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Enfortumab Vedotin in combination with Pembrolizumab in Urothelial Cancer

Rapid Review

Final Report

HTA-Information Service Rapid Review No.: 019

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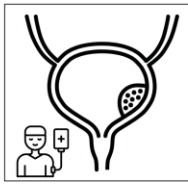

Enfortumab Vedotin in Combination with Pembrolizumab (EV+P) in Urothelial Cancer

Is EV+P as a first-line treatment for adult patients with unresectable or metastatic urothelial cancer, who are eligible for platinum-containing chemotherapy, more effective and safer compared to platinum-based chemotherapy?

What is the cost-effectiveness of the combination therapy?

Background

Urothelial carcinoma is among the most frequent malignant tumours, with a tendency to recur after initial treatment. EV, an antibody-drug conjugate (ADC), is indicated in combination with Pembrolizumab (an immune-checkpoint-inhibitor, ICI) as first-line treatment in patients eligible for platinum-containing chemotherapy with unresectable or metastatic urothelial carcinoma. By combining ICIs and ADCs, the anti-tumour efficacy is enhanced. However, the combination regimen is associated with substantial costs, underlining the need for careful clinical and economic evaluation.

Methods

Systematic literature search for systematic reviews (SR) and HTA reports + hand search for cost-effectiveness analyses and real-world studies

Effectiveness + safety

22 studies → full text analysis → 7 SRs → risk-of-bias assessment → 5 SRs and 3 HTA reports for synthesis of results;

+

Cost-effectiveness and real-world data

7 primary studies → 5 primary studies for cost-effectiveness, 2 primary studies for real-world data

Results

Included study types	SRs based on RCTs, HTA reports; primary studies for economic evaluation and real-world data
Effectiveness	OS, PFS: significant improvement
	ORR, DRC, CRR: significant improvement
QoL	not reported in SRs, data from EV302/KEYNOTE-A39 trial show slight improvement in QoL
Adverse events (AEs)	less high-grade (severe) AEs, overall acceptable safety profile
Risk-of-Bias EV302/KEYNOTE-A39 trial	***low*** *to* ***some concerns***

Interpretation

- The evidence shows clinically meaningful benefits of EV+P compared with platinum-based chemotherapy in improving OS, PFS and the ORR. In addition, the DCR and CRR improved significantly with the combination therapy. EV+P resulted in lower occurrence of high-grade (severe) AEs compared to platinum-based chemotherapy. However, results were solely based on one RCT, the EV302/KEYNOTE-A39 trial. Primary study data suggest that the combination therapy maintains global health status/ quality of life and pain control, with substantial improvement in patients with moderate to severe pain at baseline.
- Guidelines: EV+P is recommended as first-line treatment for patients with advanced or metastatic urothelial carcinoma.
- Included cost-effectiveness analyses indicate that at its current price, EV+P is not cost-effective at commonly accepted willingness-to-pay thresholds, and substantial price reductions would be necessary.
- Real-world data from Austria and Germany confirm survival benefits and good tolerability of EV+P in clinical practice.
- Limitations: limited evidence base; hand search for CEAs and real-world studies; no risk of bias assessment of primary studies.

Evidence indicates that EV+P provides improved survival outcomes compared to platinum-based chemotherapy and a generally favourable safety profile as first-line treatment in patients with unresectable or metastatic urothelial carcinoma. The evidence base is limited to one RCT, however. Substantial price reductions would be necessary for the combination therapy to be cost-effective.

ADC - antibody-drug conjugate; AE – adverse event; CEA – cost-effectiveness analysis; CRR - complete response rate; DCR – disease control rate; EV+P - Enfortumab Vedotin in combination with Pembrolizumab; ICI - immune-checkpoint-inhibitor; OS – overall survival; ORR – overall response rate; PFS – progression free survival; RCT – randomised controlled trial; SR – systematic review; QoL – quality of life

2 Deutsche Zusammenfassung

Urothelkarzinome zählen zu den häufigsten malignen Tumoren und weisen eine hohe Rezidivneigung auf. Die Kombination von Enfortumab Vedotin, einem Antikörper-Wirkstoff-Konjugat (antibody-drug conjugate, ADC), mit Pembrolizumab, einem Immun-Checkpoint-Inhibitor (immune checkpoint inhibitor, ICI), ist seit September 2024 als Erstlinientherapie für Patient:innen mit nicht resezierbarem oder metastasiertem Urothelkarzinom zugelassen, die für eine platinhaltige Chemotherapie geeignet sind. Seit der Zulassung auf Basis veröffentlichter Ergebnisse der EV302/KEYNOTE-A39-Studie, einer randomisierten kontrollierten Studie zur Untersuchung der Kombinationstherapie im Vergleich zu platinbasierter Chemotherapie als Erstlinienbehandlung des fortgeschrittenen/metastasierten Urothelkarzinoms, hat sich die ADC-ICI-Kombinationstherapie in der klinischen Praxis als neue Standard-Erstlinienbehandlung etabliert. Dem potenziellen therapeutischen Nutzen stehen jedoch die erheblich höheren Behandlungskosten der Kombinationstherapie gegenüber. Der vorliegende Rapid Review untersucht die Wirksamkeit, Sicherheit und Kosteneffektivität der Kombinationstherapie im Vergleich zur platinbasierten Chemotherapie.

Enfortumab Vedotin + Pembrolizumab seit 2024 als Erstlinientherapie für nicht resezierbares/ metastasiertes Urothelkarzinom zugelassen

in der Praxis als Erstlinienbehandlung etabliert

erheblich höhere Kosten der Kombinationstherapie im Vergleich zur platinbasierten Chemotherapie

Die Evidenzsynthese basiert auf fünf systematischen Übersichtsarbeiten hoher Qualität, die in Bezug auf die ADC-ICI-Kombinationstherapie allerdings ausschließlich auf Ergebnissen einer einzigen Studie, EV302/KEYNOTE-A39, beruhen. Diese Studie zeigte klinisch bedeutsame Vorteile gegenüber der platinbasierten Chemotherapie: Das mediane Gesamtüberleben verlängerte sich von 16,1 auf 31,5 Monate, das mediane progressionsfreie Überleben von 6,3 auf 12,5 Monate. Die objektive Ansprechrate, die Krankheitskontrollrate und die vollständige Ansprechrate verbesserten sich signifikant. Diese Vorteile zeigten sich unabhängig vom PD-L1-Expressionsstatus. Insgesamt wies die Kombinationstherapie niedrigere Raten schwerer unerwünschter Ereignisse auf, wobei spezifische Probleme wie Durchfall, Pruritus und periphere Neuropathie bei der Kombinationstherapie häufiger auftraten als in der Vergleichsgruppe. Daten zur Lebensqualität aus den systematischen Reviews lagen nicht vor, eine im Juni 2025 veröffentlichte Publikation zu patientenberichteten Endpunkten der EV302-Studie zeigt jedoch eine Aufrechterhaltung der globalen Gesundheit und Lebensqualität sowie eine Verbesserung der Schmerzkontrolle, insbesondere bei Patient:innen mit moderaten bis starken Baseline-Schmerzen. Alle identifizierten internationalen Leitlinien empfehlen die Kombinationstherapie als bevorzugte Erstlinienbehandlung. Drei HTA-Berichte aus Deutschland, Kanada und Großbritannien bestätigen die klinischen Vorteile und ein insgesamt akzeptables Sicherheitsprofil.

Ergebnisse basieren auf einem RCT, der EV302/KEYNOTE-A39 Studie

klinisch bedeutsame Vorteile gegenüber der platinbasierten Chemotherapie: signifikant erhöhtes medianes Gesamt- und progressionsfreies Überleben, Ansprechraten signifikant verbessert

weniger schwere Nebenwirkungen, aber spezifische Ereignisse

Leitlinien empfehlen Kombinationstherapie als Erstlinienbehandlung

Ein zentraler Diskussionspunkt sind die erheblichen Kosten der Kombinationstherapie. Fünf internationale Kosteneffektivitätsanalysen kommen übereinstimmend zu dem Ergebnis, dass diese trotz ihrer klinischen Vorteile zu den derzeitigen Preisen nicht kosteneffektiv ist. Erhebliche Preisreduktionen wären erforderlich. Die Übertragbarkeit dieser Analysen auf Österreich ist jedoch aufgrund fehlender Willingness-to-Pay-Thresholds, möglicher Preisunterschiede sowie Unterschieden im Gesundheitssystem limitiert.

Kosteneffektivität nicht gegeben

erhebliche Preisreduktionen erforderlich

Real-world Daten aus dem österreichischen Enfortumab-Register und dem deutschen GUARDIANS-Projekt bestätigen die Wirksamkeits- und Sicherheitsergebnisse der Zulassungsstudie in der klinischen Praxis, wobei die österreichischen Daten auf niedrigere Ansprechraten bei Patient:innen mit schwerwiegenden Komorbiditäten hinweisen.

Real-world- Daten bestätigen die Wirksamkeit und Sicherheit

Die verfügbaren Wirksamkeits- und Sicherheitsdaten sollten unter Berücksichtigung der wirtschaftlichen Implikationen interpretiert werden, eine kontinuierliche Evaluation der Übertragbarkeit auf die klinische Praxis bleibt weiterhin notwendig.

kontinuierliche Evaluation der Übertragbarkeit auf die klinische Praxis notwendig

3 Background and research questions

Urothelial carcinoma is a type of cancer that develops in the urothelium, which is the tissue lining various parts of the urinary tract. Urothelial carcinomas are categorised based on their location, dividing them into those affecting the lower urinary tract versus the upper urinary tract. This cancer type ranks among the most frequently occurring cancerous tumours and represents approximately 90% of bladder cancers and 7% of kidney cancers, affecting areas like the renal pelvis and ureter. When urothelial carcinoma occurs in either the bladder or kidneys, it tends to cause comparable symptoms and follows a similar disease course [1, 2].

Urothelkarzinome entwickeln sich im Gewebe des Harntrakts

einer der häufigsten Tumore

While these cancers respond well to treatment when detected in their early stages, they **tend to recur** after initial treatment. The probability of recurrence and progression depends on tumour type, stadium and risk profile; for non-muscle-invasive carcinomas (making approximately 75% of all urothelial carcinomas), it is calculated according to a score developed by the European Organisation for Research and Treatment of Cancer (EORTC); non-muscle invasive tumours have a higher recurrence risk than muscle-invasive tumours. Metastatic development of urothelial cacinoma impacts prognosis and treatment decisions; while non-muscle invasive tumours have limited metastatic potential, muscle-invasive tumours have a higher metastasis risk of approximately 30%. With regard to relative 5-year survival rates by tumour stage, the prognosis is significantly better in UICC stage I[1] (> 70%) and worse in stage IV[2] (< 15%) [1, 3].

im Frühstadium gut behandelbar, tendieren aber zu Rückfällen

nicht muskel-invasive Tumore haben eine höhere Rezidivwahrscheinlichkeit

muskel-invasive Tumore metastasieren häufiger als nicht muskel-invasive

Urothelial carcinomas affect men at a rate three times higher than women, with most cases diagnosed in patients over 70 years of age [1, 3, 4]. In Austria, the age-stardardised **incidence rate** of bladder cancer per 100,000 (standardised according to European standard population 2013) in 2023 was 6.3 for women and 22.8 for men [5]. The age-standardised **incidence rate** of bladder cancer (being predominantly urothelial carcinomas) per 100,000 in 2022 in Germany was 5.1 for women and 17.0 for men [6].

Männer häufiger betroffen als Frauen, höhere Inzidenz im Alter

ähnliche Inzidenz in Österreich und Deutschland

Platinum-based chemotherapy regimens have been the standard first-line treatment strategy for advanced or metastatic urothelial carcinoma in the past decades [7]; however, their survival benefit is limited, especially in patients not eligible for cisplatin [8]. Platinum-based chemotherapy drugs are used to treat many different types of cancer. Most common drugs are cisplatin and carboplatin. Platinum-based chemotherapy drugs are alkylating agents that work best against slow-growing cancers. Their therapeutic effect occurs when platinum molecules attach to the DNA within cancer cells, damaging the genetic material and ultimately killing the cells [9].

platinbasierte Chemotherapie war lange Standard Erstlinientherapie

enthält meist Cisplatin oder Carboplatin, führt zum Zelltod der Krebszellen

[1] Tumor infiltriert subepitheliales Bindegewebe (T1), keine regionalen Lymphknotenmetastasen (N0), keine Fernmetastasen (M0)

[2] Fernmetastasen in nichtregionären Lymphknoten oder andere Fernmetastasen (M1a, M1b); schließt alle Klassifikationen bezüglich des Primärtumors und bezüglich regionaler Lymphknoten ein (jedes T, jedes N)

Patients with metastatic urothelial cancer, who have not yet received any treatment, can be classified into **three categories**: cisplatin eligible, cisplatin ineligible but carboplatin eligible, and platinum ineligible (cisplatin and carboplatin ineligible). Many patients with comorbidities (e.g. renal insufficiency) are ineligible for treatment with cisplatin and/or carboplatin: nearly half of patients diagnosed with advanced urothelial carcinoma are cisplatin ineligible, and about 10% of the patients are also carboplatin ineligible [10].

drei Kategorien von Patient:innen mit Urothelkarzinom: Cisplatin-geeignet, Cisplatin-ungeeignet aber Carboplatin-geeignet, und Platin-ungeeignet

In recent years, the therapeutic landscape of urothelial carcinoma has undergone a marked transformation. The integration of immune checkpoint inhibitors (ICIs) and antibody–drug conjugates (ADCs) into sequential treatment strategies has introduced new options that demonstrate encouraging clinical outcomes [8]. The current first-line standard for advanced or metastatic disease is the combination of Enfortumab Vedotin with Pembrolizumab, representing an ADC–ICI regimen. Traditional classifications based on cisplatin or platinum eligibility are expected to be replaced or refined by frameworks that consider Enfortumab Vedotin suitability - either with or without immunotherapy - and incorporate emerging molecular biomarkers to guide treatment selection [11].

Enfortumab Vedotin+Pembrolizumab ist Standard-Erstlinientherapie bei fortgeschrittenem/ metastasiertem Urothelkarzinom

Other treatment options for patients with advanced or metastatic urothelial carcinoma, depending on their eligibility for platinum-based therapy, include [12, 13]:

alternative Therapien je nach Verträglichkeit

- for cisplatin eligible patients: Nivolumab (an ICI) plus Gemcitabine (a pyrimidine analogue) and cisplatin or cisplatin-based chemotherapy (followed by maintenance avelumab for patients without disease progression);
- for cisplatin ineligible patients: Gemcitabine plus carboplatin or other agents;
- for platinum ineligible patients with a positive immune status (PD-L1): Pembrolizumab, Atezolizumab (ICI) or single-agent chemotherapy.

Enfortumab Vedotin (brand name: Padcev®) is an ADC that is given as an intravenous infusion. It is a Nectin-4-directed antibody and microtubule inhibitor conjugate marketed by **Astellas Pharma Europe B.V**. [14, 15]. Pfizer and Astellas have a collaboration agreement to co-develop Padcev® [16]. According to the European Medicines Agency (EMA), Enfortumab Vedotin can be used in two therapeutic indications: as **monotherapy** for patients with locally advanced or metastatic urothelial cancer (cancer that has spread throughout the body), who have already received platinum-containing chemotherapy and immunotherapy drugs that target PD-1 (programmed cell death protein 1) or PD-L1 (programmed death-ligand 1) and **in combination with Pembrolizumab** for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer, and who are eligible for platinum-containing chemotherapy [15]. Enfortumab Vedotin received a marketing authorisation in the EU in April 2022 [15]. The combination of Enfortumab Vedotin and Pembrolizumab has been approved since September 2024 as first-line therapy [17].

Enfortumab Vedotin (Padcev®) ist ein Antikörper-Wirkstoff-Konjugat

als Monotherapie indiziert bei fortgeschrittenem oder metastasiertem Krebs nach platinbasierter Chemotherapie und Immuntherapie

in Kombination mit Pembrolizumab (Keytruda®) auch als Erstlinientherapie

Indikation laut FDA: lokal fortgeschrittenes/ metastasiertes Karzinom

keine Einschränkung bezüglich Platin-Verträglichkeit

According to the **U.S. Food and Drug Administration** (FDA), the indication of Enfortumab Vedotin + Pembrolizumab does not depend on platinum eligibility of patients. The **specific indication** as mentioned by the FDA is: "*PADCEV®, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer*" [18]. Enfortumab Vedotin received initial U.S. approval in 2019 [18]. In April 2023, the FDA granted accelerated approval to Enfortumab Vedotin-ejfv[3] with Pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy [19]. In December 2023, this combination therapy was approved with the now valid indication [20].

Pembrolizumab ist ein Immun-Checkpoint-Inhibitor; wird auch als Monotherapie eingesetzt

Pembrolizumab (brand name: Keytruda®) is an Immune-Checkpoint-Inhibitor (PD-1-Inhibitor) marketed by **Merck Sharp & Dohme LLC** and is used on its own or in combination with other drugs to treat certain types of cancer including cancer of the kidney, bladder, and urinary tract [21]. PD-1 is a receptor for PD-L1 that is a transmembrane protein serving as a key factor in suppressing the immune response. Testing for this surface protein on cancer cells helps determine whether patients qualify for immunotherapy treatments [22].

EV302/KEYNOTE-A39 Studie etablierte Enfortumab Vedotin + Pembrolizumab

erhöhte Therapiekosten im Vergleich zur Chemotherapie

Since the publication of the EV302/KEYNOTE-A39 trial [23], an RCT assessing Enfortumab Vedotin + Pembrolizumab combination therapy against platinum-based chemotherapy as first-line treatment for advanced/metastatic urothelial carcinoma, the ADC-ICI combination therapy has been established as the new standard first-line regimen due to its survival benefits, representing a paradigm shift in the first-line treatment of advanced/metastatic urothelial carcinoma. However, the therapeutic benefit is counterbalanced by the substantially elevated treatment costs associated with combination therapy relative to platinum-based chemotherapy.

Forschungsfragen des Rapid Review

In this context, this Rapid Review aims to answer the following questions:

Wirksamkeit und Sicherheit

- Is Enfortumab Vedotin in combination with Pembrolizumab as a first-line treatment for adult patients with unresectable or metastatic urothelial cancer, who are eligible for platinum-containing chemotherapy, more effective and safer in terms of effectiveness outcomes, safety and quality of life, compared to platinum-based chemotherapy?

Kosteneffektivität

- What is the cost-effectiveness of Enfortumab Vedotin with Pembrolizumab compared to platinum-based chemotherapy?

[3] The suffix '-ejfv' is a designation assigned by the FDA to distinguish it from other drugs; Enfortumab Vedotin and Enfortumab Vedotin-ejfv describe the same active substance.

Table 3-1: PICOs-table regarding research questions

Population	Patients with: ■ unresectable or metastatic urothelial cancer, who are eligible for platinum-containing chemotherapy and have not been treated yet According to EMA (EPAR last updated 01/2025) **Enfortumab Vedotin (EV),** in combination with **pembrolizumab**, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer, who are eligible for platinum-containing chemotherapy. *Note: eligible for platinum-containing chemotherapy means:* ■ *cisplatin eligible and* ■ *cisplatin ineligible but carboplatin eligible patients*
Intervention	**Enfortumab Vedotin** (Padcev, Antibody Drug Conjugate/ADC, Nectin-4-directed antibody and microtubule inhibitor conjugate) plus **Pembrolizumab** (Keytruda, Immune-Checkpoint-Inhibitor, PD-1-Inhibitor) Exclusion: ■ Enfortumab Vedotin as monotherapy ■ Pembrolizumab as monotherapy ■ Enfortumab Vedotin plus chemotherapy
Comparator	Platinum-based chemotherapy: cisplatin plus gemcitabine or carboplatin plus gemcitabine – as in approval study
Outcomes	■ Effectiveness: ○ overall survival (OS) ○ progression free survival (PFS) ○ objective response rate (ORR) ○ disease control rate (DCR) ○ complete response rate (CRR)[4] ■ Safety ○ (serious) adverse events ■ Quality of life ■ Additional outcomes: ○ Costs (based on hand search: cost-effectiveness analysis (CEA studies)
Study design	**Effectiveness and safety**: Systematic reviews (descending priority) based on ■ randomised controlled trials (RCTs), ■ prospective cohort studies with/without control group, ■ any study design HTA reports Publication timeframe: 2020-2025 Real-world studies for safety (if available)[5] Publication timeframe: 2020-2025 **Costs:** Primary studies (CEAs) Publication timeframe: 2020-2025

[4] This outcome was subsequently added after protocol review.

[5] Real-world studies were not part of the systematic search as initially intended but a manual hand search was conducted for this study type.

4 Methods

The systematic literature search was conducted on 17th and 18th of June 2025 in the following four databases to identify relevant studies (see Search strategies in Appendix):

systematische Literatursuche in vier Datenbanken

- Ovid Medline (17.06.2025)
- The Cochrane Library (18.06.2025)
- Epistemonikos (18.06.2025)
- HTA (INAHTA)-Db (18.06.2025)

In addition, a search for ongoing clinical trials was performed on 31st of July 2025 in the following study register:

Suche nach laufenden Studien

- ClinicalTrials.gov

To capture real-world studies and the outcome costs, a supplementary hand search was conducted in PubMed in June and September 2025. Furthermore, a hand search for clinical guidelines was conducted in the following databases in June 2025: TRIP Medical Database, Guidelines International Network (GIN), Association of the Scientific Medical Societies in Germany (AWMF), and UpToDate.

Handsuche nach Kosteneffektivitäts-Analysen, real-world Studien und Leitlinien

The literature selection was carried out in Rayyan [24]. Due to the reasonable number of abstracts, all abstracts were screened by two researchers (SE, JMF). The full-text analysis was carried out by one researcher (SE) and reviewed by a second researcher (JMF). The literature selection was based on the best available and most recent literature.

Literaturauswahl in Rayyan durch zwei Wissenschaftlerinnen

In an iterative process, all systematic reviews and HTA reports regarding the research question were searched for. From these, 22 studies and HTA reports were selected for full-text analysis. Among them were seven systematic reviews that were relevant for the research question and that were assessed for potential risk of bias by two researchers (SE, JMF) using ROBIS [25]. After these ROBIS assessments, two systematic reviews [10, 26] were excluded from further analysis (due to high risk of bias), and five systematic reviews [7, 27-30] were included in the presentation of results (due to low risk of bias). In addition to the three HTA report publications identified from the systematic search, four further HTA report publications [31-34] were identified by hand search. No risk of bias assessment was performed for HTA reports.

22 Studien zur Volltextanalyse ausgewählt

sieben SRs mit ROBIS auf Biasrisiken bewertet, fünf SR eingeschlossen

insgesamt sieben HTA-Publikationen identifiziert, keine Biasbewertung

The transferability of results from international studies or recommendations from international guidelines to the Austrian context and any implications for practice were assessed by the authors and the external expert and described by the authors in the discussion.

Übertragbarkeit der Ergebnisse in Diskussion erörtert

5 Results

Results from **five recent systematic reviews** (SR) including network meta-analyses (network MA) based on randomised controlled trials (and non-randomised prospective studies [29]) conducted in Japan [29], China [28, 30], the USA [27] and Austria/ Japan [7] were included in the evidence synthesis; publications were from 2025 [7, 29] and 2024 [27, 28, 30], respectively. Only one SR [29] investigated Enfortumab Vedotin with or without Pembrolizumab as the sole intervention of interest, while the rest of SRs investigated a range of interventions including various immune checkpoint inhibitors (ICI)-based combination therapies (for details, see Table 8-1). Four SRs [7, 27-29] compared the intervention to chemotherapy, and one SR [30] compared the efficacy and safety of different treatment measures in a network MA. Median follow-up was reported in two SRs [7, 28], and ranged from 11.8 to 41.2 months, loss to follow-up was not reported.

fünf SRs zur Ergebnisdarstellung

vorwiegend aus dem asiatischen Raum

Großteil untersucht verschiedene (Kombinations-)Therapien

Komparator Standard-Chemotherapie

Overall, the SRs included 35 partly overlapping studies; however, **only one phase 3, global, open-label RCT included in all SRs**, published by Powles et al. 2024 [23] and referred to as the **EV302 trial**, **meets our PICO criteria**. This RCT included 442 patients in the intervention arm, receiving **Enfortumab Vedotin** in combination with **Pembrolizumab** (**EV+P**)**,** and 444 patients in the control arm, receiving platinum-based chemotherapy (one third of patients in the control arm received Avelumab maintenance therapy). As this is the only study meeting our PICO criteria, results regarding effectiveness and safety of EV+P compared to platinum-based chemotherapy presented in the results section are solely based on this study.

nur ein RCT wirklich relevant für unsere PICO: EV302

andere inkludierte Studien zu EV Monotherapie, eine einarmige Studie zu Kombinationstherapie

Despite the fact that the EV302 trial is the only study meeting our PICO criteria, results from network MAs available in the included SRs were extracted and are described additionally in the results section, where relevant, to provide a broader overview of the evidence landscape. In this context, two SRs [29, 30] included an RCT investigating EV+P in comparison to EV monotherapy (EV103/ Cohort K), and one SR [29] also included a study investigating EV monotherapy compared to chemotherapy (EV301) in their network MA in addition to the EV302 trial.

zusätzliche Ergebnisse aus Network MA wo relevant

Effectiveness

Overall survival (OS) and progression free survival (PFS)

In four SRs [7, 27, 28, 30], results regarding overall survival and progression free survival were presented, based on the EV302 trial data (see Table 8-1).

In the overall patient cohort, EV+P therapy resulted in **significantly improved OS compared to chemotherapy alone** (hazard ratio [HR]: 0.47, 95% confidence interval [CI] 0.38–0.58) [7, 27, 30], meaning that median OS was 31.5 months in the EV+P group vs. 16.1 months in the chemotherapy group[6] [23].

Gesamtüberleben: signifikante Verbesserung im Vergleich zu Chemotherapie

[6] In the SRs, OS results were not presented as months gained, so these data were extracted from the primary study.

One SR [28] comparing platinum-based chemotherapy to different immunotherapy-containing regimens supported the same **favourable OS results of EV+P** compared to platinum-based chemotherapy, but presenting the EV302 data from the chemotherapy perspective (HR 1.39; 95% CI 1.27-1.52 for chemotherapy vs EV+P).

Subgruppenanalysen: signifikante Verbesserung unabhängig der PD-L1 Expression

In the subgroup of **PD-L1 positive patients** (high expression), EV+P exhibited a **significant reduction** in the risk of death (HR: 0.50, 95% CI 0.37-0.66) [27, 28]; in the subset of **PD-L1 negative patients** (low expression), EV+P also demonstrated a **significant reduction** in the risk of death (HR: 0.44, 95% CI 0.31-0.61) [27]. This means that results were favourable for both subgroups, regardless of PD-L1 expression.

Überlebensvorteile auch im Vergleich zu anderen Therapien

Results from network MAs showed that EV+P also had significant survival benefits compared with immunotherapy combined chemotherapy including Nivolumab+chemotherapy, dual-drug immunotherapy [30] and different immunotherapy-containing regimens [28]. One network MA showed a substantial advantage of EV+P in terms of OS when compared to different treatments, including Durvalumab and Durvalumab plus Tremelimumab in the subgroup of patients with high PD-L1 expression [28].

progressionsfreies Überleben: signifikante Verbesserung im Vergleich zu Chemotherapie

Regarding PFS, EV+P therapy resulted in a significant improvement when compared to chemotherapy (HR: 0.45, 95%CI 0.38–0.54) in the overall patient cohort [7, 27, 30], meaning that PFS was longer in the EV+P group than in the chemotherapy group (median, 12.5 months vs. 6.3 months)[7].

Again, the SR comparing platinum-based chemotherapy to different immunotherapy-containing regimens [28] **supported the same favourable PFS results** of EV+P compared to platinum-based chemotherapy (HR of 1.41; 95%CI 1.31-1.53 for chemotherapy vs. EV+P).

Subgruppenanalysen: Verbesserung unabhängig der PD-L1 Expression

In the subgroup of **PD-L1 positive patients**, EV+P demonstrated a substantial improvement in PFS (HR: 0.42, 95% CI 0.33-0.53); in **PD-L1 negative patients** EV+P also showed a notable PFS improvement (HR: 0.5, 95% CI 0.38-0.64) [27], meaning that results were favourable regardless of PD-L1 expression.

Objective response rate/ Overall response rate (ORR)

objektive Ansprechrate: signifikante Verbesserung im Vergleich zu Chemotherapie

All five SRs [7, 27-30] reported results for overall/ objective response rate, based on the EV302 trial data (see Table 8-1), describing a **statistically significant improvement of ORRs** of EV+P **in comparison to chemotherapy** (odds ratio [OR]: 2.62, 95% CI 1.99–3.45; OR: 2.6, 95% CI 2.0-3.5; OR: 2.62, 95% CI 1.99–3.45; OR: 3.47, 95% CI 1.49-8.09; OR: 2.63, 95% CI 2.00-3.45).

Disease control rate (DCR)

Krankheitskontrollrate: signifikant höhere Raten im Vergleich zu Chemotherapie

Only one SR [29] reported results for disease control rate (see Table 8-1): EV+P was associated with **significantly higher rates compared to chemotherapy** (OR: 2.13, 95% CI 1.13-4.01; P = .02).

[7] In the SRs, PFS results were not presented as months gained, so these data were extracted from the primary study.

Complete response rate (CRR)

Three SRs [7, 27, 28] reported results for complete response rate (see Table 8-1): **EV+P demonstrated significantly improved CRRs** (OR: 2.88, 95%CI 2.03–4.08; OR: 2.9, 95% CI 2.0-4.0) when compared to chemotherapy.

vollständige Ansprechrate: signifikante Verbesserung im Vergleich zu Chemotherapie

Quality of Life (QoL)

There was **no evidence available** in the included SRs regarding the QoL of patients treated with EV+P in comparison to chemotherapy. However, results regarding **patient-reported outcomes from the EV302 trial** were reported in a publication from June 2025 [35]: data showed a slight improvement in QoL and a trend toward better pain control (clinically meaningful improvements in worst pain and global health status/QOL with EV+P in patients with moderate to severe baseline pain), meaning that EV+P improved survival without adversely affecting QoL, pain, or functional outcomes.

Lebensqualität: keine Ergebnisse berichtet

veröffentlichte EV302 Daten zu QoL und Schmerzmanagement: Vorteil von EV+P gegenüber Chemotherapie

Safety

Four SRs [7, 28-30] included data regarding (serious) adverse events (AEs) associated with EV+P therapy compared to platinum-based chemotherapy, based on results from the EV302 trial. In addition, two SRs [29, 30] included a study evaluating EV+P compared to EV monotherapy in their network MA, and in one SR [29], results from a study evaluating EV monotherapy vs chemotherapy were included.

Yajima et al. [29] argued that due to insufficient data a comprehensive analysis of all-grade AEs was not feasible. However, the authors present results for high-grade AEs, showing numerically **lower odds of high-grade AEs** (grade 3 or higher) **for EV+P compared with chemotherapy** (OR: 0.83, 95% CI 0.26-2.69; P = .76; not statistically significant). While ORs regarding detailed high-grade AE occurrences for EV+P vs chemotherapy were favourable for anaemia, fatigue and neutropenia, they were unfavourable for diarrhoea, pruritus and peripheral neuropathy.

unzureichende Daten für Nebenwirkungen aller Schweregrade in einem SR, geringeres Risiko für schwere Nebenwirkungen

Durchfall, Juckreiz und periphere Neuropathie treten häufiger auf

Results of Yanagisawa et al. [7] indicate that **EV+P did not lead to a lower likelihood of any treatment-related AEs** (OR: 0.70, 95% CI 0.29–1.65) but showed a **lower likelihood of severe treatment-related AEs** (OR: 0.54, 95% CI 0.41–0.72) compared to chemotherapy alone. EV+P had the second-best safety profile concerning both any (67%) and severe (80%) treatment-related AEs (Durvalumab + Tremelimumab had the most favourable safety profile).

ein SR berichtet von vergleichbarem Risiko für Nebenwirkungen allgemein, weniger schwere Nebenwirkungen

In the SR by Liang et al. [28], EV+P also showed a **decreased incidence of grade ≥3 AEs when compared to chemotherapy** (OR: 0.56, 95% CI 0.42- 0.73). Results in Zhao et al. [30] support the findings that **serious adverse reactions of EV+P were significantly lower than with platinum chemotherapy** (OR: 0.55, 95% CI 0.42-0.73)[8], and in their network MA they showed that serious adverse events were significantly lower than with Pembrolizumab+platinum-

verringerte Häufigkeit von schweren Nebenwirkungen in weiteren SR

[8] In the text, Zhao et al. describe serious AEs as being significantly higher than with chemotherapy; however, when looking at results presented in figure 4B, serious adverse reactions of EV+P were significantly lower than with platinum chemotherapy. Therefore, and as the results are again based on the EV302 trial, we extracted data directly from the table.

based chemotherapy, Nivolumab+platinum-based chemotherapy and Atezolizumab+platinum-based chemotherapy.

Findings of HTA reports

Three recent HTA reports from the UK, Canada and Germany in five publications (one HTA report from IQWIG is supplemented by an Addendum, the Canadian report is split in two documents) [31, 32, 34, 36, 37], assessing the effectiveness and safety of EV+P compared to standard chemotherapy, were identified (see Table 8-2).

drei relevante HTA-Berichte inkludiert

The German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) published one report on EV+P in 2024 and an Addendum in 2025, **based on the EV302 RCT** [36, 37]. EV+P was assessed as first-line therapy in adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-based chemotherapy, either cisplatin-eligible or cisplatin-ineligible. IQWIG compared the intervention to either 1) cisplatin in combination with gemcitabine or 2) carboplatin in combination with gemcitabine, both followed by avelumab maintenance therapy for progression-free patients. The authors conclude that there is a **'Anhaltspunkt'[9] (indication) for a not-quantifiable 'Zusatznutzen' (added value) for cisplatin-eligible patients** and a **'Anhaltspunkt'[9] for a considerable 'Zusatznutzen' for cisplatin-ineligible patients**. This means that EV+P shows considerable advantages in overall survival, especially for those patients with urothelial carcinoma for whom therapy with cisplatin is unsuitable. This advantage also exists if avelumab had already been available at the start of the study. In addition, the authors describe advantages in individual endpoints of morbidity and health-related quality of life as well as an additional benefit for patients who are eligible for cisplatin-based therapy. However, this is not quantifiable based on study results. Regarding adverse events, the authors conclude that there are advantages but also disadvantages of various extent [36, 37].

IQWIG: ein Bericht zur Kombinationstherapie mit Publikationen aus 2024 und 2025

basiert auf der EV302-Studie

Anhaltspunkt für nicht-quantifizierbaren Zusatznutzen für Cisplatin-geeignete Patient:innen

Anhaltspunkt für einen erheblichen Zusatznutzen für Cisplatin-ungeeignete Patient:innen

One further IQWIG report from 2024, supplemented by an Addendum in 2025 was identified in the systematic literature search, assessing Pembrolizumab + Enfortumab Vedotin therapy as first-line therapy in adult patients with unresectable or metastatic urothelial cancer [33, 38]. As this report is based on the same RCT, the EV302 trial and comes to the same conclusion as the report on EV+P, the report is not further described here.

ein weiterer IQWIG-Bericht zu Pembolizumab+EV nicht inkludiert

The Canadian Drug Agency/L´Agence des médicaments du Canada (CDA-AMC) released one report in two publications (a Reimbursement Recommendation and a Reimbursement Review) [31, 32] in 2024 and 2025 on EV+P in patients with unresectable locally advanced or metastatic urothelial cancer with no prior systemic therapy for metastatic urothelial cancer. The report is also **based on the EV302 trial**, comparing EV+P to standard of care therapy (i.e., cisplatin plus gemcitabine or carboplatin plus gemcitabine).

ein Bericht der kanadischen Arzneimittelbehörde mit Publikationen aus 2024 und 2025
basiert auch auf EV302

[9] "Anhaltspunkt" is, according to IQWIG's methods, the lowest category of statements regarding the probability of the presence of an effect, made based on the quality of evidence. According to IQWIG, the validity of the EV302 trial was limited, particularly due to the incomplete implementation of maintenance therapy with avelumab.

The authors conclude that the evidence showed a **clinically meaningful benefit** of EV+P compared with standard of care therapy in improving PFS, OS and the ORR, and that there was little to no clinically important difference in patients' HRQoL[10]. The authors state that the safety profile of EV+P appeared to differ from that of chemotherapy at a median follow-up of 17.2 months: **overall rates of AEs were similar in both the EV+P and comparator arms**. However, some AEs (e.g., peripheral sensory neuropathy and pruritus) occurred more often in the EV+P arm. **Fewer patients in the EV+P arm reported grade 3 to 5 treatment-emergent AEs, but more patients in the EV+P arm experienced serious AEs**. According to the authors, this was consistent with the known safety profiles of EV monotherapy and P monotherapy, which were described as predictable, acceptable, and clinically manageable in most patients. CDA-AMC recommends that EV+P should only be reimbursed to treat adult patients with unresectable locally advanced or metastatic UC with no prior systemic therapy and who are in relatively good health, if prescribed by an experienced clinician and if the price of EV is reduced [31, 32].

klinisch bedeutsamer Nutzen von EV+P, kein klinisch bedeutsamer Unterschied in der Lebensqualität

vergleichbare Raten von unerwünschten Nebenwirkungen, weniger Nebenwirkungen 3.-5. Grades, aber mehr schwerwiegende Nebenwirkungen

Erstattung eingeschränkt empfohlen, wenn Preis reduziert wird

The National Institute for Health and Care Excellence (NICE) published their guidance on EV+P for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [34] in September 2025. NICE **recommends using EV+P combination therapy** as an option for first-line treatment in adults when platinum-based chemotherapy is suitable and given that the companies provide the two agents according to commercial arrangements made. The evaluation committee concluded that EV+P significantly improved PFS and OS in people with untreated unresectable locally advanced or metastatic urothelial cancer compared with platinum-based chemotherapy, based on evidence from the EV302 trial (data cut in August 2024), therefore providing a **considerable improvement in the treatment pathway** of the condition. Regarding adverse events, the committee requested that side effects of EV+P should be fully taken into account in the economic analysis.

NICE empfiehlt EV+P als Erstlinientherapie

wenn sich die Hersteller an die kommerzielle Vereinbarung halten

Evaluations-Komitee sieht eine deutliche Verbesserung im Behandlungspfad

Clinical guidelines

Nine relevant clinical guidelines regarding the treatment of urothelial carcinoma were identified in an unsystematic hand search (for details see Table 8-5 and Table 8-6 in the appendix), of which **eight involve a statement regarding the use of EV+P combination therapy** (see overview Table 5-1).

neun klinische Leitlinien wurden in die Übersicht aufgenommen

[10] In their report the following statement is made regarding QoL outcomes from the Ev302 trial: "The findings of EORTC QLQ-C30 assessed at week 26 showed that the observed HRQoL in terms of EORTC QLQ-C30 was not clinically meaningfully different between-group (enfortumab vedotin plus pembrolizumab versus platinum plus gemcitabine) or intragroup. Other patient-reported and HRQoL outcomes including time to pain progression and worst pain scores and change from baseline and EQ-5D-5L also did not show a clinically meaningful intragroup and intergroup difference from week 8 to week 71. Notably, a significant number of patients were not included in the analyses of patient-reported outcomes and HRQoL outcomes, which is an important limitation and a source of uncertainty in those outcomes." Actual trial data regarding QoL outcomes are blackened in the text.

A **recommendation for EV+P combination** as first-line therapy for patients with advanced or metastatic urothelial carcinoma is given **by seven guidelines** [1, 2, 12, 13, 39-41]; the European Society for Medical Oncology (ESMO) guideline [13] recommends EV+P irrespective of platinum eligibility. The Canadian Urological Association Guideline [42] on muscle-invasive bladder cancer recommends EV+P as first-line treatment in patients with non-metastatic, clinically unresectable tumours that are classified as cT4b or cN1-3 over standard chemotherapy.

sieben Leitlinien empfehlen EV+P als Erstlinientherapie bei fortgeschrittenem oder metastasiertem Urothelkarzinom

The German S3 guideline on bladder cancer [3] does not involve a statement regarding EV+P combination therapy.

Table 5-1: Overview of guideline recommendations regarding EV+P combination therapy as first-line treatment

Guideline	Recommendation regarding the use of EV+P as first-line therapy	Grade of recommendation	Level of evidence
Leitlinienprogramm Onkologie 2025: S3 LL Harnblasenkarzinom [3]	-	-	-
UpToDate 2025: Metastatic urothelial carcinoma of the bladder and urinary tract [12]	✓ Comment: for patients with advanced or metastatic urothelial carcinoma	-	-
Canadian Urological Association 2025: Muscle-invasive bladder cancer [42]	✓ Comment: for patients with non-metastatic, clinically unresectable cT4b or cN1-3 tumours	Strong recommendation	1
European Association of Urology 2025: Upper Urinary Tract Urothelial Carcinoma [2]	✓ Comment: to patients with advanced/ metastatic disease	Strength rating: strong	1b
European Association of Urology 2025: Muscle-invasive and Metastatic Bladder Cancer [39]	✓	Strength rating: strong	1
ESMO 2024: Advanced urothelial carcinoma [13]	✓ Comment: for advanced or metastatic urothelial cancer, irrespective of platinum eligibility	A (strongly recommended); ESMO Magnitude of Clinical Benefit Scale score: 4	I
Oncopedia 2024: Urothelial Carcinoma (Bladder Cancer) [1]	✓ Comment: for metastatic or locally non-curable disease	-	-
Alberta Health Services Cancer Guidelines 2024: Locally Advanced/Metastatic Bladder Cancer [40]	✓ Comment: for patients with unresectable disease, locally advanced disease stages T4bNxM0, TxN2-3M0	-	-
French Association of Urology Cancer Committee 2024: Upper urinary tract urothelial cancer [41]	✓ Comment: for metastatic bladder tumours	-	1

Explanation of symbols: ✓ - recommended; ✗ - not recommended; - - not mentioned

Economic evaluation

besonders hohe Kosten für die Behandlung des Urothelkarzinoms

Metastatic urothelial carcinoma is **one of the costliest cancers** to treat per patient due to frequent interventions and expensive follow-ups [43]. Systemic therapy costs range from $40,000 to over $100,000 per five-cycle course, increasing further with combination therapies such as EV+P, according to a 2025 systematic review on the financial burden of localised and metastatic bladder cancer [44].

Kombinationstherapien verursachen noch höhere Kosten

Published cost-effectiveness analyses

fünf Kosteneffektivitäts-Analysen identifiziert

Five recent cost-effectiveness analyses (CEAs) [43, 45-48] assessing the cost-effectiveness of EV+P as first-line therapy in adult patients with locally advanced or metastatic urothelial cancer compared to standard chemotherapy from a healthcare payer perspective, and **based on the EV302 trial**, were identified in an unsystematic hand search. CEAs were from the USA [45], Germany/USA [43], China/USA [46, 48] and China [47]. The CEAs were published in 2024 and 2025 (for detailed study characteristics and results see Table 8-3 and Table 8-4).

alle basieren auf der EV302-Studie

erhebliche gesundheitliche Vorteile werden bestätigt

Although the authors of included CEAs acknowledge the considerable health benefits of EV+P in comparison to standard of care chemotherapy, especially regarding OS and PFS, they agree that EV+P is **not cost-effective at its current price** as a first-line therapy at a willingness to pay (WTP) threshold of $38,133/quality-adjusted life year (QALY) (China) or at common thresholds of $100,000/QALY or $150,000/QALY. A **substantial reduction of the therapy's price would be required** to be cost-effective at commonly accepted WTP thresholds. The US American CEA [45] states that one cycle of EV costs $36,000, and one cycle of Pembrolizumab costs $11,000 compared with chemotherapy, which costs around $400. The German CEA additionally concludes that gemcitabine/cisplatin + nivolumab should be considered for first-line therapy especially in Europe, despite its lower oncological benefit [43].

Kosteneffektivität ist nicht gegeben, eine substanzielle Preisreduktion wäre notwendig

Cost-effectiveness information from HTA reports

die kanadische Arzneimittelbehörde bestätigt die Notwendigkeit einer massiven Preisreduktion

A **cost-utility analysis** included in the reimbursement recommendation by CDA-AMC [31], **based on data from the EV302 trial**, assessed EV+P based on a treatment cost of $24,547 per 28 days. In the CDA-AMC base case, EV+P is associated with an ICER of $290,563/QALY gained compared with platinum-based chemotherapy. The three-year budget impact of reimbursing EV+P was expected to be $329 million. **According to CDA-AMC, a price reduction of 78% for both EV and Pembrolizumab would be required** to achieve an ICER of $50,000/QALY gained.

NICE sieht Kosteneffektivität unter gegebenen Umständen gegeben und empfiehlt EV+P

In its guidance [34], NICE concludes that when considering the condition's severity, and its effect on quality and length of life the most likely **cost-effectiveness estimates** for EV+P compared to standard chemotherapy are **within the range that NICE considers an acceptable use of NHS resources**, using the evaluation committee's preferred assumptions and applying a severity weighting of 1.2; an ICER of around £30,000 per QALY gained was considered as being acceptable. NICE lists a price of £578 per 20-mg vial or £867 per 30-mg vial for EV and £2,630 per 100 mg in a 4-ml vial for Pembrolizumab (August 2025, excluding VAT) but states that confidential discounts apply for both therapies regulated in commercial arrangements with the manufacturers.

es gibt vertrauliche Preisabsprachen und Rabatte

According to the HTA report by IQWIG [36], EV+P costs €191,822.47 per year per patient at a three-week treatment cycle (including additional costs, e.g. for necessary statutory health insurance benefits).

Jahreskosten pro Patient:in laut IQWIG

For the Austrian context, the applicability of international CEAs is limited as no WTP thresholds are established.

Übertragbarkeit auf Österreich ist eingeschränkt

Ongoing studies

The search for ongoing studies on clinicaltrials.gov (see search strategy for study register in Appendix) yielded 20 results overall. Of those, one study was listed as 'terminated'.

20 laufende Studien identifiziert

Ten studies (nine interventional and one observational) were relevant for our PICO and research question (three Phase 1/2, five Phase 2 and one Phase 4). Study completion dates range from 2026 (n=3), 2027 (n=1), 2028 (n=4) and 2029 (n=1) to 2034 (n=1). While the interventional studies investigate the efficacy (and safety) of Enfortumab Vedotin in combination with Pembrolizumab in patients with urothelial carcinoma, the observational cohort study's aim is to measure the incidence of peripheral neuropathy in patients receiving Pembrolizumab and Enfortumab Vedotin as first line treatment for metastatic or locally advanced urothelial carcinoma. Two interventional studies include additional agents in the intervention arm: one Phase 1/2 study also includes Sacituzumab tirumotecan, another Phase 1/2 study combines Enfortumab Vedotin and Pembrolizumab with investigational agents.

zehn Studien für PICO relevant

neun Interventionsstudien und eine Kohortenstudie zu peripherer Neuropathie

Studien zwischen 2026 und 2034 abgeschlossen

A list of identified studies is available from the authors upon request.

6 Discussion

Urothelial carcinoma ranks among the most frequently occurring malignant tumours, with a tendency to recur after initial treatment. Enfortumab Vedotin, an antibody-drug conjugate, is a Nectin-4-directed antibody and microtubule inhibitor conjugate given as intravenous infusion. It is indicated as monotherapy for second-line treatment in locally advanced or metastatic urothelial carcinoma, or in combination with Pembrolizumab (an immune-checkpoint-inhibitor) as first-line treatment in patients eligible for platinum-containing chemotherapy with unresectable or metastatic cancer. The combination therapy has been approved since September 2024 and is recommended as first-line treatment by several international guidelines. By combining immune-checkpoint-inhibitors and antibody-drug conjugates, the anti-tumour efficacy is enhanced by complementary mechanisms of action, enabling better effects than with either therapeutic agent alone [49]. However, despite these therapeutic advantages, the combination regimen is associated with substantial costs, underlining the need for careful clinical and economic evaluation.

Urothelkarzinome kommen häufig vor und treten häufig erneut auf

EV+P indiziert als Erstlinientherapie bei inoperablem oder metastasiertem Urothelkarzinom

Kombinationstherapien versprechen bessere Ergebnisse

In this rapid review, the effectiveness and safety of Enfortumab Vedotin in combination with Pembrolizumab as a first-line treatment for adult patients with unresectable or metastatic urothelial cancer has been assessed compared to standard platinum-based chemotherapy. In addition, evidence regarding the cost-effectiveness of the combination therapy has been reviewed.

der Rapid Review bewertet die Wirksamkeit und Sicherheit von EV+P im Vergleich zur Chemotherapie

Although five high-quality systematic reviews including network meta-analyses were identified in the systematic search and included in evidence synthesis, we found that data regarding the combination of Enfortumab Vedotin and Pembrolizumab **meeting our PICO criteria** were **solely based on one RCT, the EV302 trial.** The evidence shows clinically meaningful benefits of Enfortumab Vedotin in combination with Pembrolizumab compared with platinum-based chemotherapy in improving OS, PFS and the ORR. In addition, the DCR and CRR improved significantly with the combination therapy. Three included HTA reports also concluded that Enfortumab Vedotin in combination with Pembrolizumab resulted in improved survival outcomes compared to platinum-based chemotherapy and was associated with good treatment response rates.

fünf systematische Übersichtsarbeiten wurden eingeschlossen

alle basieren auf einem RCT, der EV302-Studie

die Evidenz zeigt klinisch bedeutsame Vorteile bezüglich OS, PFS und ORR
DCR und CRR verbessert

The systematic reviews did not present data regarding the QoL of patients treated with EV+P in comparison to platinum-based chemotherapy. In the EV302 trial publication [23], the authors state that quality of life and other patient-reported outcomes were assessed but not reported in the paper. Due to the absence of published QoL data in the EV302 trial, CEAs included in the rapid review used literature estimates or utilities from related therapies for their analyses. A 2025 publication, reporting patient-reported outcomes from the EV302 trial, showed that EV+P resulted in improved survival outcomes while maintaining global health status/ quality of life and pain control and substantially improving these outcomes for patients with significant baseline symptoms (moderate to severe pain).

Lebensqualität: keine Daten in Originalstudie und Übersichtsarbeiten

veröffentlichte Daten: QoL und Schmerz-management verbessert, insb. Patient:innen mit moderaten bis starken Schmerzen

weniger schwere Nebenwirkungen als Chemotherapie

Durchfall, Juckreiz und periphere Neuropathie traten häufiger auf

HTA-Berichte sehen akzeptables Sicherheitsprofil

Regarding safety outcomes, three of the included SRs reported on all-grade (or any treatment-related adverse events), with insufficient data in two, and no lower likelihood in one study. These results are also based on data from the EV302 trial. Regarding high-grade (severe) adverse events, however, Enfortumab Vedotin in combination with Pembrolizumab had lower odds compared to platinum-based chemotherapy. According to one systematic review, odds ratios regarding detailed high-grade AE occurrences for Enfortumab Vedotin in combination with Pembrolizumab compared to platinum-based chemotherapy were unfavourable for diarrhoea, pruritus and peripheral neuropathy, however. Included HTA reports agree that the safety profile of Enfortumab Vedotin in combination with Pembrolizumab is acceptable compared to standard platinum-based chemotherapy.

aktuelle Analyse der EV302-Studie mit längerem Follow-Up: Ergebnisse bestätigt

positive Ergebnisse in Subgruppenanalyse

A recently published updated analysis of the EV302 trial with a median follow-up of 2.5 years [50] that is not included in identified SRs, confirmed significant improvements regarding OS, PFS and ORR in the overall population, including both cisplatin-eligible and cisplatin-ineligible patients, compared to platinum-based chemotherapy; safety outcomes were consistent with the primary analysis. In addition, a recently published exploratory subgroup analysis of the EV302 trial [51] confirmed improved OS and PFS as well as improved ORR across all prespecified subgroups (with/without liver metastasis, with visceral metastases, with lymph node-only disease).

Leitlinien empfehlen EV+P als Erstlinientherapie für fortgeschrittenes oder metastasiertes Urothelkarzinom

All identified international guidelines recommend Enfortumab Vedotin in combination with Pembrolizumab as first-line treatment for patients with advanced or metastatic urothelial carcinoma. Interestingly, there is a contradiction between the EMA indication and the ESMO guideline which recommends Enfortumab Vedotin in combination with Pembrolizumab as the preferred first-line therapy for advanced or metastatic urothelial carcinoma, irrespective of platinum eligibility, meeting the FDA's approved indication though.

hohe Kosten der Kombinationstherapie

Kosteneffektivität bei derzeitigen Preisen nicht gegeben

laufender pharmako-ökonomischer Bericht von NCPE

Übertragbarkeit der Kosteneffektivitäts-Analysen auf Österreich eingeschränkt

Einigung über akzeptable Kosten und geeignete Preismechanismen bleibt komplexe und schwierige Aufgabe

Despite the considerable health benefits of Enfortumab Vedotin in combination with Pembrolizumab, its high cost raises concerns. Five cost-effectiveness analyses included in this rapid review agree that the combination therapy is not cost-effective at its current price as a first-line therapy at commonly accepted WTP thresholds. A substantial reduction of the therapy's price would be required to be cost-effective. This conclusion is also supported by CDA-AMC's reimbursement review [32]. NICE recommends EV+P as first-line treatment for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable; commercial arrangements with manufacturers lead to cost-effectiveness estimates within the range that NICE considers an acceptable use of NHS resources [34]. The National Centre for Pharmacoeconomics Ireland (NCPE) is currently preparing a pharmacoeconomic report, which is expected to be finalised end of 2025 [52]. The transferability of international CEAs to the Austrian context is limited, though, as no WTP thresholds are established (making the assessment of clinical benefit particularly important), prices might differ compared to other countries, and differences in the health care system might also limit applicability. However, also in Austria, high costs of combination therapies raise concerns regarding the value of these treatments, questioning whether increased costs are justified by improved effectiveness outcomes and favourable safety profiles. The authors of a German cost-effectiveness analysis suggest to still consider reimbursement of high-priced therapies that show considerable improvements in effectiveness outcomes at good safety profiles, and save money where effectiveness is limited [43].

Defining the value of combination therapies and reaching consensus on acceptable costs and suitable pricing mechanisms remains a complex and challenging task; collaboration of decision makers, HTA bodies and the pharmaceutical industry is needed to make progress.

Erhaltungstherapie mit Avelumab nicht Teil der Standard-Studienmedikation in der EV302-Studie

mögliche Überschätzung der Effekte von EV+P

It is worth noting that Avelumab maintenance was not the standard therapy in the EV302 trial's control arm (platinum-based chemotherapy), and therefore, only approximately one third of patients received Avelumab maintenance therapy in the trial, meaning that the control arm of the trial did not represent what would be considered standard of care in about two thirds of the patients. Consequently, Enfortumab Vedotin in combination with Pembrolizumab as a long-term therapy was compared to chemotherapy ending after six treatment cycles, potentially resulting in an overestimation of the intervention's treatment effect. However, in addition to considerable improvements in OS, PFS and response rates, post-hoc analyses showed a benefit for Enfortumab Vedotin in combination with Pembrolizumab also in patients receiving Avelumab in the trial.

Nivolumab nicht als Komparator eingeschlossen

Alternative für Patient:innen, die EV+P nicht erhalten können

Nivolumab, a monoclonal antibody, is indicated in the ESMO and Onkopedia guidelines as an alternative treatment option for cisplatin-eligible patients. It is approved by the EMA as combination therapy with cisplatin and gemcitabine for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma [53] and has shown promising OS, PFS and ORR results compared to Gemcitabine+Cisplatin alone in the CheckMate 901 trial [54]. For our rapid review, we decided not to include Nivolumab in combination with cisplatin and gemcitabine as comparator in accordance with the external expert and the topic enquirers. It is, however, an option for cisplatin-eligible patients who cannot receive Enfortumab Vedotin in combination with Pembrolizumab, for certain patient groups or in resource-limited settings due to its lower costs.

österreichisches Enfortumab Register sammelt real-world Daten

ORR und gute Verträglichkeit in der Praxis bestätigt

real-world Daten aus Deutschland bestätigen Wirksamkeit und Sicherheit von EV+P in der Praxis

An Austrian Enfortumab registry systematically collects real-world data on the effectiveness and tolerability of Enfortumab combined with Pembrolizumab in routine clinical practice. The registry aims to generate robust real-world evidence to complement clinical trial data and support evidence-based treatment decisions. In an analysis of the registry [55], data on 103 patients with advanced urothelial carcinoma treated in 17 clinics were studied to evaluate the effectiveness and tolerability of Enfortumab Vedotin in combination with Pembrolizumab in a real-world setting. The data support the ORR described in the EV302 trial but indicate lower ORR, PFS and OS in patients with significant comorbidities. Overall, the analysed real-world data confirmed good tolerability of the therapy. In Germany, the GUARDIANS project published an abstract presenting real-world results from a retrospective data analysis of a multicentre patient cohort (215 patients for safety and 164 patients for effectiveness data), confirming the efficacy results of the EV302 trial in routine clinical practice (ORR of 60.7% and a median PFS of 13 months; median OS not reached) at an acceptable toxicity profile with no new safety signals identified; most common AEs were peripheral sensory neuropathy and skin toxicity [56].

laufende Studien zu weiteren Kombinationen

Ongoing studies indicate that Enfortumab Vedotin combined with Pembrolizumab may be further combined with additional investigational agents. While these combinations could potentially improve clinical outcomes, they are likely to increase treatment costs substantially, and the real-world benefit remains uncertain. Careful evaluation will be needed to determine the overall value of these emerging therapies.

Übertragbarkeit auf Österreich gegeben

Although included SRs primarily come from the Asian region, their results seem to be generalisable to the Austrian context as well. Published real-world analyses seem to validate efficacy and safety results of the EV302 trial, continuous evaluation of real-world data (from Austrian patients) will be important to confirm applicability, however. The decision as to whether the results of the rapid review are also relevant for their own patient population can only be made by the topic enquirers themselves.

Limitationen:

Beschränkung auf letzte fünf Jahre, englische und deutschsprachige Studien

keine Bewertung der Biasrisiken von Primärstudien und Leitlinien

nur eine Primärstudie erfüllte unsere PICO-Kriterien

This rapid review is subject to several limitations. The systematic literature search was restricted to systematic reviews and HTA reports published in the past five years and in English or German language, potentially omitting relevant evidence. Cost-effectiveness analyses, real-world studies and clinical guidelines were identified with an unsystematic hand search. No risk of bias assessment was conducted for primary studies within the included reviews. Additionally, the referenced guidelines were not qualitatively appraised, which limits the assessment of their methodological rigor. Another limitation arises from the primary studies included in two of the SRs which were partly not meeting our PICO criteria (only the EV302 trial meeting them exactly), potentially influencing the results of their analyses regarding relevance for our research questions. Three SRs have conducted network meta-analyses including only one primary study regarding Enfortumab Vedotin in combination with Pembrolizumab compared to platinum-based chemotherapy, the EV302 trial, demonstrating the limited evidence base.

7 Conclusion

verbesserte Überlebensraten und akzeptables Sicherheitsprofil im Vergleich zur Chemotherapie

klinische Leitlinien empfehlen EV+P als Erstlinientherapie

Kosteneffektivität ist nicht gegeben, Preisreduktion ist notwendig

Evidence from five systematic reviews and three HTA reports indicates that Enfortumab Vedotin in combination with Pembrolizumab provides improved survival outcomes compared to platinum-based chemotherapy and a generally favourable safety profile as first-line treatment in patients with unresectable or metastatic urothelial carcinoma. However, included evidence is derived from a single phase III, open-label trial. Data regarding patient-reported outcomes published by EV302 trial authors suggest that the combination therapy maintains global health status/ quality of life and pain control, substantially improving these outcomes for patients with moderate to severe pain at baseline. All identified international clinical guidelines recommend the combination therapy as first-line treatment.

Included cost-effectiveness analyses indicate that at its current price, Enfortumab Vedotin in combination with Pembrolizumab is not cost-effective at commonly accepted willingness-to-pay thresholds, implying that substantial price reductions would be necessary. The available efficacy and safety data should therefore be interpreted with caution, considering both the limited evidence from real-world settings and the economic implications.

8 Appendix

Flow chart of study selection

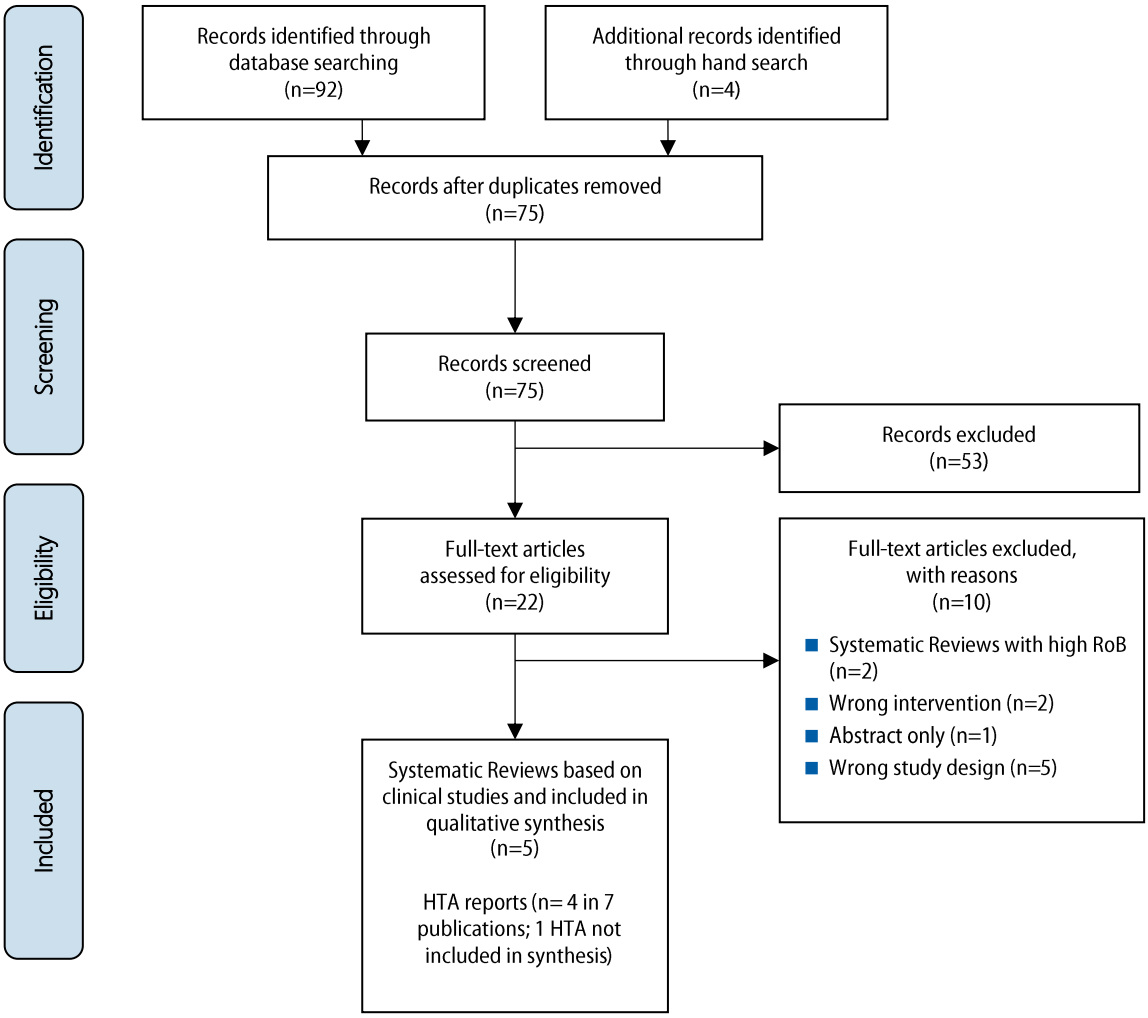

Figure 8-1: Flow chart of study selection (PRISMA Flow Diagramm)

Data extraction of included systematic reviews and meta-analyses

Table 8-1: Systematic reviews and meta-analyses of Enfortumab Vedotin in combination with Pembrolizumab

Author/ Year	Yajima 2025 [29]	Yanagisawa 2025 [7]	Zhao 2024 [30]	Hinojosa-Gonzalez 2024 [27]	Liang 2024 [28]
Country	Japan	Austria, Japan	China	USA	China
Sponsor	NR	Open access funding provided by Medical University of Vienna. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.	NR	The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Guangxi Natural Science Foundation (2024GXNSFBA010036), the Scientific Research Foundation of Guangxi Health Commission (Z-B20220930), the Scientific Research Foundation of Guangxi University of Science and Technology(20Z13), the Scientific Research Foundation of Guangxi Health Commission (Z-B20220927)
Conflict of interest of authors	None	Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen and Sanofi. Shahrokh F. Shariat received follows: Honoraria: Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Roche, Takeda Consulting or Advisory Role: Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Takeda Speakers Bureau: Astellas, Astra Zeneca, Bayer, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Richard Wolf, Roche, Takeda The other authors declare no conflicts of interest associated with this manuscript.	The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest	The authors have nothing to disclose.	The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Intervention	Enfortumab Vedotin With or Without Pembrolizumab	Immune checkpoint inhibitors (ICI)-based combination therapies	First-line treatment of advanced-stage urothelial carcinoma 12 treatments included:	Immune checkpoint inhibitors (ICIs) or the antibody-drug conjugate enfortumab vedotin in combination with pembrolizumab	Immunotherapy as first-line therapy, with or without other therapy 9 different treatment regimens:

			platinumCT, Nivolumab plus platinum-based chemotherapy (NIVO+platinumCT), Atezolizumab plus platinum-based chemotherapy (ATE+platinumCT), Pembrolizumab plus platinum-based chemotherapy (PEM +platinumCT), ATE, PEM, **PEM+EV**, EV, Durvalumab (DURVA), Durvalumab plus tremelimumab (DURVA+TRE), Durvalumab plus olaparib (DURVA+OLA), and Pembrolizumab plus lenvatinib (PEM +LEN)		(1) ICI combined with chemotherapy, including of atezolizumab plus chemotherapy (Atezo + Chemo), pembrolizumab plus chemotherapy (Pembro + Chemo), and nivolumab plus chemotherapy (Nivol + Chemo); (2) ICI alone, including of atezolizumab (Atezo), pembrolizumab (Pembro), durvalumab (Durva), and durvalumab plus tremelimumab (Durva + Treme); (3) **enfortumab vedotin plus pembrolizumab (EV + Pembro**); (4) chemotherapy alone (Chemo).
Comparator	Chemotherapy	Chemotherapy	NMA: compared the efficacy and safety of different treatment measures	Platinum-based chemotherapy	Chemotherapy as first-line therapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin)
Indication	Metastatic Urothelial Carcinoma	Advanced/metastatic Urothelial Carcinoma	Advanced-stage urothelial carcinoma (stages IV) confirmed either histologically or cytologically	Previously untreated mUC	Untreated metastatic or advanced UC
Study design of included studies	RCTs and prospective studies	RCTs	RCTs	RCTs	RCTs
Number of patients	11 included studies (3 RCTs [27.3%] and 8 nonrandomized prospective studies [72.7%]), involving 2,128 patients 563 (26.5%) received enfortumab vedotin plus pembrolizumab (n=3)	5 RCTs, encompassing 3,734 platinum-eligible advanced or metastatic UC patients treated with ICI-based combination therapy or chemotherapy 442 received enfortumab vedotin combined with pembrolizumab (n=1)	8 RCTs, involving 5,539 patients 518 received enfortumab vedotin combined with pembrolizumab (n=2)	6 RCTs, involving 5,449 patients (3,255 received either ICI monotherapy, antibody-drug conjugate or combination therapy, while 2,194 served as controls) 442 received enfortumab vedotin combined with pembrolizumab (n=1)	5 RCTs, involving 4,749 patients 442 received enfortumab vedotin combined with pembrolizumab (n=1)
Included studies with combination of EV+Pembro	**Meta-analysis:** relevant for PICO: **EV302/Powles (EV+Pembro vs Chemo)** not relevant for PICO: ■ EV103/Cohort K/O´Donnell (EV+Pembro vs EV) ■ EV103/Cohort A/Gupta (EV+Pembro single arm) **Network Meta-analysis:** relevant for PICO: **EV302/Powles (EV+Pembro vs Chemo)**	**Network Meta-analysis:** relevant for PICO: **EV302/Powles (EV+Pembro vs Chemo)**	**Network Meta-analysis:** relevant for PICO: **EV302/Powles (EV+Pembro vs Chemo)** not relevant for PICO: EV103/Cohort K/O´Donnell (EV+Pembro vs EV)	**Network Meta-analysis:** relevant for PICO: **EV302/Powles (EV+Pembro vs Chemo)**	**Network Meta-analysis:** relevant for PICO: **EV302/Powles (EV+Pembro vs Chemo)**

	not relevant for PICO: ■ EV301/Rosenberg (EV vs Chemo) ■ EV103/Cohort K/O´Donnell (EV+Pembro vs EV)				
Inclusion criteria	We included randomized clinical trials (RCTs) and prospective studies investigating the beneficial outcomes and safety of enfortumab vedotin, either as monotherapy or in combination with pembrolizumab, in adult patients with mUC. Studies were eligible for inclusion regardless of language or publication status.	Studies were included if they included patients with advanced/metastatic UC (Participants) and evaluated the efficacy of ICI-based combination therapies (Interventions) compared to the efficacy of chemotherapy (Comparisons) assessing their differential effects on OS, PFS, ORRs, CRRs, and/or rates of TRAEs (Outcomes) in RCTs (Study design).	1. Randomized controlled trials (RCTs) that enrolled patients with aUC (stages IV) confirmed either histologically or cytologically. 2. RCTs that explored the first-line treatment of aUC. 3. RCTs that were published or published in the form of conference abstracts, and reported results such as OS/PFS/ Objective Response Rate (ORR)/AEs.	Eligible articles were randomized clinical trials (RCTs) comparing the use of immune checkpoint inhibitors (ICIs) or the antibody-drug conjugate enfortumab vedotin in combination with pembrolizumab in patients with previously untreated mUC that reported the following outcomes of interest: overall survival (OS), overall response rate (ORR) as defined by RECIST criteria, progression free survival (PFS) and complete response rate (CRR) as defined by RECIST criteria.	Inclusion criteria were as follows: (1) patients with untreated metastatic or advanced UC; (2) the intervention group was administered immunotherapy as first-line therapy, with or without other therapy; (3) the controlled group was administered chemotherapy as first-line therapy; (4) at least one of the following results were documented: CR, ORR, OS, PFS and grade ≥ 3 AEs (5); Types of studies: RCTs.
Follow-up (months)	NR	Median follow up: 11.8 to 41.2	NR	NR	Median follow up (95% CI) from 11.8 (6.1–17.2) to 41.2 (37.9–43.2)
Loss to follow-up, n (%)	NR	NR	NR	NR	NR
Effectiveness					
Overall survival (OS)	**Network Meta-analysis:** NR	**Network Meta-analysis:** **EV+pembrolizumab** (HR: 0.47, 95%CI 0.38–0.58) resulted in improved OS compared to chemotherapy alone. **EV + pembrolizumab** (100%) had the highest likelihood of improving OS.	**Network Meta-analysis:** OS of **PEM+EV** significantly longer than those of other measures, and the regimen had significant survival benefits compared with immunotherapy combined chemotherapy or dual-drug immunotherapy. **PEM+EV** significantly better than **current first-line platinumCT** (HR=0.47; 95%CI: 0.38-0.58) and immune combined chemotherapy including NIVO+platinumCT (HR=0.60; 95%CI: 0.45-0.81), PEM+platinumCT (HR=0.55; 95%CI: 0.42-0.72), ATE +platinumCT (HR=0.57; 95%CI: 0.43-0.75).	**Network Meta-analysis:** overall patient cohort: **enfortumab vedotin + pembrolizumab** demonstrated the most substantial reduction in the risk of death (HR 0.47 [95% CrI: 0.38, 0.58]). **subgroup of PD-L1 positive** patients: **enfortumab vedotin + pembrolizumab** exhibited the most significant reduction in the risk of death (HR 0.50 [95% CrI: 0.37, 0.66]). **subset of PD-L1 negative** patients: only **enfortumab vedotin + pembrolizumab** demonstrated a significant reduction in the risk of death (HR 0.44 [95% CrI: 0.31, 0.61]).	**Network Meta-analysis:** **EV + Pembro** exhibited a substantial advantage in terms of OS when compared to Chemo (HR for Chemo 1.39; 1.27 - 1.52), and to all the other treatments (n=5). **EV + Pembro ranked highest** (1.000) in a ranking of the therapeutic effectiveness. **subgroup of** patients with **high PD-L1 expression:** treatment regimens involving **EV + Pembro** exhibited a substantial advantage in terms of OS when compared to Chemo, Durva, Durva + Treme, Pembro, and Pembro + Chemo, but not Atezo, Atezo + Chemo or Nivol + Chemo.

Progression free survival (PFS)	**Meta-analysis:** NR **(**Due to limited reporting, OS and PFS were not included in the meta-analysis) **Network Meta-analysis:** NR	**Network Meta-analysis**: All ICI-based combinations improved PFS compared to chemotherapy alone, with EV +pembrolizumab showing the maximum PFS benefit (100%). **EV +pembrolizumab** vs chemotherapy: HR: 0.45 (95%CI 0.38–0.54)	**Network Meta-analysis**: **PEM+EV** significantly better than **platinumCT** (HR=0.45; 95%CI:0.38-0.54) and immunotherapy combined chemotherapy including NIVO +platinumCT (HR=0.62; 95%CI: 0.48-0.82), PEM+platinumCT (HR=0.58; 95%CI: 0.45-0.74), ATE+platinumCT (HR=0.55; 95% CI: 0.43-0.69).	**Network Meta-analysis**: overall patient cohort: **enfortumab vedotin + pembrolizumab** exhibited most significant improvement in PFS, with a HR of 0.45 (95% CrI: 0.38, 0.54). **subgroup analysis of PD-L1 positive** patients: **enfortumab vedotin + pembrolizumab:** HR of 0.42 (95% CrI: 0.33, 0.53) **PD-L1 negative** patients (n=3): **Enfortumab + pembrolizumab:** HR 0.5, 95% CrI: 0.38, 0.64	**Network Meta-analysis**: **EV + Pembro** had a notable advantage in terms of PFS when compared to four alternative treatment regimens (n=4). When compared to **EV + Pembro,** the HR for Chemo, was 1.41 (1.31 -1.53). **EV + Pembro ranked highest** (0.999) in a ranking of efficacy (Chemo 0.003).
Objective response rate/ Overall response rate (ORR)	**Network Meta-analysis**[11]**:** **Enfortumab vedotin plus pembrolizumab** was associated with higher rates compared with chemotherapy (OR, 3.47; 95% CI, 1.49-8.09; P = .004).	**Network Meta-analysis**: In comparison to chemotherapy, **EV+pembrolizumab** (OR: 2.62, 95%CI 1.99–3.45) resulted in improved ORRs. Treatment rankings revealed that **EV +pembrolizumab** (99%) had the highest likelihood of improved ORRs.	**Network Meta-analysis**: **PEM+EV** has a significant benefit compared to other treatment measures, which is 2.63 times that **of platinumCT** (OR=2.63; 95%CI: 2.00-3.45), and is also significantly better than PEM+platinumCT (OR=1.77; 95%CI: 1.18-2.65) and ATE+platinumCT (OR=2.26; 95%CI: 1.53-3.34), but there is no significant difference compared with NIVO +platinumCT (OR=1.46; 95%CI: 0.96-2.22).	**Network Meta-analysis**: overall patient cohort: ORR ranging from 1.4% to 67.7% (n=6) **Enfortumab combined with pembrolizumab:** OR 2.6 [95% CrI: 2.0, 3.5]	**Network Meta-analysis**: In comparison to chemotherapy, **EV+pembrolizumab** resulted in improved ORRs: OR 2.62 (1.99 - 3.45) **EV + Pembro** ranked highest (0.995) in a ranking by efficacy.
Disease control rate (DCR)	**Network Meta-analysis**[11]: **Enfortumab vedotin plus pembrolizumab** was associated with higher response rates compared with chemotherapy (OR, 2.13; 95% CI, 1.13-4.01; P = .02)	NR	NR	NR	NR
Complete response rate (CRR)	NR	**Network Meta-analysis**: **EV + pembrolizumab** (OR: 2.88, 95%CI 2.03–4.08) demonstrated improved CRRs. Treatment rankings indicated that **EV + pembrolizumab** (96%) had the highest likelihood of improving CRRs.	NR	**Network Meta-analysis**: overall patient cohort: CRR ranging from 0.9% to 29.1% (n=6) **Enfortumab combined with pembrolizumab:** OR 2.9 [95% CrI: 2.0, 4.0]	**Network Meta-analysis**: Compared with Chemo, **EV + Pembro** had a significantly better CR (OR 2.88; 2.03 - 4.08). **EV + Pembro** ranked highest (0.969) in a ranking by efficacy.

[11] The systematic review also includes results of a meta analysis including three studies, of which two do not fit the PICO of our rapid review; therefore, results are not included in the table.

Safety					
(serious) adverse events (AEs)	Insufficient data precluded a comprehensive analysis of all-grade AEs across the 3 treatment arms. Results for **high-grade AEs: enfortumab vedotin plus pembrolizumab** had numerically lower odds of high-grade AEs compared with chemotherapy (OR, 0.83; 95% CI, 0.26-2.69; P = .76); not statistically significant. Detailed **high-grade AE occurrences for EV+Pembro (vs chemotherapy)**: Anaemia: OR 0.12 (95% CI, 0.03; 0.50; P = .003); favourable Diarrhoea: OR 4.10 (95% CI, 1.50; 11.22; P = .006); unfavourable Fatigue: OR 0.89 (95% CI, 0.41; 1.93; P = .76); favourable Neutropenia: OR 0.23 (95% CI, 0.03; 1.63; P = .14); favourable Pruritus: OR 16.83 (95% CI, 0.78; 361.74; P = .07); unfavourable Peripheral neuropathy: OR 4.15 (95% CI, 0.04; 433.89; P = .54); unfavourable	**Network Meta-analysis:** **EV+pembrolizumab** did not result in a lower likelihood of any TRAEs (OR: 0.70, 95%CI 0.29–1.65) but did show a lower likelihood of severe TRAEs (OR: 0.54, 95%CI 0.41–0.72) compared to chemotherapy alone. The treatment rankings indicated that durvalumab + tremelimumab had the highest safety profile concerning both any (99%) and severe (100%) TRAEs, followed by **EV +pembrolizumab** (67% and 80%, respectively).	**Network Meta-analysis**: Serious adverse reactions of **PEM+EV** were significantly lower than PEM+platinumCT, NIVO+platinumCT and ATE+platinumCT. EV+P had a **significantly lower HR** of 0.55 (95% CI 0.42-0.73) according to figure 4B.	Adverse effects leading to treatment discontinuation were too infrequently reported to analyse.	**Network Meta-analysis**: Grade ≥ 3 AEs: **EV + Pembro** vs. Chemo OR 0.56 (0.42- 0.73) **EV + Pembro** ranked fifth (0.492) in the safety ranking.

Quality of Life	NR	NR	NR	NR	NR
Conclusion of authors	In this meta-analysis of 11 studies, enfortumab vedotin–based therapy was associated with favorable outcomes in mUC treatment settings. **Enfortumab vedotin plus pembrolizumab** was associated with **higher response rates in the first-line setting**, while enfortumab vedotin monotherapy was associated with clinical benefit in later lines.	**Enfortumab vedotin (EV) + pembrolizumab** ranked the highest for improving OS (100%), PFS (100%), ORR (96%), and CRR (96%), followed by nivolumab + chemotherapy. **EV + pembrolizumab** combination superiority held across PD-L1 status and cisplatin eligibility. In patients who are cisplatin-eligible, **EV + pembrolizumab** significantly improved OS (HR: 0.68, 95%CI 0.47–0.99) and PFS (HR: 0.67, 95%CI 0.49–0.92) compared to nivolumab + chemotherapy. Durvalumab + tremelimumab was the safest combination for severe TRAEs, and **EV + pembrolizumab** ranked second. Our analyses **support EV + pembrolizumab combination as a first-line treatment for locally advanced or metastatic UC**. Thus, EV + pembrolizumab may become a guideline-changing standard treatment.	Through this NMA, we found that in the first-line treatment of aUC, **PEM+EV** regimen could significantly prolong OS and PFS compared with other regimens, and has a higher ORR. The incidence of ≥3AEs with **PEM+EV** were higher than chemotherapy but lower than immunotherapy combined with chemotherapy (ATE +platinumCT, PEM+platinumCT, NIVO+platinumCT).	The combination of **enfortumab vedotin and pembrolizumab** emerged as a highly promising strategy, significantly improving survival and response rates across all patients regardless of PDL1 status.	**EV + Pembro** as first-line therapy resulted in considerably improved efficacy and safety compared to chemotherapy for advanced or metastatic UC.

Legend: AE – adverse events, ATE – atezolizumab, aUC advanced urothelial carcinoma, CRR - complete response rate, CT – chemotherapy, EV - enfortumab vedotin, ICI - immune checkpoint inhibitors, NIVO – nivolumab, NR – not reported, ORR - overall response rate, OS - overall survival, PD-L1 - programmed death-ligand 1, Pem/Pembro - pembrolizumab, PFS - progression free survival, RCT - randomized controlled trial, TRAEs - treatment-related adverse events

Data extraction of identified health technology assessment reports

Table 8-2: Health technology assessment reports of Enfortumab Vedotin in combination with Pembrolizumab

Author/ Year	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) Enfortumab Vedotin + Pembrolizumab 2024 [36] + Addendum: Enfortumab Vedotin + Pembrolizumab 2025 [37] See note below table	Canada´s Drug Agency/L´Agence des médicaments du Canada (CDA-AMC) Enfortumab Vedotin 2024 (Reimbursement Recommendation) [31] + Enfortumab Vedotin 2025 (Reimbursement Review) [32]	National Institute for Health and Care Excellence (NICE) 2025 Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [34]
Country	Germany	Canada	UK
Intervention	Enfortumab vedotin with pembrolizumab	Enfortumab vedotin with pembrolizumab	Enfortumab vedotin with pembrolizumab
Indication	Erstlinientherapie bei erwachsenen Patientinnen und Patienten mit nicht rezesierbarem oder metastasiertem Urothelkarzinom, für die eine platinhaltige Chemotherapie infrage kommt und 1) für die eine Cisplatin-basierte Therapie geeignet ist 2) für die eine Cisplatin-basierte Therapie nicht geeignet ist	Unresectable locally advanced or metastatic urothelial cancer (mUC) with no prior systemic therapy for mUC	Untreated unresectable or metastatic urothelial cancer
Comparator	3) Cisplatin in Kombination mit Gemcitabin gefolgt von Avelumab als Erhaltungstherapie (Erhaltungstherapie mit Avelumab nur für Patientinnen und Patienten, die progressionsfrei sind) 4) Carboplatin in Kombination mit Gemcitabin gefolgt von Avelumab als Erhaltungstherapie (Erhaltungstherapie mit Avelumab nur für Patientinnen und Patienten, die progressionsfrei sind)	Standard of care chemotherapy (cisplatin plus gemcitabine or carboplatin plus gemcitabine)	Platinum-based chemotherapy

Study design (studies included)	**RCT (EV302)**	**RCT (EV302)**	**RCT (EV302)** data cut in August 2024
Conclusion of authors	5) Patient:innen, für die eine cisplatinbasierte Therapie geeignet ist: Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen 6) Patient:innen, für die eine cisplatinbasierte Therapie nicht geeignet ist: Anhaltspunkt für einen erheblichen Zusatznutzen In der Gesamtschau zeigen sich für Enfortumab Vedotin + Pembrolizumab im Vergleich zur zweckmäßigen Vergleichstherapie sowohl positive als auch negative Effekte unterschiedlichen Ausmaßes. Für die Mortalität beziehen sich die beobachteten Effekte auf den gesamten Beobachtungszeitraum. Insbesondere für die Endpunkte der Nebenwirkungen beziehen sich die beobachteten Effekte hingegen auf einen verkürzten Zeitraum und bilden nur etwa die ersten 6 Monate nach Randomisierung ab und somit im Vergleichsarm lediglich den Zeitraum der Chemotherapie, nicht aber den Zeitraum einer möglichen Erhaltungstherapie mit Avelumab, sowie im Interventionsarm lediglich die ersten 6 Monate einer möglicherweise länger andauernden Therapie. Zusammenfassend gibt es für erwachsene Patientinnen und Patienten mit nicht resezier barem oder metastasiertem Urothelkarzinom in der Erstlinientherapie, für die eine cisplatin basierte Therapie geeignet ist, einen Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen von Enfortumab Vedotin + Pembrolizumab gegenüber der zweckmäßigen Vergleichstherapie. Zusammenfassend gibt es für erwachsene Patientinnen und Patienten mit nicht resezierbarem oder metastasiertem Urothelkarzinom in der Erstlinientherapie, für die eine cisplatinbasierte Therapie nicht geeignet ist, einen Anhaltspunkt für einen erheblichen Zusatznutzen von Enfortumab Vedotin + Pembrolizumab gegenüber der zweckmäßigen Vergleichstherapie.	Evidence from the EV-302 trial showed that EV + P demonstrated a clinically meaningful benefit compared with PLAT + GEM in improving PFS, OS, and the ORR for the treatment of patients with locally advanced or metastatic UC. Based on the EORTC QLQ-C30 Global Health Status (GHS) results, EV + P may result in little to no clinically important difference in patients' HRQoL compared with PLAT + GEM, which was expected for this population. The safety profile of EV + P appeared to differ from that of PLAT + GEM. The safety profile of EV + P was consistent with the known safety profiles of enfortumab vedotin monotherapy and pembrolizumab monotherapy, which are predictable, acceptable, and clinically manageable in most patients. No new safety signals were identified in the EV-302 trial. Padcev, in combination with pembrolizumab, should only be covered to treat adult patients with unresectable locally advanced UC or mUC with no prior systemic therapy for mUC and who are in relatively good health. Eligible patients include those who have received chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant) and experienced disease recurrence more than 12 months after the completion of treatment or received adjuvant immunotherapy with nivolumab and experienced disease recurrence more than 6 months after the completion of treatment. Padcev, in combination with pembrolizumab, should only be reimbursed if prescribed by a clinician who has experience treating patients with locally advanced UC or mUC and if the price of Padcev is reduced Why Did CDA-AMC Make This Recommendation? • Evidence from a phase III clinical trial demonstrated that Padcev in combination with pembrolizumab resulted in improved survival compared to standard chemotherapy (platinum plus gemcitabine chemotherapies) and was associated with good response to treatment, which are outcomes identified as important by patients. • Based on the assessment of the health economic evidence by Canada's Drug Agency (CDA-AMC), Padcev, in combination with pembrolizumab, does not represent good value to the health care system at the public list price. A price reduction is therefore required. Based on the public list price, Padcev, in combination with pembrolizumab, is estimated to cost the public drug plans approximately $329 million over the next 3 years	The results from EV-302 showed that enfortumab vedotin with pembrolizumab offered statistically significantly better PFS (hazard ratio [HR] 0.481, 95% confidence interval [CI] 0.407 to 0.570) and OS (HR 0.513, 95% CI 0.428 to 0.614) compared with platinum-based chemotherapy. Subgroup analyses based on cisplatin eligibility showed similar results, but the trial was not statistically powered for this analysis. The committee concluded that enfortumab vedotin with pembrolizumab statistically significantly improved PFS and OS in people with untreated unresectable locally advanced or metastatic urothelial cancer compared with platinum-based chemotherapy. Enfortumab vedotin with pembrolizumab can be used, within its marketing authorisation, as an option for untreated unresectable or metastatic urothelial cancer in adults when platinum-based chemotherapy is suitable. Enfortumab vedotin with pembrolizumab can only be used if the companies provide them according to their commercial arrangements.

Legend: EV+P – Enfortumab Vedotin + Pemprolizumab, HRQoL – health related quality of life, ORR – objective response rate, OS – overall survival, PFS – progression free survival, PLAT + GEM - platinum-based chemotherapy + Gemcitabine, RCT - randomized controlled trial, UC – urothelial carcinoma

Note: There also exists an IQWiG report regarding Pembrolizumab + Enfortumab Vedotin 2024 [33] and an Addendum Pembrolizumab + Enfortumab Vedotin 2025 [38] which are not included in the extraction table as they are based on the same trial (EV302) as the other report on Enfortumab Vedotin + Pembrolizumab.

Data extraction of identified cost-effectiveness studies

Table 8-3: Cost-effectiveness analyses of Enfortumab Vedotin in combination with Pembrolizumab

Author/ Year	Chiddarwar et al. 2025 [45]	Rieger et al. 2025 [43]	Zhu et al. 2025 [48]
Country	USA	Germany/ USA	China/ USA
Sponsor	supported by the grant #U01CA265750 from the National Cancer Institute (NCI) as part of the Cancer Intervention and Surveillance Modeling Network (CISNET)	None	supported by the Clinical Research Project of Xiangya Hospital (Grant/Award Number: 2016L06 to H.Z.) and the Changsha Natural Science Foundation of Hunan Provincial of China (Grant/Award Number: kq2208376 to H.Z.)
Conflict of interest of authors	NR	Honoraria: Medac Germany, Bayer, Pfizer, Janssen, AstraZeneca, MSD, BMS, Amgen, Astellas, AstraZeneca, Clovis Oncology, Takeda; Consulting fees: MSD; Travel: Bayer, Janssen; Advisory board: BMS, Janssen, MSD, Pfizer Astellas, Bayer, MMS; Research grant: BMS	None
Study design/ method used	cost-effectiveness analysis cohort state-transition model	cost-effectiveness analysis Markov transition model; Monte Carlo simulation (three different treatment strategies)	cost-effectiveness analysis Markov model; Monte Carlo simulation
Sensitivity/ Uncertainty Analysis	Yes: deterministic (clinical parameters were varied by the reported confidence intervals from the literature and the costs of drugs, disease management, and toxicities by ±25%) and probabilistic sensitivity analyses (parameters were varied simultaneously with prespecified distributions, using 10 000 PSA simulation)	Yes: probabilistic sensitivity analysis (10 000 iterations), one-way sensitivity analysis, univariate sensitivity analysis (different WTP thresholds)	Yes: one-way sensitivity analysis (parameters were varied within ±20% of the baseline), probabilistic sensitivity analyses (10.000 simulations, various WTP thesholds)
Intervention	combination of enfortumab vedotin and pembrolizumab (EV+P)	■ enfortumab vedotin + pembrolizumab (EV+P) ■ gemcitabine/cisplatin + nivolumab	enfortumab vedotin + pembrolizumab (EV+P)
Comparator	Standard of care: platinum-based chemotherapy	Standard of care: gemcitabine/cisplatin ± avelumab	Standard of care: platinum-based chemotherapy
Indication/ population	first-line treatment for metastatic urothelial cancer in adult patients (median age 69 years as in EV-302 trial)	first-line treatment for adult patients with unresectable locally advanced bladder cancer or metastatic urothelial carcinoma (according to EV-302/A39 and Keynote-901 trials)	first-line treatment for locally advanced or metastatic urothelial carcinoma in adult patients (based on EV-302/KEYNOTE-A39 trial)
Perspective	US healthcare payer perspective	Payer perspective (primarily the statutory or private health insurance)	perspectives of the healthcare systems in the United States and China
Cost types/cost categories	direct medical costs: costs of the drugs, drug administration, adverse events, and disease management	direct costs of therapy, side effects, and consecutive therapy lines	direct medical costs: costs of drugs, AE management, administration, PD-L1 testing, tumor imaging, BSC, and terminal care
Time horizon	Lifetime horizon (available data from the trial up to 32 months, extrapolation of overall and progression-free survival for a lifetime horizon)	30-year lifetime horizon	Lifetime horizon
Discount rate	3% annual discount rate (for costs and outcomes)	annual discount rates of 0–3%	annual 3% (USA) and 5% (China) discounts

Author/ Year	Chiddarwar et al. 2025 [45]	Rieger et al. 2025 [43]	Zhu et al. 2025 [48]
Outcomes	■ cost and quality-adjusted life years (QALYs) ■ life years (LY) ■ incremental cost-effectiveness ratio (ICER) for EV+P relative to chemotherapy ■ factors influencing the cost-effectiveness	■ total costs (average lifetime costs) ■ quality-adjusted life years (QALYs)12 ■ incremental cost-effectiveness ratio (ICER) ■ NMB (net monetary benefit)	■ Life years (LY) ■ quality-adjusted life-years (QALYs) ■ incremental cost-effectiveness ratios (ICERs) ■ incremental net health benefit (INHB)
Results			
Cost and quality-adjusted life years (QALYs), life years	chemotherapy cost: $80,874 (79,991-81,757), yielding 1.26 QALYs (1.25-1.27) and 1.69 (1.68-1.7) life years EV+P cost: $752,637 (738,772-766,500), yielding 2.54 (2.51-2.56) QALYs, 1.28 (1.27-1.29) incremental QALY and 3.31 (3.29-3.33) life years, 1.62 (1.61-1.63) incremental life years	Standard of care cost: €163,424 (USA: $518.041[13])/lifetime horizon, yielding 1.21 QALYs and 1.73 life years EV+P cost: € 401,170 (USA: $ 1228,455) per patient/liefetime horizon, yielding 2.31 QALYs and 3.17 life years Gemcitabine/cisplatin + nivolumab cost: €206,853 (USA: $597,802), yielding 1.71 QALYs and 2.36 life years	chemotherapy cost: $24,773–$267,568, yieding1.04–1.06 QALYs EV+P cost: $288,347–$532,362, yielding 2.07–2.16 QALYs, and 1.25-1.34 life years longer than with chemotherapy
incremental cost-effectiveness ratio (ICER) relative to SoC	$525,239 (520,529-529,852)/QALY[14] and $414,927 (410,374-419,403)/life year To achieve cost-effectiveness at a $150.000/QALY threshold[15], the price of the combination therapy would need to be reduced by 76%.	EV+P €216,140 (Germany) $700,408 (USA) Gemcitabine/cisplatin + nivolumab €87,340 (Germany) $281,142 (USA) At a WTP threshold of €/$100 000/QALY, EV + P would require a price reduction of 46% (USA: 82%) to be cost-effective. A significant cost reduction of at least 20% (USA: 75%) is required for EV + P to be cost-effective at a high WTP threshold of €/$150.000/QALY.	United States: $267,491/QALY China: $254,339/QALY incremental net health benefits: −0.87 QALYs (USA; WTP threshold of $150,000/QALY) or −6.45 QALYs (China; WTP threshold of $35,173/QALY) To achieve greater cost-effectiveness, EV costs would need to be reduced by over 75% and 10% in the United States and China, respectively (WTP thresholds of $150,000/QALY and $35,173/QALY, respectively).

[12] Willingness To Pay thresholds at €/$50 000/QALY, €/$100 000/QALY, and €/$150 000/QALY. According to the World Health Organization, a WTP threshold is usually set at 2–3x the gross domestic product per capita.

[13] In table 5 and in the abstract, $458.006 is mentioned.

[14] In the conclusion, it says 'We found that the combination of EV+P resulted in an ICER of $509,100/QALY compared with the standard chemotherapy'.

[15] The threshold of $150.000 per QALY is commonly used in US-based economic evaluations, reflecting the willingness-to-pay for health interventions in the context of high-income countries [45].

Author/ Year	Chiddarwar et al. 2025 [45]	Rieger et al. 2025 [43]	Zhu et al. 2025 [48]
factors influencing the cost-effectiveness	survival hazard ratio for the combination therapy, cost of enfortumab and the utility in the progression-free state EV+P was cost-effective in 0% of the simulations. When the cost-effectiveness threshold exceeds $500.000/QALY, the probability of being cost-effective rises above 50%.	NR	body weight, the cost of EV and mean utility values There was a 0% chance of EV plus pembrolizumab being a cost-effective alternative to chemotherapy at a WTP of $150,000/QALY (USA) or $35,173/ QALY (China).
Conclusion of authors	Although EV+P therapy is effective, it is **not cost-effective at its current price as a first-line therapy in the United States** at a cost-effectiveness threshold of $150.000/QALY. A substantial reduction in its drug cost is required to be cost-effective at commonly accepted willingness-to-pay thresholds.	QALYs nearly double with EV + P compared with the current SoC; yet **current costs may not be justified from a strict socioeconomic perspective**. Despite its lower oncological benefit, gemcitabine/cisplatin + nivolumab should be considered for first-line therapy due to favorable cost effectiveness, especially in Europe. Establishing individual risk factors is essential for optimizing therapeutic response and treatment costs in the future.	While first-line EV plus pembrolizumab has significant health benefits compared to chemotherapy for patients with previously untreated la/mUC, **this regimen is not cost-effective at the current price in the United States or Chin**a. Efforts to reduce EV costs may be highly effective as a means of improving the accessibility of this innovative therapeutic regimen in the clinic.

Table 8-4: Cost-effectiveness analyses of Enfortumab Vedotin in combination with Pembrolizumab cont.

Author/ Year	Li et al. 2024 [46]	You et al. 2024 [47]
Country	China/USA	China
Sponsor	National Natural Science Foundation of China (grant number 71874209); the research project of the Health Commission of Hunan province (grant number 202113050283); the Fundamental Research Funds for the Central Universities of Central South University (grant number 2023ZZTS0924); Hunan Provincial Natural Science Foundation of China (grant number 2023JJ60503)	supported in part by grants from Natural Science Foundation of Ningde (Grant number: 2022J29). This study was not supported by any pharmaceutical company
Conflict of interest of authors	None	None
Study design/ method used	cost-effectiveness analysis Markov model, Monte Carlo simulation	cost-effectiveness analysis Markov model, Monte Carlo simulation
Sensitivity/ Uncertainty Analysis	Yes: One-way (each parameter is independently and singly varied within ±20% of the baseline value or within its 95% confidence interval), two-way (utility values for both treatment arms were simultaneously varied, ranging from -50% of the baseline value up to 1) and probabilistic sensitivity analyses (1,000 simulations with the parameters simultaneously varied with a specific pattern of distribution); scenario analyses assuming different unit prices for EV and pembrolizumab	Yes: one-way sensitivity analysis: adjusting parameters within specified ranges to identify those that affected the ICER. All parameters were varied within their 95% confidence intervals derived from the literature, using benchmark values of ±20% in the absence of data. The discount rate varied between 0% and 8%. Probabilistic sensitivity analysis: through 1,000 Monte Carlo simulations were performed to evaluate how simultaneous alterations in multiple parameters affected the model outcomes. All parameters followed pre-determined distributions calculation of the ICER for EVPEMB compared to chemotherapy was repeated by continuously decreasing the price of EV and pembrolizumab to determine the price of EV and pembrolizumab at which EV-PEMB could be cost-effective
Intervention	combination of EV with pembrolizumab	combination of EV with pembrolizumab
Comparator	chemotherapy consisting of cisplatin or carboplatin plus gemcitabine	chemotherapy (gemcitabine in combination with cisplatin or carboplatin)
Indication/ population	first-line treatment in adult patients with metastatic urothelial carcinoma (based on EV-302 study)	first-line treatment in adult patients with metastatic urothelial carcinoma (consistent with the target group of the EV-302 trial)
Perspective	U.S. payer perspective	perspective of the Chinese healthcare system
Cost types/cost categories	direct medical costs: cost of the drug, administration, best supportive care, maintenance therapy and management of adverse events	direct medical costs: drugs, tests, routine follow-up, BSC, end-of-life care, and management of grade 3 and higher adverse reactions with an incidence exceeding 5%
Time horizon	Lifetime horizon	15 years
Discount rate	annual discount rate of 3%	0% to 8% discount rate
Outcomes	■ total costs ■ life-years (LYs) ■ quality-adjusted life-years (QALYs) ■ incremental cost-effectiveness ratios (ICERs)	■ total costs ■ quality-adjusted life years (QALYs) ■ incremental cost-effectiveness ratios (ICERs)
Results		

Author/ Year	Li et al. 2024 [46]	You et al. 2024 [47]
Cost and quality-adjusted life years (QALYs), life years	EV+P Cost: $1,493,868, yielding 3.3 QALYs and 4.2 life years Chemotherapy Cost: $531,627.2, yielding 1.5 QALYs and 2.1 life years	EV+P Cost: $375,420.24, yielding 3.22 QALYs Chemotherapy Cost: $23,369.67, yielding 1.7 QALYs
incremental cost-effectiveness ratio (ICER) relative to SoC	$558,973/QALY; $458,390.1/life year Subgroup analyses: $563,128.5/QALY (in platinum-eligible patients) to $536135.5/QALY (in platinum-ineligible patients) Reducing the unit price of EV to $20 per milligram would result in a 50% probability of cost-effectiveness compared to chemotherapy at a WTP threshold of $150,000. Additionally, if the unit prices of both EV and pembrolizumab were simultaneously reduced by 80%, there would be a 75% probability of cost-effectiveness at the specified WTP threshold.	$232,256.16/QALY EV-PEMB had the probability of being a cost-effective regimen for the treatment of advanced UC compared to chemotherapy only when the prices of EV and pembrolizumab simultaneously decreased to 13.1% of the original, i.e., $208.7 and $333.9 for EV and pembrolizumab, respectively
factors influencing the cost-effectiveness	body weight, unit cost of EV, HR for PFS and OS, and discount rate At a WTP threshold of $150,000 per QALY, the likelihood of the combination therapy of EV with pembrolizumab being cost-effective compared to chemotherapy was 0%.	discount rate, the patient's weight, the price of EV, and the price of pembrolizumab The probability that the EV-PEMB group was cost-effective compared to the chemotherapy group was 0 at the WTP threshold of $38,133/QALY.
Conclusion of authors	Our study suggests that from the perspective of U.S. payers, **EV in combination with pembrolizumab is estimated not to be cost-effective compared with chemotherapy in the first-line setting** for patients with mUC at a WTP threshold of $150,000 per QALY.	From the perspective of the Chinese healthcare system, EV-PEMB is **unlikely to be a cost-effective first-line treatment option** for advanced UC compared to chemotherapy when the WTP threshold is $38,133 per QALY. Substantial reductions in the price of EV and pembrolizumab are necessary to make EV-PEMB cost-effective.

Risk of bias assessment of included systematic reviews

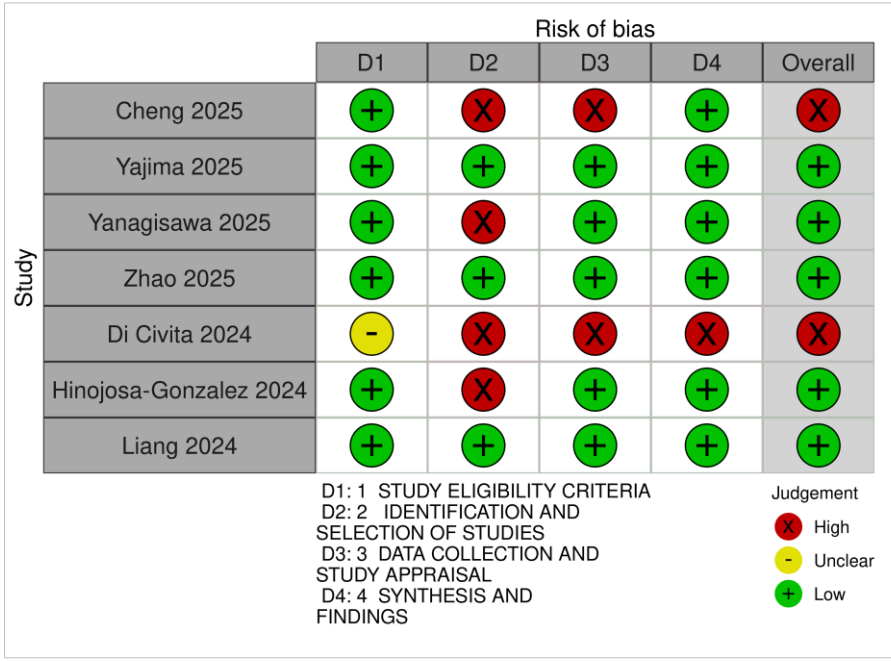

Figure 8-2: Risk of bias assessment of systematic reviews with ROBIS

ROBIS source: Resources | Bristol Medical School: Population Health Sciences | University of Bristol
Figure source: Risk of bias tools - robvis (visualization tool)

Cheng 2025 [26]: Only two search engines used (PubMed and Embase), no detailed search strategy provided (only two search terms stated), no information if abstracts were screened independently, RoB Jadad scale was used (very simple) – no information if done by two independent reviewers.

Di Civita 2024 [10]: No protocol was published, it did not specifically say if objectives and eligibility criteria were specified in advance. Only two search engines used (MEDLINE and CENTRAL), no supplementary search for citations etc., no search terms or search strategy were listed, no indication that abstracts were screened independently. No indication that standardised data extraction forms were used; limited information on study characteristics; no risk of bias assessment of included studies done. The main characteristics table only shows four studies, but the analysis included five studies as indicated in the Prisma flow diagram. There was great heterogeneity among the study population. No sensitivity analysis done.

Data extraction of clinical guidelines

Table 8-5: Clinical guidelines for Enfortumab Vedotin in combination with Pembrolizumab

Author/ Year	Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF) 2025 [3]	UpToDate 2025 [12]	Canadian Urological Association 2025 [42]	European Association of Urology (EAU) 2025 [2]	European Association of Urology (EAU) 2025 [39]
Title	S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms	Treatment of metastatic urothelial carcinoma of the bladder and urinary tract	2025 Canadian Urological Association Expert Report: Muscle-invasive bladder cancer	EAU Guidelines on Upper Urinary Tract Urothelial Carcinoma	EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer
Duration of validity	31.03.2030	NR	NR	NR	NR
Statement regarding Enfortumab Vedotin in combination with Pembrolizumab	Not mentioned	For patients with advanced or metastatic urothelial carcinoma, we recommend initial therapy with **enfortumab vedotin plus pembrolizumab** rather than platinum-based chemotherapy with maintenance immunotherapy. In a phase III trial, enfortumab vedotin conferred a large overall survival (OS) benefit as first-line therapy, with an acceptable toxicity profile.	Patients with non-metastatic, clinically unresectable cT4b or cN1-3 tumours should be offered **enfortumab vedotin plus pembrolizumab (EV+P)** or nivolumab plus GC (nivo+GC) over standard GC chemotherapy (LE 1, Strong recommendation). In jurisdictions where **EV+P** or nivo+GC are not available, induction (primary) cisplatin-based combination chemotherapy with either GC or dd-MVAC, if eligible, or a carboplatin-based combination regimen if cisplatin-ineligible, should be offered (LE 1, Strong recommendation). Patients who are platinum-ineligible may be offered immunotherapy (if available), an alternative combination chemotherapy regimen, or enrolment in a clinical trial, if possible (LE 2, Moderate recommendation).	**Enfortumab vedotin + Pembrolizumab** offers an overall survival benefit compared to gemcitabine-cisplatin in the first-line setting (LE: 1b) Offer **Enfortumab vedotin in combination with pembrolizumab** as first-line treatment to patients with advanced/metastatic disease. (Strength rating: strong)	**Enfortumab vedotin in combination with pembrolizumab** in the first-line setting demonstrated significant survival benefit as compared to chemotherapy (LE: 1) First-line treatment if eligible for combination therapy: use antibody drug conjugate **enfortumab vedotin (EV) in combination with checkpoint inhibitor (CPI) pembrolizumab** (Strength rating: strong)
Grade of recommendation (GoR)	NR	NR	Strong recommendation	Strength rating: strong	Strength rating: strong
Level of Evidence (LoE)	NR	NR	1	1b	1

Legend: EAU- European Association of Urology, GC - gemcitabine plus cisplatin, LE – level of evidence, NR – not reported

Table 8-6: Clinical guidelines for Enfortumab Vedotin in combination with Pembrolizumab (continued)

Author/ Year	European Society for Medical Oncology (ESMO) 2024 [13]	Onkopedia 2024 [1]	Alberta Health Services Cancer Guidelines 2024 [40]	French Association of Urology (AFU) Cancer Committee [41]
Title	ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma	Urothelial Carcinoma (Bladder Cancer)	Locally Advanced/Metastatic Bladder Cancer	French AFU Cancer Committee Guidelines – Update 2024–2026: Upper urinary tract urothelial cancer (UTUC)
Duration of validity	NR	NR	NR	NR
Statement regarding Enfortumab Vedotin in combination with Pembrolizumab	**Enfortumab vedotine-pembrolizumab** is recommended as the preferred first-line therapy for advanced or metastatic UC, irrespective of platinum eligibility [I, A; ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4; Food and Drug Administration (FDA) approved, not European Medicines Agency (EMA) approved]. After progression on enfortumab vedotine-pembrolizumab, standard platinum-based ChT without maintenance avelumab in unselected patients or erdafitinib in selected FGFR-altered tumours can be recommended [IV, B]. Rechallenge with a single-agent ICI is not encouraged without further evidence [V, D]. Patients not able to receive enfortumab vedotine-pembrolizumab should be treated with nivolumab plus up to six cycles of gemcitabine-cisplatin (if cisplatin eligible only) [I, A; ESMO-MCBS v1.1 score: 2; FDA and EMA approved] or up to six cycles of platinum-based ChT (gemcitabine plus cisplatin or carboplatin) [I, A], followed by maintenance avelumab (for nonprogressing tumours) [I, A; ESMO-MCBS v1.1 score: 4]. Single-agent ICIs have a limited role in first-line advanced disease and should not be routinely recommended [I, D]. There are two changes for treatment after first-line platinum-based ChT and an ICI (given concurrently, sequentially or as second-line therapy):	First-line therapy for metastatic or locally non-curable disease: The new preferred first-line therapy is the combination of **pembrolizumab with the immunotoxin conjugate enfortumab vedotin (EV),** which is directed against *nectin-4*. In a randomized comparison with first-line chemotherapy, this combination led to a significant increase in median overall survival from 16.1 to 31.5 months in the *KEYNOTE-A39/EV-302* trial	Management of Locally Advanced Disease (Stages T4bNxM0, TxN2-3M0) Primary Therapy A. Patients with pre-operatively identified locally advanced disease should be reviewed in multidisciplinary rounds to determine intent of therapy. B. Eligible patients with unresectable disease should initially receive systemic therapy. **Enfortumab Vedotin + Pembrolizumab** i. **Enfortumab Vedotin + Pembrolizumab** was evaluated in the EV302 study with inclusion of locally advanced patients. This demonstrated an improvement in PFS (HR 0.45), OS (HR 0.47) compared to platinum-based chemotherapy in the ITT population. a. **Enfortumab Vedotin + Pembrolizumab**: EV 1.25mg/kg Day 1 and Day 8 (max of 125mg), Pembrolizumab 200mg IV Day 1, every 3 weeks. Maximum of 35 cycles of pembrolizumab. Last revision: October 2024 Guideline Resource Unit 4 b**. EV+P** is Health Canada approved (August 2024) and is currently available by patient support program. Funding decisions are pending Management of Metastatic Disease (TxNxM1) First-line Therapy **Enfortumab Vedotin + Pembrolizumab**	First-line treatment strategies. For metastatic disease, the choice of treatment takes into account prognostic factors such as the patient's general condition and the possibility of receiving treatment with anti-PD- (L)-1 therapy or cisplatin. As for metastatic bladder tumours, the first-line treatment is the **combination of enfortumab vedotin with pembrolizumab**, given the overall survival benefit (HR 0.53 [0.34–0.83]) over platinum-based chemotherapy in the UTUC subgroup (n = 239; 27%) of the EV-302 study [144] (Level of evidence 1). 4.3.2.2. Second-line treatment strategies. In patients pretreated with a combination of enfortumab vedotin and pembrolizumab, platinum-based chemotherapy may be offered as a second-line treatment (Level of evidence 4).

Author/ Year	European Society for Medical Oncology (ESMO) 2024 [13]	Onkopedia 2024 [1]	Alberta Health Services Cancer Guidelines 2024 [40]	French Association of Urology (AFU) Cancer Committee [41]
	o Erdafitinib is recommended in patients with selected FGFR DNA fusions and mutations who have previously been treated with ChT and an ICI [I, A; ESMO-MCBS v1.1 score: 4; FDA approved, not EMA approved]. o Sacituzumab govitecan can be recommended in patients previously treated with ChT and an ICI [III, B; ESMO-MCBS v1.1 score: 2; FDA approved, not EMA approved]. For patients with progression after enfortumab vedotine pembrolizumab, treatments not previously given may be considered for third- and fourth-line therapy [V, C]		i. Enfortumab Vedotin + Pembrolizumab was compared to standard platinum-based chemotherapy in the EV302 study. Patients were eligible if they were ECOG ≤2, platinumeligible, eGFR>30 ml/min, and EV and IO eligible. EV+P demonstrated improvements in PFS Last revision: October 2024 Guideline Resource Unit 6 (HR 0.45) and OS (HR 0.47) compared to platinum-based chemotherapy. EV+P is Health Canada approved and available by patient support program (Sept 2024). a. Enfortumab vedotin (1.25 mg/kg body weight IV day 1 and 8) and pembrolizumab (200mg IV day 1) q3 weekly. b. [Enfortumab Vedotin monograph] [Pembrolizumab monograph] Second-Line Therapy: A. For patients who have progressed on enfortumab vedotin + pembrolizumab, subsequent therapy is not well defined. Options may include: i. Platinum-based chemotherapy. ii. Erdafitinib for patients with FGFR alterations. iii. Clinical trials where available.	
Grade of recommendation (GoR)	A	NR	NR	NR
Level of Evidence (LoE)	I	NR	NR	1

Legend: AFU - Association Française d'Urologie" (French Association of Urology), ChT – chemotherapy, ESMO - European Society for Medical Oncology, ESMO-MCBS - ESMO Magnitude of Clinical Benefit Scale, ICI - immune checkpoint inhibitor, NR – not reported, UC – urothelial carcinoma, UTUC - upper tract urothelial carcinomas

Search strategies

MEDLINE via Ovid

Database: Ovid MEDLINE(R) ALL <1946 to June 16, 2025>
Search Strategy:
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1 urothel*.mp. (30697)
2 urin*.mp. (794284)
3 urologic*.mp. (72490)
4 exp Urologic Neoplasms/ (163062)
5 1 or 2 or 3 or 4 (923126)
6 enfortumab*.mp. (553)
7 ags 22c3*.mp. (2)
8 ags22c3*.mp. (0)
9 ags 22ce*.mp. (0)
10 ags22ce*.mp. (0)
11 ags 22m6e*.mp. (1)
12 ags22m6e*.mp. (0)
13 ags 22me*.mp. (0)
14 ags22me*.mp. (0)
15 asp 7465*.mp. (0)
16 asp7465*.mp. (0)
17 padcev*.mp. (21)
18 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (562)
19 5 and 18 (484)
20 limit 19 to (meta analysis or "systematic review") (17)
21 (((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence or safety or effectiveness)).mp. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (890707)
22 19 and 21 (52)
23 20 or 22 (52)
24 limit 23 to yr="2020 - 2025" (52)
25 remove duplicates from 24 (52)
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17.06.2025

The Cochrane Library

Search Name: Enfortumab
Last Saved: 18/06/2025 16:32:38
Comment: HTA-Infodienst (SE/JMF)

ID Search
#1 (urothel*) (Word variations have been searched)
#2 (urin*) (Word variations have been searched)
#3 (urolog*) (Word variations have been searched)
#4 MeSH descriptor: [Urologic Neoplasms] explode all trees
#5 #1 OR #2 OR #3 OR #4

#6 (enfortumab*) (Word variations have been searched)
#7 (ags NEXT 22c3*) (Word variations have been searched)
#8 (ags22c3*) (Word variations have been searched)
#9 (ags NEXT 22ce*) (Word variations have been searched)
#10 (ags22ce*) (Word variations have been searched)
#11 (ags NEXT 22m6e*) (Word variations have been searched)
#12 (ags22m6e*) (Word variations have been searched)
#13 (ags NEXT 22me*) (Word variations have been searched)
#14 (ags22me*) (Word variations have been searched)
#15 (asp NEXT 7465*) (Word variations have been searched)
#16 (asp7465*) (Word variations have been searched)
#17 (padcev*) (Word variations have been searched)
#18 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 #5 AND #18
#20 #5 AND #18 in Cochrane Reviews, Cochrane Protocols

0 Hits

Epistemonikos

Full query: (title:(enfortumab* OR padcev*) OR abstract:(enfortumab* OR padcev*))

Limited to last 5 years

32 Hits

Date of search: 18.06.2025

HTA (INAHTA)

Search step #	Search query,"Hits","Searched At"
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4	(padcev*) OR (enfortumab*),"8","2025-06-18T14:55:28.000000Z"
3	(padcev*) OR (enfortumab*),"8","2025-06-18T14:55:16.000000Z"
2	padcev*,"1","2025-06-18T14:51:45.000000Z"
1	enfortumab*,"7","2025-06-18T14:51:28.000000Z"

Total hits	8
Date of search	18.06.2025

Search strategy study register

Urothelial Cancer | Other terms: Urothelial Carcinoma | Enfortumab vedotin AND Pembrolizumab

Total hits: 20

Date: 31.07.2025

Search strategy real-world studies

PubMed: real world AND Enfortumab* AND Pembrolizumab*

Total hits: 23

Date: 24.09.2025

PubMed: real world AND Padcev* AND Keytruda*: 23 hits

Total hits: 23

Date: 24.09.2025

9 References

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