72) | 0.046 | 0% |
| Response to ICI (non-resp /resp) | 595 | 1.51 (1.12-2.04) | 0.017 | 0% |
| PD-L1 immunostaining (negative /positive) | 338 | 0.70 (0.43-1.16) | 0.113 | 0% |
| FGFR3 alteration (positive /negative) | 346 | 0.84 (0.33-2.16) | 0.504 | 0% |
| NLR (≥5 / <5) | 288 | 1.17 (0.13-10.73) | 0.789 | 46% |
| GFR (≥60 / <60) | 400 | 0.59 (0.47-0.74) | 0.010 | 0% |




## B) OS

| Parameters (ref/comparator) | n | Pooled HR (95% CI) | *p* value | $I^2$ |
|---|---|---|---|---|
| Sex (male /female) | 221 | 0.85 (0.58-1.24) | 0.386 | 0% |
| Age (<75 / ≥75 years) | 523 | 1.16 (0.83-1.62) | 0.382 | 0% |
| ECOG status (0-1 / >1) | 236 | 2.93 (1.64-5.22) | <0.001 | 68% |
| Liver metastasis (absent /present) | 538 | 1.38 (1.10-1.74) | 0.005 | 0% |
| Tumor location (bladder /upper tract) | 480 | 1.16 (0.87-1.55) | 0.317 | 0% |
| Histology (pure urothelial /mixed histology) | 337 | 1.17 (0.85-1.62) | 0.328 | 0% |
| PD-L1 immunostaining (negative /positive) | 159 | 1.03 (0.61-1.72) | 0.922 | 0% |
| FGFR3 alteration (positive /negative) | 221 | 1.44 (0.84-2.46) | 0.185 | 0% |
| NLR (≥5 / <5) | 85 | 1.65 (0.89-3.03) | 0.109 | 0% |
| Hemoglobin level (<10 g/dl /≥ 10 g/dl) | 105 | 0.69 (0.55-0.86) | 0.001 | 0% |




## C) PFS

| Parameters (ref/comparator) | n | Pooled HR (95% CI) | *p* value | $I^2$ |
|---|---|---|---|---|
| Sex (male /female) | 330 | 0.92 (0.69-1.24) | 0.726 | 0% |
| ECOG status (0-1 / >1) | 235 | 2.14 (1.60-2.86) | <0.001 | 0% |
| Liver metastasis (absent /present) | 302 | 1.07 (0.79-1.44) | 0.671 | 0% |
| Tumor location (bladder /upper tract) | 312 | 0.99 (0.74-1.31) | 0.926 | 0% |
| Histology (pure urothelial /mixed histology) | 168 | 1.62 (1.10-2.38) | 0.015 | 0% |
| FGFR3 alteration (positive /negative) | 221 | 1.22 (0.72-2.07) | 0.460 | 0% |
| NLR (≥5 / <5) | 85 | 0.97 (0.61-1.54) | 0.884 | 0% |
| Hemoglobin level (<10 g/dl /≥10 g/dl) | 167 | 0.67 (0.56-0.79) | <0.001 | 0% |




**Fig. 3 – Forest plots of the effect of different patient characteristics on (A) ORR, (B) OS, and (C) PFS. ECOG = Easter Cooperative Oncology Group; GFR = glomerular filtration rate (ml/min); HR = hazard ratio; ICI = immune checkpoint inhibitor; NLR = neutrophil/lymphocyte ratio; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; resp = response.**

metastasis, histology variants, and *FGFR3* mutations showed no association with EV sensitivity.

The pooled ORR for 14 studies (clinical trials and real-world data) was 48%, with a significantly higher rate for the real-world data (51%) than for the clinical trials (44%). Pooled median survival times were 10.4 mo for OS and 5.5 mo for PFS, with comparable values for the clinical trial and real-world data.

ECOG PS is widely used to evaluate patient suitability for treatments such as chemotherapy and radiotherapy and for participation in clinical trials, and is an independent prognostic factor for OS in advanced/metastatic UC treated with PBC [38,39]. Our meta-analysis revealed significantly shorter OS and PFS and poor ORR for patients with worse ECOG PS, suggesting that patients with favorable PS may benefit more from EV therapy. Liver metastasis, another key parameter, was significantly associated with poor OS, but not PFS or ORR, suggesting its role as a prognostic rather than a predictive factor for EV treatment. The Bellmunt risk score (calculated using ECOG PS, hemoglobin level, and presence of liver metastasis) has been identified as a prognostic factor for advanced UC [39]. Our assessment of the association of the Bellmunt score with ORR in five studies revealed a 43% lower ORR to EV therapy for patients with a Bellmunt score >1.

Our meta-analysis revealed a significant 51% higher response rate to EV when patients had a complete or partial response to prior-line ICI therapy. An even stronger association was observed for PBC treatment, showing over 2.5 times higher ORR for responders. Taken together, these associations suggest that patients with higher sensitivity to platinum and ICI treatment benefit more from EV therapy, which may further increase the outcome disparity between responders and non-responders. A mechanistic analysis of these associations may reveal their molecular background and may help in strategies to overcome therapy resistance. In addition, these results may characterize a subgroup of patients with enhanced therapy resistance who are in need of novel therapies and are therefore good candidates for further clinical trials.

Routine laboratory parameters are optimal predictive factors for therapy, as they are easy to assess, quick to obtain, and cost effective, and are thus widely accessible across various health care settings. Hemoglobin, NLR, and GFR have been associated with therapy response and survival among UC patients treated with ICI therapy [40,41]. By contrast, we found no similar associations for EV, suggesting that NLR as a measure of systemic inflammatory conditions is predictive of response to ICI therapy but not EV, and thus may help in optimizing therapeutic decision-making.

Secondary histology subtypes or variants are present in one-third of UCs and are associated with diverse molecular backgrounds, a higher risk of disease progression, and differences in therapeutic sensitivity. However, there are limited prospective data on the therapeutic sensitivity of histology subtypes, as specific subtypes are rare and tumors carrying secondary histological subtypes are generally excluded. In a recent study of EV-treated patients, Minato et al. [35] found similar ORR and OS but longer PFS for pure UC versus UC with secondary histological subtypes. Our meta-analysis revealed shorter PFS but similar OS and ORR for UC with histological subtypes versus pure UC. Notably, these analyses are limited as we grouped all secondary variants together, despite their distinct morphological and molecular features. Therefore, larger data sets are needed to assess EV sensitivity across different histological subtypes in a statistically relevant manner.

Molecular analyses are increasingly involved in therapeutic decision-making in UC. *FGFR3* alterations may be an indication for targeted FGFR inhibitor therapy in patients with advanced UC. For EV, similar to other antibody-drug conjugates, membranous expression of its molecular target NECTIN4 seems to be a reasonable predictive factor. The initial EV-101 trial used positive membranous NECTIN4 immunostaining as a selection criterion [24]. However, this criterion was later dropped because the vast majority of UCs in the initial study exhibited robust NECTIN4 expression [7,23,24,30]. In addition, later studies found lower NECTIN4 positivity rates in advanced UC specimens, and lower expression in metastasis biopsies [20]. For our meta-analysis. NECTIN4 expression data were available from three studies involving 222 patients [24,25,30]. Our SMD calculation for NECTIN4 expression revealed that the combined effect size across these studies was essentially zero (SMD = −0.00, 95% CI −1.11 to 1.10), which indicates that there was no significant overall difference in NECTIN4 expression. This can be explained by differences in study design (one study included only NECTIN4-positive cases), staining methods (different antibodies), and staining evaluation (membranous ± cytoplasmic staining). The latter may be critical for predictions of response to a drug that targets a cell-surface protein. Overall, NECTIN4 immunostaining in advanced UC may be overestimated and could be lower at distant metastatic sites, and its predictive accuracy could be affected by methodological factors. In this context, it is important to note that Klümper and Eckstein [42] reported that *NECTIN4* amplification was relatively frequent (25%) in advanced UC, was less volatile in comparison to immunostaining, and exhibited a strong association with ORR to EV treatment.

PD-L1 immunohistochemistry is routinely used to decide between carboplatin and ICI for first-line treatment of cisplatin-ineligible patients with UC, whereas tumor mutational burden (TMB) and microsatellite instability can also be used to predict responses to ICI treatment. In our analysis of four studies involving 338 EV-treated patients, ORR tended to be higher in the PD-L1-negative group. This is in accordance with an analysis of an independent data set (published as a conference abstract and thus excluded from this meta-analysis) that showed that PD-L1 positivity was significantly correlated with shorter OS and lower ORR among EV-treated patients [43]. In addition, TMB-high tumors were associated with better OS in the EV-treated population [43].

The association between EV sensitivity and *FGFR3* alterations is of specific clinical interest, as FGFR inhibitor therapy (erdafitinib) is available in the third-line setting for molecularly selected patients with UC. To answer the question of whether EV or anti-FGFR therapy is more effective in

patients with *FGFR3* alterations, we extracted data on *FGFR3* alteration status from three publications (346 patients). Our meta-analysis revealed no significant impact of *FGFR3* alterations on the ORR for EV, which suggests that *FGFR3* alterations have no major impact on the efficacy of EV. Notably, Koshkin et al. [2] observed responses to EV in a subset of patients previously treated with the *FGFR3* inhibitor erdafitinib (two of five patients experienced a partial response). This suggests that EV can be used sequentially in patients with UC and *FGFR3* alterations after previous erdafitinib treatment. Our conclusions regarding PD-L1, *FGFR3,* and NECTIN4 must be interpreted with caution because of limited sample sizes and substantial heterogeneity in analysis methods, patient selection, and reporting. Our intention was to present a structured synthesis of currently available data, identify gaps, and emphasize the need for prospective biomarker-driven studies. An important limitation of the use of tissue biomarkers is that tumor samples may be obtained in earlier disease or treatment settings, and may not fully reflect the molecular landscape at the time of later-line therapy, which reduces the accuracy of biomarker-based predictions of treatment response.

### 4.1. Strengths and limitations

This is the first meta-analysis to assess prognostic and predictive clinical and molecular factors for EV sensitivity. By combining clinical trials results and real-world data, we were able to evaluate a large number of clinical, pathological, and molecular parameters in a large number of patients for three different endpoints to identify both prognostic and predictive effects. We used a prospectively established methodology that was registered on PROSPERO. We also assessed patient-level data from two large retrospective studies, which provides good flexibility in data analysis.

Our study is not without limitations. There was considerable heterogeneity in study design, as well as in clinical and methodological factors, across the studies. Retrospective studies inherently have a higher degree of heterogeneity because of variations in study design, patient populations, prior treatment, and data collection methods, which may affect the consistency and generalizability of our findings. One study was considered to have high RoB due to potential confounding. However, leave-one-out analyses did not identify this study as being influential on the overall results [33]. In addition, despite significant mitigation efforts, there may be minor cohort overlap between the studies by Koshkin et al. [2] and Jindal et al. [18,36] for patients treated at University of California-San Francisco between 2020 and 2022. However, the maximum number of overlapping patients is estimated to be <2% of all patients included in this meta-analysis.

Owing to a lack of patient-level data, we could not perform multivariable analyses, which limited our ability to adjust for potential confounders.

Furthermore, while the availability of data for some of the molecular parameters met the minimum criteria for statistical analysis, the number of studies with data available was relatively low. For other molecular markers, a quantitative synthesis was not feasible because of inconsistent reporting, which limits the conclusions for these markers. Future research involving prospective studies and larger sample sizes is warranted to confirm our findings.

### 4.2. Implications for practice and research

Our findings identified significant differences in EV sensitivity across clinical and molecular subgroups in UC, and highlight prognostic and predictive parameters that may guide therapeutic decisions. Although none of the markers discussed are currently recommended for routine clinical use, some physicians request targeted staining to support their clinical decision-making. Our results suggest that these analyses should be interpreted with caution, as current evidence supporting their validity remains limited. Nevertheless, they may be used to inform future trial design. Large real-world data sets are needed to evaluate EV responses in rare molecular or histological subgroups, which could potentially improve treatment for these patients. The practical application of scientific findings is crucial [44,45], so mechanistic research exploring how the molecular factors identified influence EV sensitivity is warranted.

## 5. Conclusions

EV is an effective treatment option for patients with advanced UC, even in less-selected real-world populations. Importantly, clinical parameters that are routinely available—such as ECOG PS, hemoglobin and GFR levels, response to prior chemotherapy or immunotherapy, and Bellmunt risk score—can be used to stratify patients according to their expected benefit. Integration of these factors into clinical decision-making can help to identify the patients who are most likely to respond to EV and those who should be considered for intensified or alternative strategies.

***Author contributions***: Tibor Szarvas 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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*Supervision*: Szarvas.
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***Data sharing statement*:** The data sets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2025.10.011.

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