Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende enfortumab vedotin i kombination med pembrolizumab til førstelinjebehandling af urotelialkræft

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. enfortumab vedotin i kombination med pembrolizumab
2. Ansøgers endelige ansøgning vedr. enfortumab vedotin i kombination med pembrolizumab

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

20.11.2024
DBS/CAF/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	18. december 2024
Leverandør	Astellas
Lægemiddel	Padcev (enfortumab vedotin) + Keytruda (pembolizumab)
Ansøgt indikation	Padcev (enfortumab vedotin) i kombination med Keytruda (pembrolizumab) til førstelinjebehandling af urotelialkræft
Nyt lægemiddel / indikationsudvidelse	indikationsudvidelse

Prisinformation

Amgros har følgende pris på Padcev (enfortumab vedotin):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Aftalepris SAIP (DKK)	Rabatprocent ift. AIP
Padcev	20 mg	1 stk.	4.643,30	[redacted]	[redacted]
Padcev	30 mg	1 stk.	6.964,14	[redacted]	[redacted]

Aftaleforhold

Amgros har en aftale på Padcev, der er gælder til den 31.12.2025 med mulighed for forlængelse. Leverandøren har mulighed for at justere prisen i aftaleperioden.

Amgros har en aftale på Keytruda (pembolizumab), som er en del af et dynamisk udbud sammen med Opdivo (nivolumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Bavencio (avelumab) og Imfinzi (durvalumab). I den nuværende aftale er der mulighed for prisregulering når Amgros vurderer det som fordelagtigt ift. markedssituationen.

Konkurrencesituationen

Medicinrådet anbefalede i oktober 2024 Opdivo i kombination med cisplatin og gemcitabin til behandling af patienter med inoperabel eller metastatisk urotelialt carcinom i førstelinje. Kombinationen af Padcev og Keytruda er den anden kombinationsbehandling til indikationen.

Tabel 2 viser lægemiddeludgiften for et års behandling med Padcev i kombination med Keytruda.

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Padcev	30 mg	1 stk.	1,25 mg/kg på dag 1 og 8 hver 3. uge*	[redacted]	[redacted]
Keytruda	25 mg/ml	4 ml	2 mg/kg hver 3. uge	[redacted]	[redacted]
Total lægemiddeludgift					[redacted]

* Gennemsnitsvægt 76 kg jf. Medicinrådets vurderingsrapport

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering
Sverige	Under vurdering	Link til vurdering

Konklusion

[redacted]

Application for the Assessment of Enfortumab Vedotin in combination with Pembrolizumab for Unresectable or Metastatic Urothelial Carcinoma

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

Contact information	
Name	**Kamilla Juhl Nørgaard**
Title	HEOR lead
Phone number	+ 45 40 62 89 58
E-mail	kamilla.norgaard@astellas.com
Name	**Sara Nordling**
Title	Market Access, Associate Director
Phone number	+ 45 22 72 02 83
E-mail	sara.nordling@astellas.com

Table of contents

Tables and Figures

List of Tables

List of figures

Abbreviations

Abbreviation	Full name
AACR	American Association for Cancer Research
AIP	Pharmacy purchasing prices
ASCO	American Society of Clinical Oncology;
AUA	American Urological Association
BC	Bladder cancer
BICR	Blinded independent central review
BPI-SF	Brief Pain Inventory - Short Form
BSC	Best supported care
CaG	Carboplatin and gemcitabine
CADHT	Canadian Agency for Drugs and Technologies in Health
CCTR	Cochrane Central Register of Controlled Trials
GBA	German Federal Joint Committee
CG	Cisplatin and gemcitabine
CEM	Cost-effectiveness model
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DaBlaCa	Danish Bladder Cancer Group
DCR	Disease control rate
DKK	Danish Krone
DMC	The Danish Medicines Council
DRG	Danish diagnosis related groups
DOR	Duration of treatment response
EAU	European Association of Urology

ECOG	Eastern Cooperative Oncology Group.
Embase	Excerpta Medica dataBASE
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EORTC-QLQ-C30	Measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ESMO	European Society for Medical Oncology
EQ-5D-5L	EuroQOL Five Dimensions Questionnaire 5L
EV	Enfortumab vedotin
GC	Gemcitabine plus cisplatin
Gem	Gemcitabine
GFR	Glomerular filtration rate
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ICERe	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
laUC	Locally advanced urothelial cancer
MCID	The minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MEDLINE	Medical Literature Analysis and Retrieval System Online
mUC	Metastatic urothelial cancer
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NCI	National Cancer Institute
NMIBC	Non-muscular invasive bladder cancer
NYHA	New York Heart Association Classification
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
P	Pembrolizumab
Plat	Platinum-based chemotherapy (cisplatin and carboplatin)
PD	Progressed disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Parti
PRO	Patient reported outcome
PS	Performance status
PT	Preferred item
QALYs	Quality-adjusted life years
QoL	Quality of life

RECIST	Response Evaluation Criteria in Solid Tumors
PSM	Partitioned survival model
SAF	Safety analysis set
SLR	Systematic literature review
SOC	Standard of care
SOCL	System organ class
SUO	Society of Urologic Oncology
TTPP	Time to pain progression
TNM	Tumour-Node-Metastasis
UC	Urothelial carcinoma
UTC	Urinary tract cancers

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Padcev™ + Keytruda®
Generic name	Enfortumab vedotin in combination with pembrolizumab
Therapeutic indication as defined by EMA	Enfortumab vedotin, 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.
Marketing authorization holder in Denmark	Padcev: Astellas Pharma Europe B.V. Keytruda: Merck Sharp & Dohme B.V.
ATC code	Enfortumab vedotin: L01FX13 Pembrolizumab: L01FF02
Combination therapy and/or co-medication	Enfortumab vedotin in combination with pembrolizumab
(Expected) Date of EC approval	Enfortumab vedotin, in combination with pembrolizumab, received CHMP positive opinion on the 25th of July 2024 for the indication: first line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy. Enfortumab vedotin in combination with pembrolizumab is expected to be approved by EC during August/September 2024.

Overview of the medicine	
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	The combination of enfortumab vedotin and pembrolizumab is not approved in other indications by EMA.
Other indications that have been evaluated by the DMC (yes/no)	Enfortumab vedotin was assessed and not recommended for advanced urothelial cancer after prior treatment with a PD-L1 inhibitor and platinum-based chemotherapy. On January 5th a reassessment was endorsed and decision from DMC is planned for the 28th of August 2024. Pembrolizumab has been recommended as a possible standard treatment for urothelial cancer for: • Patients in performance status 0-2 and combined positive PD-L1 score > 10 who are not candidates for cisplatin-based chemotherapy (1st line). • Patients in performance status 0-1 with disease progression after platinum-based chemotherapy (2nd line).
Joint Nordic assessment (JNHB)	No. Different requirements apply for HTA assessments of new indications across the Nordics. In this case it is expected to be more efficient and suitable to tailor the assessment to each national agency specifically.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	*Enfortumab vedotin 20 mg*. Powder for concentrate for solution for infusion. Intravenous use vial (glass) 1 vial. *Enfortumab vedotin 30 mg.* Powder for concentrate for solution for infusion. Intravenous use vial (glass) 1 vial. *Pembrolizumab 25 mg/ml.* Concentrate for solution for infusion. Intravenous use vial (glass) 4 ml 1 vial.

Source: EMA[1,2]

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Enfortumab vedotin, 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.
Dosage regiment and administration	Enfortumab vedotin: 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. Pembrolizumab: a dose of 200 mg as an intravenous infusion after the enfortumab vedotin infusion on day 1 of each 3-week cycle.
Choice of comparator	Gemcitabine + platinum-containing chemotherapy consisting of either cisplatin or carboplatin.
Prognosis with current treatment (comparator)	In a Danish study, the median overall survival (OS) for 1st line chemotherapy was 14 months for cisplatin-based chemotherapy and 9.8 months for carboplatin-based chemotherapy.[3]
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	Dual primary endpoints: Median OS was 31.5 months in the EV+P arm and 16.1 months in the Plat+Gem (HR: 0.468; 95% CI: 0.376, 0.582; 2-sided p-value <0.00001)[4] Median PFS was 12.5 months in the EV+P arm and 6.3 months in the Plat+Gem arm (HR: 0.450; 95% CI: 0.377, 0.538; 2-sided p-value <0.00001)[4] Key secondary endpoint: Confirmed ORR by BICR was 67.7% (CR, 29.1%; PR, 38.7%) in the EV+P arm and 44.4% (CR, 12.5%; PR, 32%) in the Plat+Gem[4]
Most important serious adverse events for the intervention and comparator	In the EV+P arm, the most common serious TEAEs included [redacted]. In the Plat + Gem arm, the most common serious TEAEs included [redacted] Overall, the profile of serious TEAEs reported in both arms was generally consistent with the known adverse reactions of the respective treatments and/or underlying disease, preexisting comorbidities, and advanced age of the study population.

Summary	
Impact on health-related quality of life	Clinical: The humanistic value of EV monotherapy and EV+P was assessed via PROs using three instruments, the EORTC QLQ-C30, which have been validated in an la/mUC population, the EQ-5D, and the Brief Pain Inventory short form (BPI-SF). Descriptive characteristics of EQ-5D-5L were summarized from baseline assessment through the last available data. Frequency and the percentage of reported problems for each level for each dimension were provided. All time point data were to be included and summarized. EQ-5D-5L visual analogue scale (VAS) scores were summarized by treatment arm at each visit using descriptive statistics (mean, SD, median, minimum and maximum). In summary, patients receiving EV+P consistently demonstrated their QoL, functioning, and symptom experience was not compromised compared with patients receiving Plat+Gem. Health economic: Treatment with EV+P is associated with a QALY-gain compared to standard of care.
Type of economic analysis that is submitted	Cost-utility analysis based on a partitioned survival model
Data sources used to model the clinical effects	EV-302 trial to extrapolate OS, PFS and ToT
Data sources used to model the health-related quality of life	EQ-5D-5L collected in EV-302 updated with Danish tariff.
Life years gained	XXXX years (discounted)
QALYs gained	XXXX QALYs (discounted)
Incremental costs	DKK XXXXXXXX
ICER (DKK/QALY)	DKK XXXXXXXX per QALY
Uncertainty associated with the ICER estimate	The most important uncertainty of the ICER estimate, is the choice of parametric curves, which is explained by the short follow-up time of the EV-302 trial. Other important parameters were proportion of patients actually receiving avelumab maintenance, discount rates, utility values for the progression free health states

Summary	
Number of eligible patients in Denmark	Incidence: Annually, approximately 150 patients receive systemic oncology treatment for newly diagnosed advanced urothelial cancer Prevalence: Approximately 150 patients, since median OS about 12 month for patients receiving 1st line chemotherapy.5 As such, no difference between prevalent and incident population is expected.
Budget impact (in year 5)	[redacted]

Sources: Omland et al., 2021[4]; Balar et al., 2017[6]; Powles et al., 2024[4]
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PFS, progression-free survival; Plat, platinum-based chemotherapy (cisplatin and carboplatin); PR, partial response

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Urothelial carcinoma (UC) is the most common type of bladder cancer (BC), accounting for more than 90% of all cases of BC.[7,8] UCs originate in the transitional cells in the inner lining of the bladder, urethra, ureter, or renal pelvis. Even though UCs are not confined exclusively to the bladder and can be found in other parts of the urinary tract, more than 90% of UCs originate in the bladder.

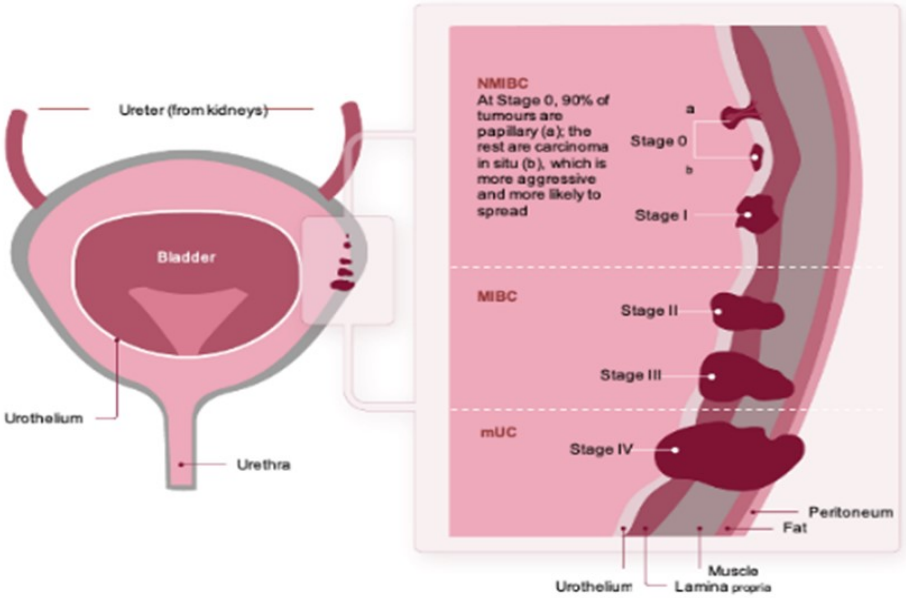
UC is usually characterized clinically by the extent of invasion and can be non-muscle invasive (NMIBC), muscle-invasive (MIBC), or metastatic.[5] A disease that involves regional metastasis is referred to as locally advanced.[9] UC is considered unresectable when it has invaded tissues outside the bladder wall, including the adjacent pelvic or abdominal structures.[5,10] At presentation, approximately 70% of patients have NMIBC, with MIBC and metastatic UC representing approximately 20% and 10% of newly diagnosed BC cases, respectively.[5,10]

- Clinical staging is inaccurate, and therefore pathological staging is considered the gold standard (although this is limited by transurethral resection specimens and by cautery and distortion artifacts).[10,11] Pathological staging is according to the Tumour-Node-Metastasis (TNM) classification, based on: [12]
- Primary tumour size and extent (T)
- Regional lymph node involvement (N)

- Presence or absence of distant metastases (M, where M0 indicates no distant metastasis and M1 indicates metastasis to distant organs [beyond regional lymph nodes])

This information is combined to assign an overall Stage of 0, I, II, III or IV. Figure 1 illustrates the staging of UC and is adapted from Berdik, 2017.[13]

Figure 1. Staging of urothelial carcinoma



Abbreviations: mUC, metastatic urothelial carcinoma; MIBC, muscle invasive bladder cancer; NMIBC, non-muscle invasive bladder cancer; UC, urothelial carcinoma.
Source: Adapted from Berdik, 2017.[13]

The most important risk factor for BC is smoking; tobacco smoking increases risk, progression, and development of BC.[5] Another risk factor is male sex, as the incidence of BC is approximately 4-fold higher in men than women (32.4 per 100,000 in men vs 8.0 per 100,000 in women), according to Surveillance, Epidemiology and End Results (SEER) data for 2015–2021)[14], and similar data have been reported by GLOBOCAN for 2020.[15] This is supported by statistics reported by NORDCAN (Cancer statistics for the Nordic countries) in Denmark from 2017-2021, showing that, on average, 74% of patients with BC or other urinary tract cancers (UTC) in 2018 were male.[16] For Danish men, the bladder it is the fourth most common cancer site; and the eight for women.[16]

BC has one of the highest mortality rates among cancer populations, with a worldwide ASR of 1.9 per 100,000 according to GLOBOCAN 2020.[15] Age-standardized mortality rates for individual countries range from 0.2–9.3 per 100,000. NORDCAN reports a mortality rate of about 13.1 per 100,000 per year in Denmark among men, and 4.6 in 100,000 for women.[16] BC and UC represents 4.4% of all cancer deaths in Denmark for men, and 2.3% (per NORDCAN- please check + reference) for women.[16]

Patients in the mUC stage have a more aggressive cancer than patients with BC without metastases, and the mortality rate increases drastically; SEER data (2012–2018) indicate that 5-year relative survival is 7.7% in those with distant metastases. [17] SEER data (2001–

2010) report median OS to be 4 months in (second line) mUC, with OS probability decreasing from 23% at 1 year to 11% at 2 years and 8% at 3 years.[18] Another analysis of SEER data (2010–2014; all treatment lines) found that median OS was 5 months, in patients with mUC.[19] The survival outcomes in mUC were worse than for adenocarcinoma (6 and 25 months, respectively) and patients with multiple metastatic sites had a worse OS and cancer-specific survival (CSS). A recent Danish study assessed the real-world treatment patterns and outcomes of patients with locally advanced, unresectable, and metastatic urinary tract cancers initiating 1st line chemotherapy. The median OS for 1st line chemotherapy was 14 months for cisplatin-based chemotherapy and 9.8 months for carboplatin-based chemotherapy.[5]

Patients with UC often present with urinary symptoms (polyuria, dysuria, urinary retention, and haematuria), and lower back or abdominal pain. In addition, patients with metastatic disease may also experience fatigue, weight loss, appetite loss, and/or pain specific to the site of metastasis. Patients are impacted by worsening physical function, role function, pain, and overall quality of life (QoL) as metastatic UC progresses.[20-22]

Metastatic disease is associated with systemic symptoms which vary between patients according to the site(s) of metastases. These include pain associated with bone and liver metastases, fractures associated with bone metastases, cough and shortness of breath associated with lung metastases, and liver dysfunction associated with liver metastases.[20,21] In addition, fatigue, weight loss, and appetite loss, which may be present in patients with locally advanced disease, become more prominent in patients with metastatic disease.[20-22] Metastatic disease is associated with systemic symptoms which vary between patients according to the site(s) of metastases. These include pain associated with bone and liver metastases, fractures associated with bone metastases, cough and shortness of breath associated with lung metastases, and liver dysfunction associated with liver metastases. [20,21] In addition, fatigue, weight loss, and appetite loss, which may be present in patients with locally advanced disease, become more prominent in patients with metastatic disease.[20-22]

3.2 Patient population

There is limited published data on the epidemiology of unresectable locally advanced or metastatic urothelial carcinoma, hereafter referred to as la/mUC, with few studies and databases containing data specific to this population. As such, data for BC are considered a good proxy, given that UC accounts for approximately 90% of BC cases. BC is the 10th most common cancer worldwide, with 573,300 newly diagnosed cases in 2020.[23]

In the years 2017-2021, an average of 2,300 new cases and 550 deaths related to BC were reported in Denmark, which also correspond to approximately 23,000 people in Denmark were living with a diagnosis of BC or UC.[16] A recent Danish study in a real-world setting reported that approximately 1,100 patients are diagnosed with UTC in Denmark every year, of which 3 in 4 are men. The study further reported a median age of 69 (Interquartile range (IQR), 63-75) years at the initiation of first-line chemotherapy.[3] The DMC has estimated that each year, approximately 150 patients

receive systemic oncological treatment for newly diagnosed advanced urothelial cancer.[24]

Table 1. Incidence, prevalence, death of bladder cancer and mUC chemo treated patients in Denmark in the past 5 years

Year	2019	2020	2021	2022	2023
Bladder cancer					
Incidence[1]	2,340	2,340	2,340	2,340	2,340
Prevalence[1]	22,746	22,746	22,746	22,746	22,746
Death[1]	552	552	552	552	552
mUC chemo treated patients[2]					
Incidence/prevalence[2]	150	150	150	150	150

Source: 1) Nordcan average data 2017-2021[16]; 2) Medicinrådet, udkast[24]

Patient populations relevant for this assessment

The patient population relevant for this assessment is adult patients with la/mUC who are eligible for platinum-based chemotherapy. The DMC has estimated that each year, approximately 150 patients receive systemic oncological treatment for newly diagnosed advanced urothelial cancer (Table 2).[24] Astellas estimate that EV+P is assumed to replace the current treatment for approximately XXXX of the eligible patients, corresponding to XXXX patients per year

Table 2. Estimated number of patients eligible for EV+P treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	150	150	150	150	150

3.3 Current treatment options

The treatment recommendations for la/mUC from the Danish Bladder Cancer Group (DaBlaCa) version 1.3 published in 2023[25] are aligned with international guidelines published before the EV-302 data disclosure.[26] Majority of la/mUC patients in Denmark are currently recommended a systemic chemotherapy as a first line treatment. The highest response rates are observed with cisplatin-based chemotherapy and is recommended to patients with ECOG PS 0-1 and normal renal function combined with

gemcitabine (CG) as first-line standard of care.[25] A more detailed description of DaBlaCa treatment recommendations is presented in Current treatment algorithm Figure 2.

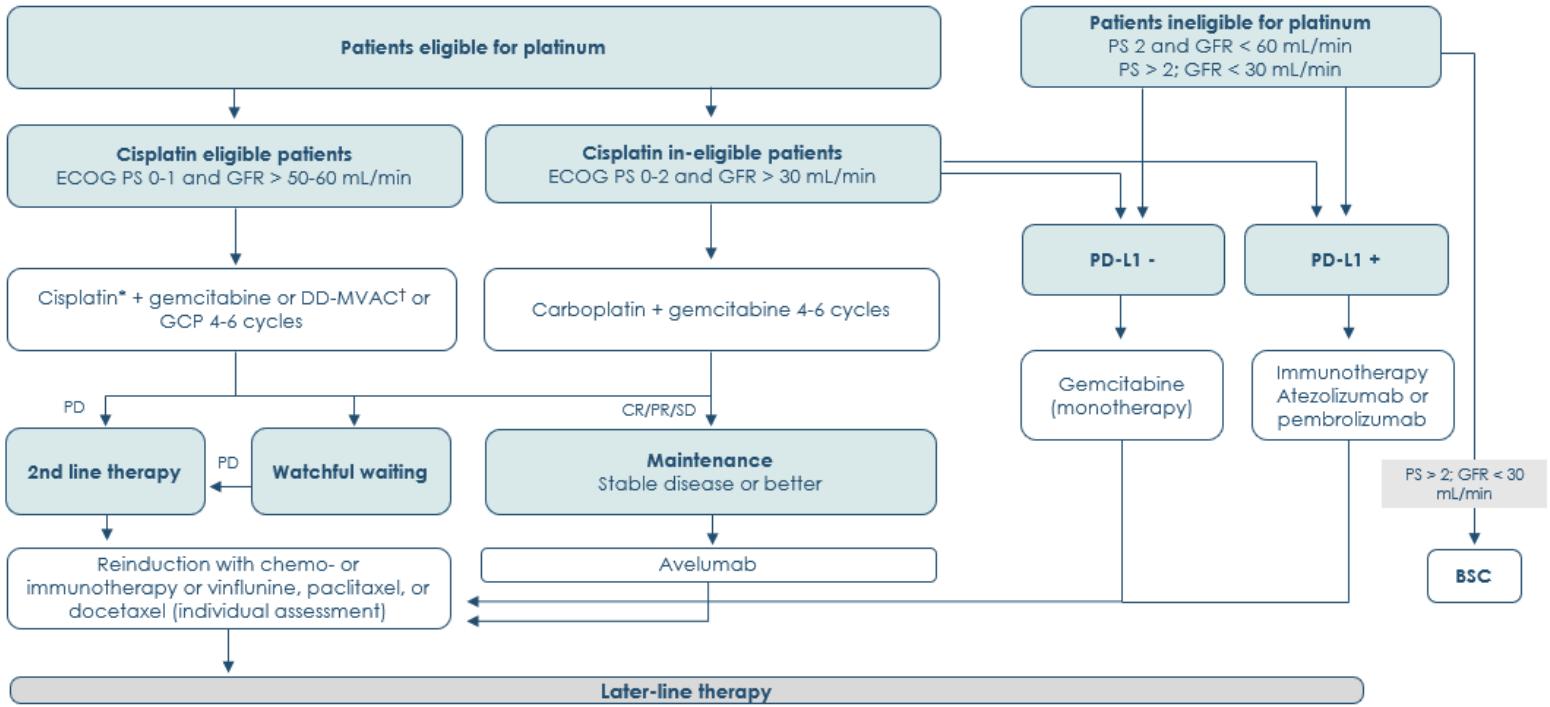
Patients with la/mUC who are unfit to receive cisplatin-based chemotherapy, due to severe comorbidities, reduced renal function, substantial hearing loss, peripheral neuropathy, or heart failure can be offered carboplatin-gemcitabine instead. Patients who develop stable disease or response to first-line cisplatin- or carboplatin-containing combination therapy are advised to continue maintenance therapy with immunotherapy; avelumab.[25]

For patients who are unable to tolerate platinum-based combination chemotherapy in the first-line, single-agent treatment with gemcitabine can be offered. Alternatively, if the patient is PD-(L)-1 positive, immunotherapy with pembrolizumab or atezolizumab can be considered. Treatment-naive patients who are not candidates for platinum-based therapies have shown poor prognostic outcomes. Thus, the adoption of best supportive care (BSC) emerges as a pragmatic treatment approach for these individuals. [25]

The second line treatment initiated at disease progression after first line treatment and maintenance treatment is individually tailored and could consist of the re-induction of platinum-based chemotherapy. For patients with advanced or la/mUC who progress on a platinum-based regimen, DaBlaCA recommends treatment with single-agent immunotherapy where pembrolizumab is the first choice due to strongest data but nivolumab and atezolizumab are also recommended by DaBlaCa for these patients. Chemotherapeutic agents such as vinflunine, docetaxel, or paclitaxel, either as monotherapy or in combination with gemcitabine, could also be used as a second line treatment.[25] In the event of disease progression following platinum-based combination chemotherapy and subsequent immunotherapy, EV as a monotherapy could be an option if DMC recommend the treatment the 28th of August.[24]

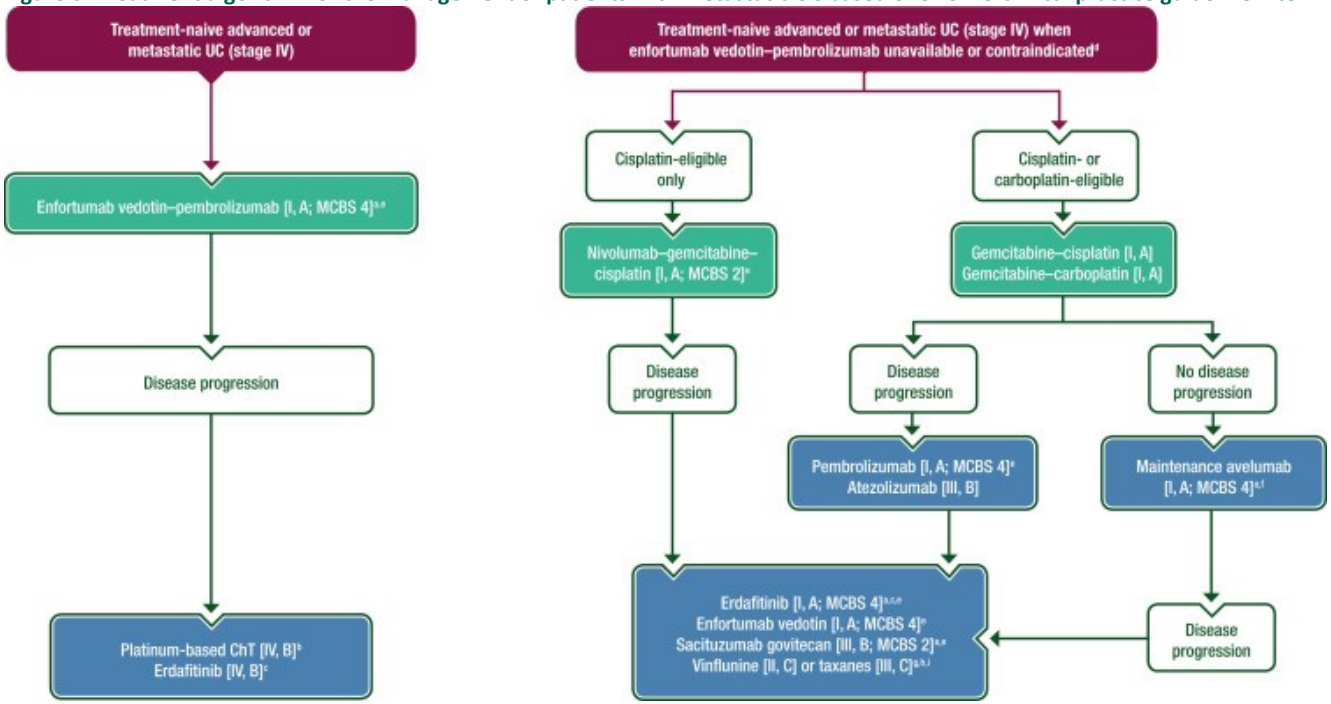
The latest ESMO guideline in advanced urothelial carcinoma dated 1 March 2024, recommends EV+P as the new standard of care in first-line advanced urothelial carcinoma, with an evidence grade A. The recommendation is based on the significant and clinically meaningful results on PFS and OS in EV-302.[4] Instead of recommending a systemic chemotherapy as a first line treatment for the majority of the patients, EV+P is recommended by ESMO for the vast majority of patients irrespective of platinum eligibility or PD-(L)-1 status (Figure 3).[27] As per the ESMO guidelines, the adoption of EV+P as the new SoC for first-line treatment in la/mUC will also alter subsequent treatment strategies. Treatment recommendation from DaBlaCA will probably differ from ESMO guidelines since treatments as erdafitinib and sacituzumab govitecan is not available in Denmark (Figure 2).

Figure 2. Current treatment algorithm



Abbreviations: BSC , best supportive care; CR, complete response; DD-MVAC, dose dense methotrexate vinblastine doxorubicin cisplatin; DMC, Danish Medicines Council; ECOG, Eastern Cooperative Oncology Group; GCP, gemcitabine/cisplatin/paclitaxel; GFR, glomerular filtration rate; IO, immunotherapy; PD, progressed disease; PD-L1, programmed cell death ligand 1; PR, partial response; PS, performance status; SD, stable disease.
*Standard of care
Adapted from: the DMC in the assessment report of Enfortumab vedotin of UC and DaBlaDa[24,25]

Figure 3. Treatment algorithm for the management of patients with metastatic UC based one ESMO clinical practice guideline interim update on first-line therapy



Purple: algorithm title; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
Abbreviations: ChT, chemotherapy;; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; UC, urothelial carcinoma.
a FDA approved; not EMA approved., b Rechallenge with single-agent ICI is not encouraged without further evidence [V, D], c In tumours with selected FGFR DNA fusions and mutations, d Enfortumab vedotin–pembrolizumab is preferred over platinum-based ChT irrespective of platinum eligibility. e ESMO-MCBS v1.110 was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms), f This should be assessed within 10 weeks of completion of ChT, g Rechallenge with platinum-based ChT may be considered if progression occurred 12 months after the end of previous platinum-based ChT or 12 months after the end of previous platinum-based ChT and maintenance avelumab, h Platinum doublets to be considered if the treatment-free interval from the last platinum-based ChT is >1 year, i To be considered when other therapies are not available.
Source: EMSO, 2024[27]

Unmet needs

Changes in the management of la/mUC have been infrequent due to a lack of novel treatments demonstrating a significant survival benefit vs standard of care (SOC) chemotherapy. Many patients are not suitable for currently available therapies and there is a high attrition rate between the first-line and second-line setting. As such, there remains a significant need for an effective first-line treatment option for which majority of the patients are suitable.

Clinical outcomes are poor for patients with la/mUC despite clinical advances.[28] Cisplatin-based chemotherapy is the SOC for first-line mUC; however, 30–50% of patients are ineligible to receive this therapy.[29,30] Alternatives to cisplatin-based chemotherapy, such as carboplatin-based chemotherapy, result in inferior outcomes.[31] Moreover, while guidelines recommend that patients who do not progress on first-line Plat+Gem receive maintenance therapy with avelumab, it is not possible to predict at first-line treatment initiation which patients will achieve and maintain stable disease and therefore be eligible for maintenance therapy. Just 58% of patients are projected to be eligible for maintenance avelumab (based on PFS data from the KEYNOTE-361 chemotherapy arm at 5.6 months post-initiation of first-line Plat+Gem).[32,33] United States (US) real world evidence (RWE) suggests that 54–80% of patients with la/mUC who receive first-line Plat+Gem may be eligible to receive first-line avelumab maintenance therapy [34,35] but only approximately 24–37% of patients eligible for maintenance therapy [34-36] and approximately 20–37% of patients who receive first-line Plat+Gem receive maintenance avelumab.[35-38] In a recent published RWE study in Denmark (COBRA study [39]), out of 1,278 identified la/mUC patients between 2015-2020, only 51% received a first-line systemic treatment and of those, only 44% (268 pts) received a second line treatment. This has also been demonstrated in US RWE studies where 42–77% of patients with la/mUC receive first-line treatment, only 15–44% of patients receiving first-line treatment receive second-line therapy.[38,40-43] Therefore, there is an unmet need for an efficacious and well-tolerated therapy to improve survival rates and clinical outcomes for previously untreated patients with la/mUC in first line.

3.4 The intervention

Enfortumab vedotin, an antibody-drug conjugate (ADC) in combination with pembrolizumab, a programmed cell death protein 1 (PD-1) receptor inhibitor, is indicated for *the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy*.

CHMP positive opinion was obtained the 25th of July 2024 and the expected EC decision is based on the results from the phase III trial, EV-302.[4]

Based on preclinical enhancement of antitumor activity and antitumor immunity, it was hypothesized that combining EV with P has the potential to improve clinical outcomes relative to either agent alone in patients with la/mUC. Checkpoint inhibitors, such as the PD-1 inhibitor pembrolizumab, unleash the antitumour activity of T lymphocytes by targeting the T-cell inhibition pathway.[44] Preclinical data show enhanced antitumour

activity when EV is combined with immune checkpoint inhibitors across multiple in vivo tumour models. EV has also demonstrated induction of immunogenic cell death of Nectin-4 positive tumours, an increase in inflammatory mediators, and recruitment of innate inflammatory cells to the tumour microenvironment consistent with the increased tumour immunogenicity demonstrated with other MMAE ADCs preclinically.[45] In addition, preclinical studies demonstrated that EV-induced immunomodulatory effects may generate lasting antitumour immunity and enhanced antitumour activity when EV is combined with a PD-1 inhibitor. These findings demonstrate that for EV, and consistent with preclinical data with other ADCs that contain the same MMAE drug linker, enhanced antitumour activity may be achieved when used in combination with checkpoint inhibitors due to the complementary mechanisms of MMAE-induced cell cytotoxicity and induction of immunogenic cell death, and the up-regulation of antitumour immune function by PD-1 inhibition.[46] In Table 3 an overview of the two products is presented.

Table 3. Key descriptive information of enfortumab vedotin in combination with pembrolizumab

Overview of intervention	PADCEV (enfortumab vedotin) in combination with Keytruda (pembrolizumab)
Therapeutic indication relevant for the assessment	Enfortumab vedotin, 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
Method of administration	*Enfortumab vedotin* is administered as an IV infusion *Pembrolizumab* is administered as an IV infusion
Dosing	*Enfortumab vedotin* as an intravenous infusion (at a dose of 1.25 mg per kilogram of body weight with a maximum of 125 mg per dose) on days 1 and 8 *Pembrolizumab* as an intravenous infusion (at a dose of 200 mg) after the enfortumab vedotin infusion on day 1 of each 3-week cycle.
Dosing in the health economic model (including relative dose intensity)	Enfortumab vedotin in combination with pembrolizumab (3-week cycles) • *Enfortumab vedotin*: 1.25 mg/kg; IV on days 1 and 8 of each cycle with XXXX relative dose intensity • *Pembrolizumab*: 200 mg; IV on day 1 of each cycle with XXXX relative dose intensity. Maximum cycles: 35
Should the medicine be administered with other medicines?	Combination of enfortumab vedotin and pembrolizumab

Overview of intervention	PADCEV (enfortumab vedotin) in combination with Keytruda (pembrolizumab)
Treatment duration / criteria for end of treatment	Until disease progression or unacceptable toxicity. For pembrolizumab a 24-month stopping rule applies (35 cycles).
Necessary monitoring, both during administration and during the treatment period	Enfortumab vedotin: • Patients should be monitored starting with the first cycle and throughout treatment for skin reactions, for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction, or discontinuation of EV, and for ocular disorders. • There is no known antidote for overdosage with EV. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate taking into consideration the half-life of 3.6 days (antibody-drug conjugate (ADC)) and 2.6 days (monomethyl auristatin E (MMAE)). Pembrolizumab: • There is no known antidote for overdosage with pembrolizumab. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No.
Package size(s)	• Enfortumab vedotin (Padcev) 20 mg. Powder for concentrate for solution for infusion. Intravenous use vial (glass) 1 vial. • Enfortumab vedotin (Padcev) 30 mg. Powder for concentrate for solution for infusion. Intravenous use vial (glass) 1 vial. • Pembrolizumab 25 mg/ml. Concentrate for solution for infusion. Intravenous use vial (glass) 4 ml 1 vial.

Abbreviations: EV, enfortumab vedotin; mg, milligram; ml, millilitre
Source: EMA[1,2]

3.4.1 The intervention in relation to Danish clinical practice

Based on the study results of EV-302[4] and the updated international guidelines (ESMO; EAU)[27], platinum-based chemotherapy regimens plus gemcitabine (Plat+Gem) are assumed to be totally or partly replaced when EV+P is recommended in Denmark in the first-line treatment of mUC patients. As per the ESMO guidelines, the adoption of EV+P as the new SoC for first-line treatment in la/mUC will alter subsequent treatment strategies. However, treatment recommendation from DaBlaCA will likely differ from ESMO guidelines since treatments as erdafitinib and sacituzumab govitecan are not available in Denmark.

3.5 Choice of comparator(s)

The relevant comparator, Plat+Gem, for this submission matches the current clinical practice as per DaBlaCa.[25]

Patients receiving Plat+Gem can also receive avelumab as a maintenance treatment. Such a practice was also reflected in the EV-302 clinical trial.[4] Avelumab maintenance treatment is therefore also reflected in this submission for a proportion patient receiving Plat+Gem. Avelumab maintenance is not included in the EV+P arm, as per EV-302 protocol.[47]

Table 4. Key descriptive information of platinum-based chemotherapy (cisplatin or carboplatin) in combination with gemcitabine

Overview of comparator	Platinum-based chemotherapy (cisplatin or carboplatin) in combination with gemcitabine
Generic name	Platinum-based chemotherapy: • Cisplatin • Carboplatin Gemcitabine following platinum-based chemotherapy
ATC code	Cisplatin (L01XA01) Carboplatin (L01XA02) Gemcitabine (L01BC05)
Mechanism of action	*Cisplatin*: Alkylating agents work by three different mechanisms: 1) attachment of alkyl groups to deoxyribonucleic acid (DNA) bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA, 2) DNA damage via the formation of cross-links (bonds between atoms in the DNA) which prevents DNA from being separated for synthesis or transcription, and 3) the induction of mispairing of the nucleotides leading to mutations. *Carboplatin*: Carboplatin predominantly acts by attaching alkyl groups to the nucleotides, leading to the formation of monoadducts, and DNA fragmenting when repair enzymes attempt to correct the error. 2% of carboplatin's activity comes from DNA cross-linking from a base on one strand to a base on another, preventing DNA strands from separating for synthesis or transcription. *Gemcitabine*: Gemcitabine is a potent and specific deoxycytidine analog. After uptake into malignant cells, gemcitabine is phosphorylated by deoxycytidine kinase to form gemcitabine monophosphate, which is then converted to the active compounds, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). These active metabolites are nucleosides that mediate antitumour effects.

Overview of comparator	Platinum-based chemotherapy (cisplatin or carboplatin) in combination with gemcitabine
	dFdCTP competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA, thereby competitively inhibiting DNA chain elongation. Incorporation of dFdCTP into the DNA chain ultimately leads to chain termination, DNA fragmentation, and apoptotic cell death of malignant cells.
Method of administration	*Cisplatin* or *carboplatin* on day 1 of every 21-day cycle, with adequate pre- and post-hydration, by IV infusion per institutional standards. *Gemcitabine* via IV infusion on days 1 and 8 of every 21-day cycle
Dosing	*Gemcitabine* at 1000 mg/m2 as an IV infusion on days 1 and 8 of every 21-day cycle, and either cisplatin (70 mg/m2) or carboplatin (AUC 4.5, or AUC 5 according to guidelines) on day 1 of every 21-day cycle, with adequate pre- and post-hydration, by IV infusion per institutional standards. *Cisplatin*, *carboplatin* and/or *gemcitabine* could be administered for a maximum of 6 cycles or a protocol-defined reason for treatment discontinuation occurs, whichever occurred first.
Dosing in the health economic model (including relative dose intensity)	**Gemcitabine + cisplatin dosing regimen:** • *Gemcitabine*: 1000mg/m2 on days 1 and 8, every 3rd week. Relative dose intensity was 79.0%. • *Cisplatin*: 70mg/m2 on day 1, every 3rd week of max 6 cycles. Relative dose intensity was 91.5%. **Gemcitabine + carboplatin dosing regimen:** • *Gemcitabine*: 1000mg/m2 on days 1 and 8, every 3rd week. Relative dose intensity was 79.0%. • *Carboplatin*: assumed dose of 450 mg on day 1, every 3rd week of max 6 cycles. Relative dose intensity was 100% (not captured in EV-302).
Should the medicine be administered with other medicines?	Combination treatment: platinum-based chemotherapy plus gemcitabine
Treatment duration/ criteria for end of treatment	Cisplatin, carboplatin and/or gemcitabine can be administered for a maximum of 6 cycles or a protocol-defined reason for treatment discontinuation occurs, whichever occurred first. Treatment may be continued until disease progression or until unacceptable toxicity occurs.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.

Overview of comparator	Platinum-based chemotherapy (cisplatin or carboplatin) in combination with gemcitabine
Package size(s)	**Gemcitabine concentrate for solution for infusion:** • Intravenous use vial (glass) 40 mg/ml x 25 ml 1 vial. • Intravenous use vial (glass) 40 mg/ml x 50 ml 1 vial. • Intravenous use vial (glass) 38 mg/ml x 1 g 1 vial. • Intravenous use vial (glass) 38 mg/ml x 2 g 1 vial. • Intravenous use vial (glass) 38 mg/ml x 23 ml 1 vial. **Gemcitabine solution for infusion:** • Intravenous use vial (glass) 10 mg/ml x 120 ml 1 vial • Intravenous use vial (glass) 10 mg/ml x 140 ml 1 vial • Intravenous use vial (glass) 10 mg/ml x 160 ml 1 vial • Intravenous use vial (glass) 10 mg/ml x 180 ml 1 vial • Intravenous use vial (glass) 10 mg/ml x 200 ml 1 vial • Intravenous use vial (glass) 10 mg/ml x 220 ml 1 vial **Cisplatin concentrate for solution for infusion**: • Intravenous use vial (glass) 1 mg/ml x 50 ml 1 vial. • Intravenous use vial (glass) 1 mg/ml x 100 ml 1 vial. **Carboplatin concentrate for solution for infusion:** • Intravenous use vial (glass) 10 mg/ml x 15 ml 1 vial. • Intravenous use vial (glass) 10 mg/ml x 45 ml 1 vial.

Abbreviations: AUC, area under the curve; dCTP, deoxycytidine triphosphate; dFdCDP, gemcitabine diphosphate; dFdCMP, gemcitabine monophosphate; dFdCTP, gemcitabine triphosphate; DNA, deoxyribonucleic acid, IV, intravenous; mg, milligram
Source: EMA.[48-50]

3.6 Cost-effectiveness of the comparator(s)

Platinum-based regimens have not been previously assessed by the DMC for treatment for adult patients with la/mUC. As stated in Section 3.3, DaBlaCa[25] recommends that patients with la/mUC who are able to tolerate platinum containing chemotherapy should be treated with cisplatin or carboplatin, with cisplatin as the preferred treatment option, in combination with gemcitabine. According to the DMC methods guideline, if a comparator has not previously been assessed by the DMC, a comparison against placebo should be made, including cost-effectiveness.[51]

However, Plat+Gem are widely recognized as the established SOC for treating patients with la/mUC in Denmark, in accordance with the consensus statement of the European Association of Urology and European Society for Medical Oncology (EAU-ESMO).[25,52] In this context, an additional analysis appears redundant.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

OS, PFS, and clinical response (measured by objective response rate [ORR], disease control rate [DCR], and duration of response [DOR]) are relevant outcomes in this

application. These outcomes have been previously deemed relevant by the DMC to assess the efficacy of EV in adult patients with la/mUC after first-line of systemic therapies.[53] The efficacy outcomes are defined in Table 5.

Table 5. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Duration of progression-free survival (PFS)	8 August 2023 (17.2 months)	Defined as the time from randomization to first documentation of disease progression per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 by blinded independent central review (BICR), or to death due to any cause, whichever comes first.	Per RECIST v1.1 by BICR. Kaplan-Meier (KM) estimates were used for analysis.
Duration of Overall survival (OS)	8 August 2023 (17.2 months)	OS is defined as the time from date of randomization to date of death due to any cause.	KM estimates were used for analysis.
Objective response rate (ORR)	8 August 2023 (17.2 months)	Defined as the proportion of subjects with confirmed CR or PR according to RECIST v1.1	Per RECIST v1.1 by BICR.
Duration of response (DOR)	8 August 2023 (17.2 months)	Defined as the time from first documented response of CR or PR (that is subsequently confirmed) to the first documented disease progression per RECIST v1.1, or to death due to any cause, whichever comes first	Per RECIST v1.1 by BICR. KM estimates were used for analysis
Disease control rate (DCR)	8 August 2023 (17.2 months)	Defined as the proportion of subjects with confirmed CR, PR, or SD according to RECIST v1.1	Per RECIST v1.1 by BICR

* Time point for data collection used in analysis (follow up time for time-to-event measures)
Abbreviations: BPI-SF, Brief Pain Inventory - Short Form; BICR, blinded independent central review; CR, Complete response; DCR, disease control rate; DOR, Duration of response; EORTC-QLQ-C30, European; Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, the EuroQOL Five Dimensions Questionnaire 5L; KM, Kaplan-Meier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease
Source: ClinicalTrial.gov[54]

Validity of outcomes

OS is considered an important clinical endpoint in clinical trials within oncology. For many years it has been considered the gold-standard endpoint for establishing clinical benefit. However, using OS can be associated with certain limitations as it may be affected by subsequent therapy.[53] PFS is also a commonly used endpoint within oncology trials. It is used to assess the time during which patients are alive without progressive

disease. PFS is not affected by the impact of subsequent treatment in the same manner as OS, and therefore serves as a relevant supplement to OS.[53]

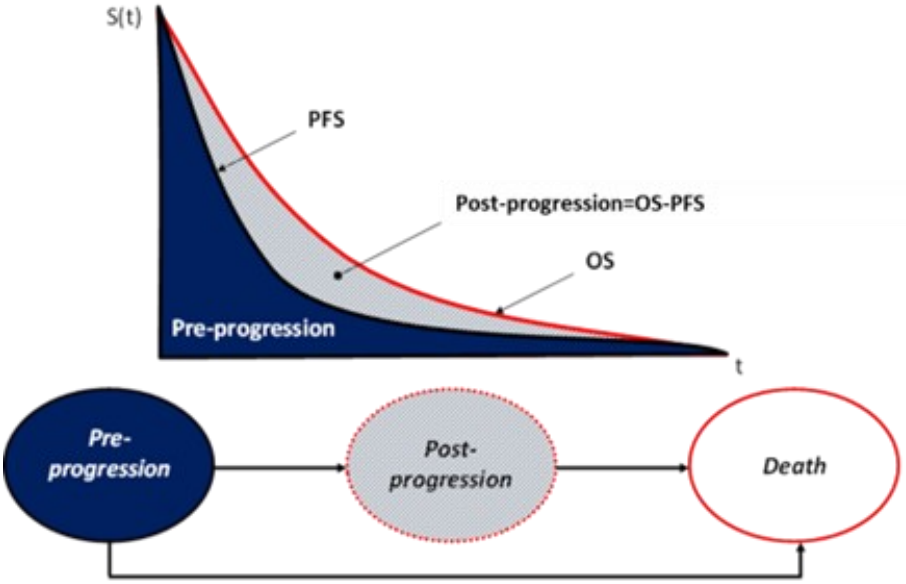
4. Health economic analysis

A cost-utility analysis was conducted based on a Danish adaptation of an Excel-based cost-effectiveness model (CEM). The objective of the CEM is to assess the cost-effectiveness of EV+P versus Plat+Gem in subjects with la/mUC. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained.

4.1 Model structure

A standard partitioned survival model (PSM) structure was identified as being most suitable for this evaluation. The PSM structure, illustrated in Figure 4, is a well-established modelling approach for the cost-effectiveness analysis of oncology therapies and commonly used for submissions to the DMC. Like state transition approaches (the most frequently used alternative), the PSMs typically categories patients into three main health states: pre-progression, post-progression, and dead. Patients in the PFS health state received either EV+P or Plat+Gem and were either stable or responding to therapy. Over time, patients could transition directly to the death health state or to the post-progression health state where they received subsequent treatment before moving to the death health state.

Figure 4. Illustration of partitioned survival model structure



Abbreviations: OS, overall survival; PFS, progression-free survival.

Occupancy in the model health states over time were fully determined by the transitions from pre-progression and post-progression, which are irreversible and defined based on objective clinical measures (disease progression and death). The proportion of patients in the pre-progression health state decreases over time according to the treatment-specific hazard rates at which patients leave this state, which corresponds to the PFS curve. The proportion of patients who have died increase over time according to treatment-specific death rates corresponding to the complement of the OS over time (1 – OS). The difference between the proportion of patients alive (i.e., OS) and the proportion of patients in the pre- progression health state (PFS) identifies the proportion of patients in the post-progression health state at any point in time. The proportion of patients in the pre- and post-progression health states were multiplied by associated HSUVs, summated over time to obtain estimates of expected quality-adjusted life years (QALYs), and discounted over time to obtain the net present value. The utility value associated with the death state was assumed to be zero. In the base-case analysis, it was assumed that the costs associated with la/mUC include costs those directly related to the treatment of the underlying disease and the cost of patient time and transport, aligning with the DMC guidelines[55]. Expected costs by treatment arm were calculated given treatment received and resource use associated with pre- and post-progression health state, weighted according to patient distribution across health states, and terminal care costs, with all costs discounted over time. The impact of grade 3+ treatment-emergent adverse events (TEAEs) were included in the model, where costs and utility decrements associated with AE management and detrimental health effects related to active treatments were front-loaded in the first cycle of the model. The occurrence of these events was assumed not to affect any transitions between the health states in the model explicitly.

4.2 Model features

The features of the economic model are presented in Table 6.

Table 6. Features of the economic model

Model features	Description	Justification
Patient population	La/mUC patients that are eligible for platinum-based chemotherapies	According to EMA indication
Perspective	Limited societal perspective	According to DMC guidelines[47]
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	7 days	To facilitate the modelling of dosing regimens that may not be aligned with larger timeframes.

Half-cycle correction	Yes	To account for costs and benefits which can occur any time during the cycle.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	EV+P	Intervention of interest
Comparator(s)	Plat+Gem	According to national treatment guidelines.
Outcomes used to model efficacy	OS, PFS, and ToT	Key trial data outcomes are used to populate the partitioned-survival model.

Abbreviations: mUC, metastatic urothelial cancer; EMA, European Medicines Agency; EV+P, enfortumab vedotin plus pembrolizumab; Plat+Gem, platinum-based chemotherapy plus gemcitabine; OS, overall survival; PFS, progression free survival; ToT, time on treatment; ICER, incremental cost-effectiveness ratio

5. Overview of literature

5.1 Literature used for the clinical assessment

A head-to-head study, EV-302, comparing EV+P to Plat+Gem was identified and thus a literature search was omitted in accordance with to the DMC guidelines[55]. An overview of the study is presented in Table 7.

Table 7. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Powles T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med. 2024;390(10):875-888. doi:10.1056/NEJMoa2312117[56]	EV-302	NCT04223856	Start: 30/03/2020 Completion: 08/08/2023 Data cut-off: 08/08/2023 Future data cut-offs 03/09/2027	EV+P vs. Plat+Gem for patients with unresectable or metastatic urothelial carcinoma

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life data for the estimation of health state utility values was solely obtained from the EV-302 head-to-head study. The EQ-5D-5L data from EV-302 trial with Danish preference weights was used to calculate the health state utility values. Disutilities for adverse events were obtained based on literature. The references are presented in Table 8 and the literature search to identify the inputs is described in Appendix I.

Table 8. Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Seagen Inc. EV-302 clinical study report and IPD analysis (August 2023 DBL): An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer. 2023.[57]	The health state utility values for pre-progressed and post-progressed health states were derived from a mixed-effect model. Treatment-specific utility values were also calculated, but these were not used in the base case.	The application of the data is presented in Section 10.1 and 10.2.
Technology appraisal guidance: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies. TA772[58]	Disutility decrement for: • Acute kidney injury • Neuropathy (Grade 2) • Peripheral neuropathy (Grade 3+)	Section 10.3
Technology appraisal guidance: Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy TA788[59]	Disutility decrement for: • Anaemia • Fatigue • Urinary tract infection	Section 10.3
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84. Published 2008 Oct 21. doi:10.1186/1477-7525-6-84[59]*	Disutility decrement for: • Neutropenia • Rash maculo-papular • Neutrophil count decreased	Section 10.3
Technology appraisal guidance: Nivolumab with ipilimumab for untreated advanced renal cell carcinomaTA780/581[60]	Disutility decrement for: • Thrombocytopenia • Platelet count decreased	Section 10.3
Technology appraisal guidance: Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma TA858, assumed as anaemia[61]	Disutility decrement for: • Hyperglycaemia • Hyponatraemia	Section 10.3

*Identified through TA788

5.3 Literature used for inputs for the health economic model

Besides data from EV-302, two additional references were identified to provide input to the health economic model (excluding cost sources, SmPCs, DRG tariffs etc), which are presented in Table 9. The literature search to identify the inputs is described in Appendix I.

Table 9. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Seagen Inc. EV-302 clinical study report and IPD analysis (August 2023 DBL): An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer. 2023.[57]	Efficacy OS, PFS and ToT. Adverse event rates.	Trial of interest / systematic literature review	Section 8 and
Technology appraisal guidance: Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy TA788[59] (Javelin Bladder 100 study)	Adverse event rates for avelumab maintenance treatment	Targeted literature review	Section 9.1
Rigshospitalet. Cisplatin og Gemcitabin - Behandling af kræft i blæren med. n.d. https://www.rigshospitalet.dk/undersoegelse-og-behandling/find-undersoegelse-og-behandling/Sider/Cisplatin-og-Gemcitabin---Behandling-af-kraeft-i-blaeren-med--2875866.aspx.[62]	Chair time	Targeted literature review	Section 0.

6. Efficacy

6.1 Efficacy of enfortumab vedotin in combination with pembrolizumab

6.1.1 Relevant studies

This application builds on the EV-302 head-to-head trial (NCT04223856) investigating the efficacy and safety of EV+P versus Plat+Gem. EV-302's design (randomised, controlled, and multicentre) currently aligns with national treatment guidelines for la/mUC in Denmark. Therefore, EV-302 was used in this submission as the main source of evidence for the direct comparison of EV+P with Plat+Gem, and no indirect comparison or data synthesis was necessary.

The EV-302 analysis (data cut 8 August 2023) was published in March 2024 in the New England Journal of Medicine by Powles et al.[30] This article together with the supplementary appendix will be the main reference for this application together with data on file from the same data cut. An overview of the EV-302 study is presented in Table 10. Further details are provided in Appendix A.

Table 10. Overview of study design for studies included in the comparison

EV-302(KN-A39), NCT04223856	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
EV+P vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer (EV-302), NCT04223856 Powles et al., 2024[30] Hoimes et al. 2023[48]	Phase III open-label, two-arm randomized, controlled multicenter study	The study was initiated in March 2020, and the primary completion was in August 2023. The median survival follow-up time for this data-cut is 17.2 months. The study is still on going with estimated full completion in September 2027.	Patients with previously untreated locally advanced or metastatic urothelial cancer	Enfortumab vedotin + pembrolizumab. Enfortumab vedotin at a dose of 1.25 mg per kg of body weight IV on days 1 and 8 of every 3-week cycle. Pembrolizumab at a dose of 200 mg IV on day 1 of every 3-week cycle with a maximum of 35 treatment cycle.	Gemcitabine + platinum-containing chemotherapy (cisplatin or carboplatin). Chemotherapy was used for a maximum of six 3-week cycles. Gemcitabine as an IV infusion on days 1 and 8 of every 3-week cycle. Cisplatin administered as IV infusion on day 1 of each 3-week cycle, or carboplatin dosed according to local guidelines and administered as IV infusion on day 1 of each 3-week cycle.	-Duration of progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by blinded independent central review (BICR) [August 2023] -Duration of Overall survival (OS) [August 2023] -Objective response rate (ORR) per RECIST v1.1 by BICR [August 2023] -Time to pain progression (TTPP) [August 2023] -Mean change from baseline in worst pain at Week 26 -Duration of PFS per RECIST v1.1 by investigator assessment [August 2023] -ORR per RECIST v1.1 by investigator assessment [August 2023] -Duration of response (DOR) per RECIST v1.1 by BICR [August 2023] -DOR per RECIST v1.1 by investigator assessment [August 2023] -Disease control rate (DCR) per RECIST v1.1 by BICR [August 2023] -DCR per RECIST v1.1 by investigator assessment [August 2023] -Change from baseline in patient reported outcome assessment measured by the EuroQOL Five Dimensions Questionnaire 5L (EQ-5D-5L) [August 2023] -Mean scores in patient reported outcome assessment measured by the EQ-5D-5L [August 2023] -Change from baseline in patient reported outcome assessment measured by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) [August 2023] -Mean scores in patient reported outcome assessment measured by EORTC QLQ-C30 [August 2023] -Incidence of adverse events (AEs) [August 2023] -Incidence of laboratory abnormalities [August 2023] -Treatment discontinuation rate due to AEs [August 2023]

6.1.2 Comparability of studies

Not relevant. Comparison based on head-to-head study EV-302.

6.1.2.1 Comparability of patients across studies

Subjects enrolled in EV-302 were representative of a previously untreated la/mUC population, and demographics were generally similar across both treatment arms (Table 11). Subjects were enrolled globally, including 41.6% in Europe, 21.2% in North America, and 37.1% in other regions. Overall, most subjects were male (76.7%), white (67.5%) and elderly (≥65 years, 68.5%), with a median age of 69.0 years (range: 22–91) across arms. In both arms, most subjects had an ECOG PS score of 0 or 1; an ECOG PS of 2 was reported for a total of 2.9% of subjects. Across both arms, the site of disease origin was lower tract disease and upper tract disease for 72.7% and 27.0%, respectfully. 71.8% of subjects in both arms had visceral metastases and 23.4% exhibited lymph node-only disease.[4]

Table 11. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	EV+P(N=442)	Plat+Gem (N=444)	Total (N=886)
Median age, years (range)	69.0 (37. 87)	69.0 (22.91)	69.0 (22.91)
Age group, n (%)			
<65 years	144 (32.6)	135 (30.4)	279 (31.5)
65 to <75 years	196 (44.3)	201 (45.3)	397 (44.8)
≥75 years	102 (23.1)	108 (24.3)	210 (23.7)
Male sex, n (%)	344 (77.8)	336 (75.7)	680 (76.7)
Geographic region, n (%)			
North America	103 (23.3)	85 (19.1)	188 (21.2)
Europe	172 (38.9)	197 (44.4)	369 (41.6)
Rest of world	167 (37.8)	162 (36.5)	329 (37.1)
ECOG performance status, n (%)			
0	223 (50.5)	215 (48.4)	438 (49.4)
1	204 (46.2)	216 (48.6)	420 (47.4)
2	15 (3.4)	11 (2.5)	26 (2.9)
Missing	0	2 (0.5)	2 (0.2)
BMI, n (%)			

<25 kg/m²	206 (46.6)	185 (41.7)	391 (44.1)
25 to <30 kg/m²	144 (32.6)	155 (34.9)	299 (33.7)
≥30 kg/m²	89 (20.1)	101 (22.7)	190 (21.4)
Missing	3 (0.7)	3 (0.7)	6 (0.7)
HbA_{1c}, n (%)			
<5.7%	205 (46.4)	208 (46.8)	413 (46.6)
≥5.7 and <6.5%	155 (35.1)	140 (31.5)	295 (33.3)
≥6.5%	41 (9.3)	44 (9.9)	85 (9.6)
Missing	41 (9.3)	52 (11.7)	93 (10.5)
Primary tumour location, n (%)			
Upper tract	135 (30.5)	104 (23.4)	239 (27.0)
Lower tract	305 (69.0)	339 (76.4)	644 (72.7)
Metastasis category, n (%)			
Visceral metastases	318 (71.9)	318 (71.6)	636 (71.8)
Lymph nodes only disease	103 (23.3)	104 (23.4)	207 (23.4)
Not applicable[†]	21 (4.8)	22 (5.0)	43 (4.9)
Subjects who were cisplatin ineligible at randomization	202	202	404

Abbreviations: BMI, body mass index; ECOG: Eastern Cooperative Oncology Group; EV, enfortumab vedotin; HbA1c: glycosylated haemoglobin; ITT, Intent-to-treat; n, number; P, pembrolizumab; Plat+Gem, platinum-based chemotherapy plus gemcitabine

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The targeted patient population includes all adult patients eligible for first-line treatment of unresectable or metastatic urothelial cancer who are suitable for platinum-containing chemotherapy.

As there is limited published data on the epidemiology of la/mUC with few studies and databases containing data specific to this population[63], data for BC were used as a proxy for UC given that UC accounts for approximately 90% of BC cases.[13] A Danish real-world study reported a median age of 69 years (63-75) in the baseline characteristics of a mUC cohort initiating first-line chemotherapy.[3] BC and other urinary tract cancers are more frequent in men than in women, and approximately 75% of patients diagnosed in 2020 were male.

Approximately 50% of patients are ineligible for first-line cisplatin-based chemotherapy due to impaired kidney function, poor overall health, or other organ diseases such as

heart failure. For patients with contraindications to cisplatin-based chemotherapy, the combination of carboplatin and gemcitabine is the best-documented alternative.[31] This was also confirmed by Omland et al., in a Danish registry study.[3]

Patient characteristics used in the model were based on EV-302 trial data.[56] Generally, participants in the EV-302 trial are comparable to the Danish patient population for both age, gender distribution and cisplatin eligibility. An overview of the comparability of the study population with Danish patients eligible for treatment are provided Table 12.

Table 12. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population[25]	Value used in health economic model [56]
Age	69.0 years[3]	XXXXXXX
Gender, proportion of males %	75.0%[25]	77.0% [56]
Patient weight (kg)	N/A	75.9[56]
Body surface area (m^2)	N/A	1.9 [56]
Cisplatin eligible (%)	50.0%[3]	55.4%[56]

Abbreviations: kg, kilograms

6.1.4 Efficacy – results per EV-302

In the following sections, a summary of key efficacy findings obtained from the EV-302 study included in the comparative analysis is provided. The EV-302 data presented in this assessment is based on the primary analysis (cut-off date 8 August 2023). Detailed information about the results of all outcomes included in the comparative analysis alongside the method for each analysis are provided in Appendix B. For HRs, graphical checks of the proportional hazard assumption are also provided in Appendix B.

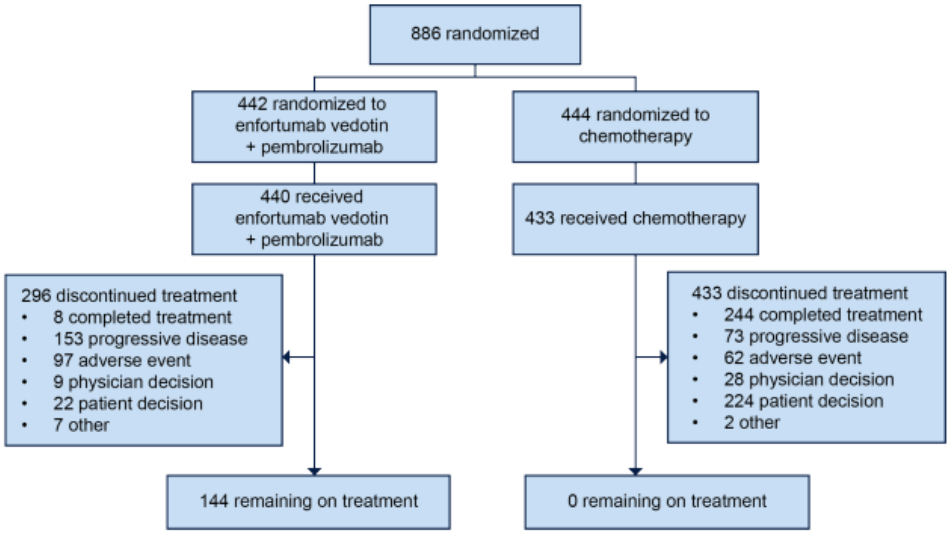
Patient disposition

From March 2020 (date of first signed informed consent), a total of 1,297 subjects with previously untreated la/mUC gave informed consent to participate in the study. Of these subjects, 886 were randomized to Arm A, EV+P (n=442), or Arm B, Plat+Gem (n=444), with 440 and 433 of these subjects, respectively, receiving treatment with any study drug.[64]

As of the 8 Aug 2023 data cut-off, 32.6% of subjects randomized in the EV+P arm remained on the study drug (Figure 5). Progressive disease (34.6%) and adverse events (21.9%) were the most common primary reasons for treatment discontinuation. The maximum number of cycles of therapy in the Plat+Gem was 6. As of the data cut-off date, 55.0% of subjects had completed 6 cycles, and no subjects remained on the study drug. Progressive disease (16.4%) and adverse events (14.0%) were the most common primary reasons that subjects in the Plat+Gem arm were unable to complete 6 cycles of therapy.

As of the 8 Aug 2023 data cut-off, 33.0% of subjects in the EV+P arm and 54.3% of subjects in Arm B had discontinued the study (Figure 5). The most common reason for study discontinuation in both arms was death (29.9% and 50.9%, respectively). Most deaths were considered related to underlying disease.[64]As of the 8 Aug 2023 data cut-off, 33.0% of subjects in the EV+P arm and 54.3% of subjects in Arm B had discontinued the study (Figure 5). The most common reason for study discontinuation in both arms was death (29.9% and 50.9%, respectively). Most deaths were considered related to underlying disease.[64]

Figure 5. Patient disposition, EV-302



Abbreviations: EV, enfortumab vedotin; gem, gemcitabine; pembro, pembrolizumab.
Source: Powles et al.[57]

The primary analysis of OS and PFS used the ITT analysis set. All subjects who were randomized were included in the ITT analysis set. For primary endpoints of OS and PFS, a log-rank test stratified by randomization stratification factors was used to compare the experimental arm to the control arm. The estimated HR and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model was also presented. Graphical check of the proportional hazard assumption are presented in Appendix D. The median survival time was estimated using the Kaplan-Meier method and was reported along with the corresponding 95% confidence interval by treatment arm. Similar estimation methods were used for the other time-to-event endpoints. DOR was summarized descriptively by Kaplan-Meier methods for subjects with a confirmed response (complete response or partial response per RECIST v1.1). ORR, DCR, and DOR were analysed using the response evaluable set. P-values for the comparison of ORR and DCR in the experimental arm and the control arm, using the Cochran Mantel-Haenszel test stratified by randomization stratification factors, were reported. Table 13 summarizes the analysis sets used in this application.

Table 13. Analysis sets – EV-302

Analysis set	Description
ITT Analysis Set	Includes all randomized subjects. Subjects were analysed according to the treatment arm assigned at randomization regardless of the actual treatment received.
Response Evaluable Analysis Set	Includes all randomized subjects who had measurable disease per RECIST v1.1 at baseline. Subjects were analysed according to the treatment arm assigned at randomization regardless of the actual treatment received.
SAF (Safety Analysis Set)	Includes all subjects who receive any study treatment. Subjects were analysed according to the actual treatment received.
PRO Full Analysis Set	Includes all randomized subjects who received any study treatment and completed at least one PRO assessment at baseline. Subjects were analysed according to the treatment arm assigned at randomization.

Abbreviations: EV: Enfortumab vedotin; ITT: Intent-to-treat; PRO: Patient reported outcomes; RECIST: Response Evaluation Criteria in Solid Tumours

6.1.4.1 Overall survival

OS was defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date the subject was known to be alive. The time from randomization to OS event or censoring was calculated as event/censoring date – randomization date + 1.[65]

The primary analysis population for OS was the ITT analysis set. The Kaplan-Meier (KM) method was used to estimate the median OS, and the 95% CI for the median was computed. The OS KM curve was provided for each treatment arm, including number at risk over time, and was compared in the two treatment groups with the use of a stratified log-rank test. The HR and 95% CI for EV+P versus the Plat+Gem arm was estimated using a Cox proportional hazards model; both unadjusted HRs and HRs stratified by the stratification factors of the trial (i.e., cisplatin eligibility, PD-L1 expression, and liver metastases) were reported.[65]

Analyses of OS were conducted using the ITT population for validation purposes, and then analyses were conducted in the seven subgroups of interest (i.e., cisplatin-eligible, cisplatin-ineligible, PD-L1 high, PD-L1 low, cisplatin-ineligible and PD-L1 high, cisplatin-ineligible and PD-L1 low, and avelumab maintenance accessible), and the four subgroups of the control arm based on avelumab eligibility and receipt. If a subgroup was a stratification factor (i.e., cisplatin eligibility or PD-L1 expression), then stratified HRs were controlled for the remaining stratification factors. Note that no statistical hypothesis tests were conducted for any of the control arm subgroups based on avelumab eligibility and receipt.[65]

Kaplan Meier estimates of OS – ITT Analysis Set

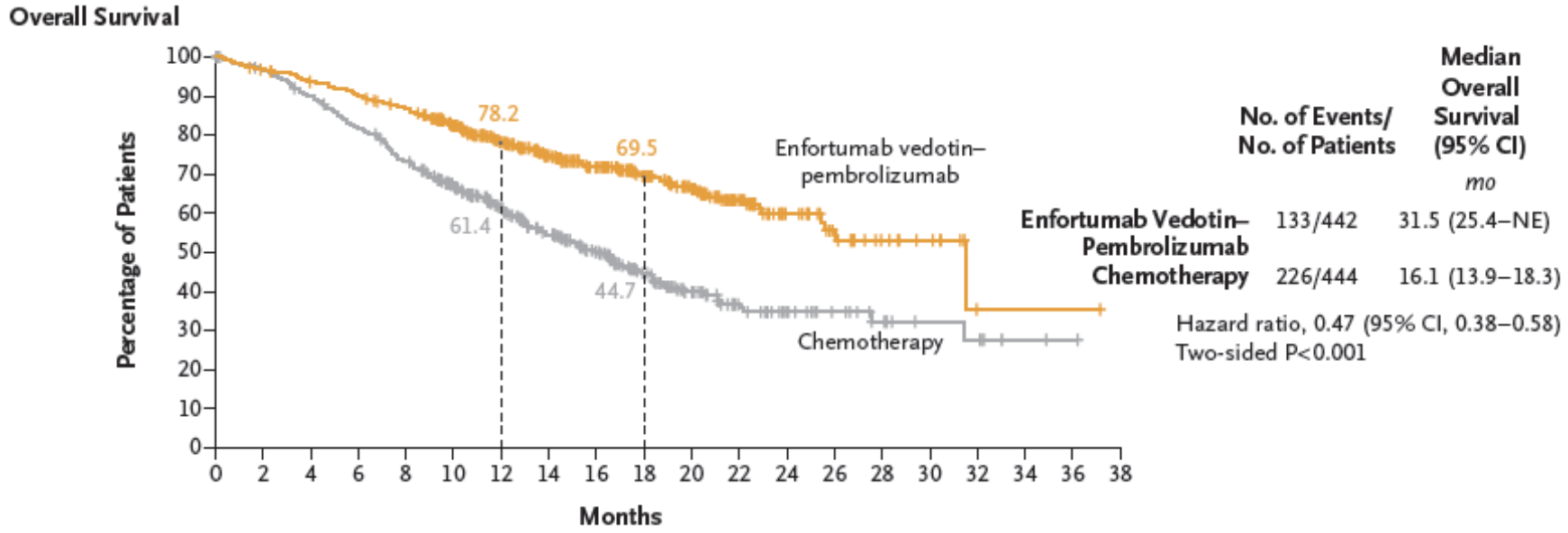
At the time of the data cut-off, 359 deaths had occurred (133 in the EV+P arm and 226 in the Plat+Gem arm), which was 73.4% (359 of 489 events) of the required number of events for the final analysis of OS. EV+P demonstrated a statistically significant and clinically meaningful improvement in OS in the ITT population compared to Plat+Gem with a 53.2% reduction in the hazard of death (HR: 0.468; 95% CI: 0.376, 0.582; 2-sided p-value <0.00001) (Table 14; Figure 6). Overall, 30.1% of subjects in the EV+P arm and 50.9% of subjects in the Plat+Gem arm died. After a median follow-up of 17.2 months (range: 0.07–37.16) for both treatment groups combined, the median OS was 31.5 months in the EV+P arm and 16.1 months in the Plat+Gem arm.[4] (Table 14; Figure 6).

Table 14. Overall survival by treatment arm – EV-302 ITT analysis set

	EV+P (N=442)	Plat+Gem (N=444)
Number of deaths, n (%)	133 (30.1)	226 (50.9)
Stratified analysis[a]		
Hazard ratio[b] (95% CI)	0.468 (0.376, 0.582)	
Two-sided p-value[c]	<0.00001	
Overall survival (OS)[d] (months)		
Median (95% CI[e])	31.5 (25.4, -)	16.1 (13.9, 18.3)
Q1, Q3	13.8, -	7.6, -
Observed min, max	0.26, 37.16+	0.07+, 36.21+
OS rate[d] (%)		
6 months (95% CI[e])	90.2 (87.0, 92.6)	81.9 (77.9, 85.2)
12 months (95% CI[e])	78.2 (73.9, 81.9)	61.4 (56.6, 65.9)
18 months (95% CI[e])	69.5 (64.4, 74.1)	44.7 (39.2, 50.1)
Number of subjects censored, n (%)	309 (69.9)	18 (49.1)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; Plat+Gem, platinum-based therapy
a. Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization.
b. Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favours the EV+Pembro arm.
c. Calculated using stratified log-rank test. The p-value threshold for statistical significance is 0.01548.
d. As estimated using Kaplan-Meier method
e. Calculated using the complementary log-log transformation method (Collett, 1994).[52]
+ indicates censoring.
Data cutoff date: 08 August 2023
Source: Powles et al.[4]

Figure 6. Kaplan Meier plot of overall survival – EV-302 ITT analysis set



Abbreviations: CI, confidence interval; EV, enfortumab vedotin; gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; pembro, pembrolizumab; OS, overall survival; plat, platinum-based therapy.
Data cutoff date: 08 August 2023
Source: Powles et al.[4]

Kaplan Meier estimates of OS - Subgroup analyses

A consistent OS benefit was observed with EV+P over Plat+Gem in all pre-specified subgroups, including greater benefit in the EV+P arm regardless of baseline cisplatin eligibility (eligible or ineligible), PD-L1 expression status (high [CPS ≥ 10] or low [CPS < 10]), or liver metastases (present or absent), with HRs ranging from 0.428 to 0.528 in favour of EV+P across these subgroups (Figure 7). In the cisplatin-eligible group and the cisplatin-ineligible group, the HR was 0.528 (95% CI: 0.389, 0.718) and 0.428 (95% CI: 0.313, 0.585) respectively.[4] The HR for the subgroup analysis of the North American region was associated with a wider CI than other regions, due to the comparatively smaller sample size of this subgroup (Figure 7). The HR point estimate for the North American subgroup analysis may have been influenced by baseline imbalances across treatment groups, as a higher percent of subjects with poor prognostic factors, including liver metastases and ECOG performance status of 1 or 2, were enrolled in the EV+P arm in North America.[4]

Figure 7. Subgroup analyses of overall survival – EV-302 ITT Analysis Set

Subgroup Analysis

Subgroup	Enfortumab Vedotin–Pembrolizumab	Chemotherapy	Hazard Ratio for Death (95% CI)
	mo (no. of events/no. of patients)		
Overall	31.5 (133/442)	16.1 (226/444)	0.47 (0.38–0.58)
Age			
<65 yr	NE (39/144)	19.7 (58/135)	0.46 (0.30–0.71)
≥65 yr	31.5 (94/298)	14.6 (168/309)	0.48 (0.38–0.63)
Race			
White	26.1 (104/308)	15.3 (162/290)	0.47 (0.36–0.60)
Other	NE (29/134)	19.3 (64/154)	0.46 (0.29–0.72)
Geographic region			
North America	25.6 (40/103)	21.2 (42/85)	0.71 (0.44–1.12)
Europe	NE (56/172)	13.9 (110/197)	0.40 (0.28–0.56)
Rest of the world	NE (37/167)	16.4 (74/162)	0.41 (0.27–0.61)
Sex			
Female	25.4 (32/98)	14.6 (54/108)	0.51 (0.32–0.80)
Male	31.5 (101/344)	16.6 (172/336)	0.47 (0.36–0.60)
ECOG performance-status score			
0	NE (44/223)	18.4 (94/215)	0.36 (0.25–0.53)
1 or 2	25.4 (89/219)	13.1 (131/227)	0.54 (0.41–0.72)
Primary site of origin of disease			
Upper tract	NE (38/135)	18.4 (45/104)	0.53 (0.34–0.83)
Lower tract	31.5 (94/305)	15.6 (180/339)	0.46 (0.36–0.59)
Liver metastases			
Present	19.1 (43/100)	10.1 (67/99)	0.47 (0.32–0.71)
Absent	NE (90/342)	17.9 (159/345)	0.47 (0.36–0.61)
PD-L1 expression			
Low (CPS <10)	NE (53/184)	15.5 (99/185)	0.44 (0.31–0.61)
High (CPS ≥10)	31.5 (79/254)	16.6 (125/254)	0.49 (0.37–0.66)
Cisplatin eligibility status			
Eligible	31.5 (69/244)	18.4 (106/234)	0.53 (0.39–0.72)
Ineligible	NE (64/198)	12.7 (120/210)	0.43 (0.31–0.59)
Site of metastasis			
Visceral site	25.6 (108/318)	13.6 (182/318)	0.47 (0.37–0.60)
Lymph node only	NE (22/103)	27.5 (39/104)	0.46 (0.27–0.78)
Renal function			
Normal	26.1 (24/84)	18.4 (44/95)	0.51 (0.30–0.86)
Mild impairment	NE (42/165)	16.4 (78/162)	0.44 (0.30–0.65)
Moderate or severe impairment	31.5 (67/193)	13.3 (104/187)	0.50 (0.37–0.69)

Enfortumab Vedotin–Pembrolizumab Better **Chemotherapy Better**

Liver metastases and cisplatin eligibility subgroups are based on post-randomization corrections CRF. Randomization was stratified by PD-L1 status (high or low) based on information available at screening. For subgroup analyses by PD-L1 status (low or high), subjects whose tissue sample was found to be unsuitable for

PD-L1 22C3 per testing guidelines after randomization were not included in analyses by PD-L1 status.
- indicates not reached.
Abbreviations: CPS, combined positive score; CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; gem, gemcitabine; ITT, intent to treat; pembro, pembrolizumab; plat, platinum-based chemotherapy; OS, overall survival.
Data cutoff date: 08 August 2023
Source: Powles et al.[4]

6.1.4.2 Progression free survival

PFS was defined as the time from randomization to first documentation of disease progression per RECIST v1.1 by blind independent central review (BICR), or to death due to any cause, whichever came first. Patients who progressed or died after missing two or more consecutive tumour assessments were censored at the date of last radiological assessment. If a subject had neither progressed nor died, the subject was censored at the date of last radiological assessment. Subjects who received new anticancer therapy (excluding maintenance therapy following first-line platinum-containing chemotherapy) for la/mUC before disease progression or death were censored at the date of the last radiological assessment before the anticancer therapy started. Patients without any post-baseline tumour assessments were censored at the date of randomization. The time from randomization to PFS event or censoring was calculated as event/censoring date – randomization date + 1.[65]

PFS was analysed using the same methods described in the previous section for OS. Efficacy analyses on PFS were conducted using the ITT population for validation purposes, and then analyses were conducted in the seven subgroups of interest (i.e., cisplatin-eligible, cisplatin-ineligible, PD-L1 high, PD-L1 low, cisplatin-ineligible and PD-L1 high, cisplatin-ineligible and PD-L1 low, and avelumab maintenance accessible), and the four subgroups of the control arm based on avelumab eligibility and receipt. Note that no statistical hypothesis tests were conducted for any of the control arm subgroups based on avelumab eligibility and receipt.[65]

Kaplan Meier estimates of PFS – ITT Analysis Set

The hazard of disease progression or death was 55% lower in the EV+P arm than in the Plat+Gem arm (HR: 0.45; 95% CI, 0.38 to 0.54; P<0.001). The median duration of PFS was 12.5 months (95% confidence interval [CI], 10.4 to 16.6) in the EV+P arm and 6.3 months (95% CI, 6.2 to 6.5) in the Plat+Gem arm. Overall, there were 223 PFS events reported in the EV+P arm and 307 events reported in the Plat+Gem arm, and median PFS was 12.5 months and 6.3 months, respectively.[30] (Table 15; Figure 8).

Table 15. PFS per RECIST v1.1 by BICR – EV-302 ITT analysis set

	EV+P (N=442)	Plat+Gem (N=444)
Subjects with progression or death, n (%)	233 (50.5)	307 (69.1)
Stratified analysis[a]		
Hazard ratiob (95% CI)	0.450 (0.377, 0.538)	
Two-sided P-value[c]	<0.00001	
Progression-free survival (PFS)[d] (months)		
Median (95% CI[e])	12.5 (10.4; 16.6)	6.3 (6.2; 6.5)
Q1, Q3	5.1, -	4.1, 10.4
Observed min, max	0.03+, 30.42+	0.03+, 32.99+
PFS rate [d] (%) at:		
6 months (95% CI††)	72.8 (68.3, 76.8)	60.7 (55.7, 65.4)
12 months (95%, CI††)	50.7 (45.6, 55.5)	21.6 (17.2, 26.2)
18 months (95%, CI††)	43.9 (38.5, 49.1)	11.7 (8.0, 16.1)
Number of subjects censored	216 (49.5)	137 (30.9)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; P, pembrolizumab; Plat+Gem, platinum-based therapy; Q, quartile; RECIST, Response Evaluation Criteria in Solid Tumors

a. Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization.

b. Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+Pembro arm.

c. Calculated using stratified log-rank test. The p-value threshold for statistical significance is 0.005.

d. As estimated using Kaplan-Meier method.

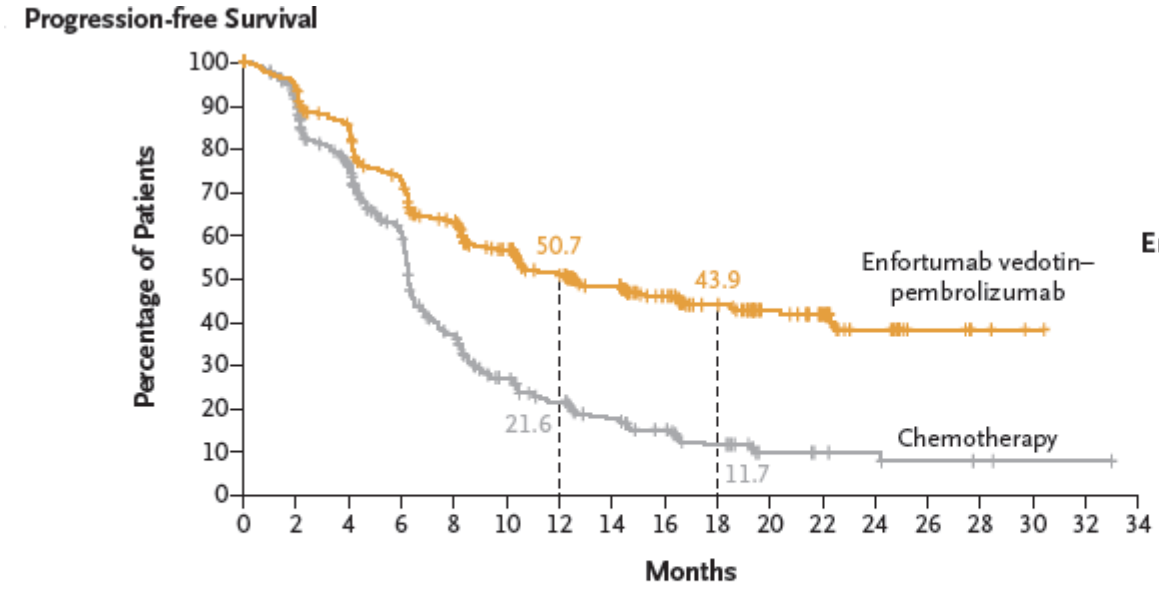
e. Calculated using the complementary log-log transformation method (Collett, 1994) [52]

+ indicates censoring.

Data cutoff date: 08 August 2023.

Source: Powles et al.[4]

Figure 8. Kaplan-Meier plot of progression-free survival per RECIST v1.1 by BICR – EV-302 ITT analysis set



	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	223/442	12.5 (10.4–16.6)
Chemotherapy	307/444	6.3 (6.2–6.5)

Hazard ratio, 0.45 (95% CI, 0.38–0.54)
Two-sided P<0.001

No. at Risk

Enfortumab vedotin–pembrolizumab	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Abbreviations: BICR, blinded independent central review; CI, confidence interval; EV, enfortumab vedotin; gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; pembro, pembrolizumab; PFS, progression-free survival; plat, platinum-based therapy.
Data cutoff date: 08 August 2023
Source: Powles et al.[4]

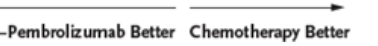
Kaplan Meier estimates of PFS - Subgroups

The treatment effect of EV+P on PFS by BICR was consistent across all pre-specified subgroups (Figure 9). PFS benefit was observed regardless of cisplatin eligibility (eligible or ineligible), PD-L1 expression status (high [CPS ≥10] or low [CPS <10]), or liver metastases (present or absent); HRs ranged from 0.415 to 0.534 in favour of EV+P across these subgroups. The HR was 0.483 (95% CI: 0.377, 0.619) in the cisplatin-eligible group and 0.429 (95% CI: 0.333, 0.553) in the cisplatin-ineligible group.[4]

Figure 9. Subgroup analyses of progression-free survival per RECIST v1.1 by BICR – EV-302 ITT analysis set

Subgroup Analysis

Subgroup	Enfortumab Vedotin–Pembrolizumab	Chemotherapy	Hazard Ratio for Disease Progression or Death (95% CI)
	mo (no. of events/no. of patients)		
Overall	12.5 (223/442)	6.3 (307/444)	0.45 (0.38–0.54)
Age			
<65 yr	12.7 (75/144)	6.4 (88/135)	0.45 (0.32–0.62)
≥65 yr	12.0 (148/298)	6.2 (219/309)	0.45 (0.36–0.56)
Race			
White	10.4 (168/308)	6.2 (207/290)	0.48 (0.39–0.60)
Other	22.3 (55/134)	6.5 (100/154)	0.39 (0.27–0.55)
Geographic region			
North America	12.0 (58/103)	6.3 (55/85)	0.56 (0.38–0.82)
Europe	10.4 (94/172)	6.3 (144/197)	0.50 (0.38–0.66)
Rest of the world	NE (71/167)	6.2 (108/162)	0.35 (0.26–0.48)
Sex			
Female	10.4 (55/98)	6.1 (74/108)	0.49 (0.34–0.71)
Male	14.6 (168/344)	6.3 (233/336)	0.44 (0.36–0.54)
ECOG performance-status score			
0	22.3 (93/223)	6.7 (146/215)	0.36 (0.28–0.48)
1 or 2	9.3 (130/219)	6.1 (161/227)	0.53 (0.42–0.68)
Primary site of origin of disease			
Upper tract	12.7 (69/135)	6.2 (70/104)	0.50 (0.35–0.71)
Lower tract	12.5 (152/305)	6.3 (236/339)	0.44 (0.35–0.54)
Liver metastases			
Present	8.2 (66/100)	6.0 (78/99)	0.53 (0.38–0.76)
Absent	16.4 (157/342)	6.4 (229/345)	0.43 (0.35–0.52)
PD-L1 expression			
Low (CPS <10)	10.5 (105/184)	6.3 (127/185)	0.50 (0.38–0.65)
High (CPS ≥10)	18.5 (116/254)	6.2 (176/254)	0.42 (0.33–0.53)
Cisplatin eligibility status			
Eligible	14.6 (117/244)	6.5 (149/234)	0.48 (0.38–0.62)
Ineligible	10.6 (106/198)	6.1 (158/210)	0.43 (0.33–0.55)
Site of metastasis			
Visceral site	10.4 (176/318)	6.2 (238/318)	0.45 (0.37–0.55)
Lymph node only	NE (38/103)	8.3 (55/104)	0.40 (0.26–0.62)
Renal function			
Normal	18.7 (38/84)	6.7 (61/95)	0.46 (0.30–0.71)
Mild impairment	12.7 (79/165)	6.3 (114/162)	0.46 (0.34–0.62)
Moderate or severe impairment	10.5 (106/193)	6.2 (132/187)	0.47 (0.36–0.61)



Liver metastases and cisplatin eligibility subgroups are based on post-randomization corrections CRF. Randomization was stratified by PD-L1 status (high or low) based on information available at screening. For subgroup analyses by PD-L1 status (low or high), subjects whose tissue sample was found to be unsuitable for PD-L1 22C3 per testing guidelines after randomization were not included in analyses by PD-L1 status.
- indicates not reached.
Abbreviations: BICR, blinded independent central review; CPS, combined positive score; CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; gem, gemcitabine; ITT, intent to treat; pembro, pembrolizumab; plat, platinum-based chemotherapy; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumours.
Data cutoff date: 08 August 2023
Source: Powles et al.[4]

6.1.4.3 Clinical response

In this assessment, the clinical response includes the overall response rate (ORR), disease control rate (DCR), and duration of response (DOR).

The secondary endpoint of ORR was defined as the percentage of subjects who achieved confirmed complete response (CR) or partial response (PR) based on RECIST v1.1. ORR by BICR was the first secondary endpoint tested after both PFS and OS were statistically significant. The secondary endpoint of DCR was defined as the proportion of subjects with confirmed CR, PR, or stable disease according to RECIST v1.1. The number and proportion of patients who achieved ORR, CR, PR, and DCR were summarized by treatment arm. Comparisons of ORR and DCR between the treatment arms was analysed using the two-sided Cochran-Mantel-Haenszel (CMH) test controlled for stratification factors (liver metastases: present or absent; PD-L1 expression: high or low; cisplatin eligibility: eligible or ineligible) at randomization), and the resulting odds ratio (OR) and 95% CI were presented. The RTSM variables were used as stratification factors.[65]

The secondary endpoint of DOR per RECIST v1.1 was assessed by BIC. DOR was defined as the time from first documentation of ORR (that is subsequently confirmed) to first documentation of objective tumour progression or death due to any cause, whichever comes first. The KM method was used to estimate the median DOR, and the 95% CI for the median was computed.[65]

Objective response rate, duration of treatment response, and disease control rate

The confirmed ORR was higher in the EV+P arm than in the Plat+Gem arm (67.7% [95% CI, 63.1 to 72.1] vs. 44.4% [95% CI, 39.7 to 49.2]; P<0.001) (Table 16). A CR was observed in 29.1% (127 of 437) of the patients in the EV+P arm and in 12.5% (55 of 441) of those in the Plat+Gem arm. The results of the analysis of ORR were consistent between the ITT population and all the prespecified subgroups (Powles et al., 2024 - Fig. S5 in supplementary appendix). DCR by BICR for the [redacted] was [redacted] for the Plat+Gem.[57] Median time to response (TTR) was 2.10 months in both arms. The median DOR was not reached in the EV+P arm and was 7.0 months in the Plat+Gem arm.[4] (Figure 10).[57] Median time to response (TTR) was 2.10 months in both arms. The median DOR was not reached in the EV+P arm and was 7.0 months in the Plat+Gem arm.[4] (Figure 10)

Table 2. Overall Response and Duration of Response.*

Variable	Enfortumab Vedotin–Pembrolizumab (N=437)	Chemotherapy (N=441)
Confirmed best overall response — no. (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Could not be evaluated†	0	4 (0.9)
No assessment‡	21 (4.8)	32 (7.3)
Confirmed overall response (95% CI) — %§	67.7 (63.1–72.1)	44.4 (39.7–49.2)
Median time to response (range) — mo	2.1 (1.3–12.3)	2.1 (1.6–8.3)
Median duration of response (95% CI) — mo	Not reached (20.2–NE)	7.0 (6.2–10.2)

Table 16. Objective response rate (ORR), duration of response (DOR) per RECIST by BICR - EV-302 response evaluable set by BICR

	EV+P (N=437)	Plat+Gem (N=441)
ORR, n (%)	296 (67.7)	196 (44.4)
95% CI†	(63.1, 72.1)	(39.7, 49.2)
2-sided p-value‡	<0.00001	
Best overall response§, n (%)		
CR	127 (29.1)	55 (12.5)
PR	169 (38.7)	141 (32.0)
SD	82 (18.8)	149 (33.8)
PD	38 (8.7)	60 (13.6)
NE¶	0	4 (0.9)
No assessment††	21 (4.8)	32 (7.3)
Median TTR (range) – months	2.1 (1.3-12.3)	2.1 (1.6-8.3)
Median DOR (96% CI) - months	Not reached (20.2-NE)	7.0 (6.2-10.2)

ORR and DOE, as assessed by blinded independent central review according to RECIST, version 1.1, were evaluated in all the patients in the ITT population who had measurable disease at baseline according to RECIST, version 1.1. NE denotes could not be estimated. Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; EV, enfortumab vedotin; gem, gemcitabine; NE: not evaluable; ORR, overall response rate;,P pembrolizumab; plat, platinum-based chemotherapy (cisplatin or carboplatin); PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

† Computed using the Clopper-Pearson method

‡ Cochran-Mantel-Haenszel test (CMH) controlling for stratification factors (liver metastases: present or absent; PD-L1 expression: high or low; cisplatin eligibility: eligible or ineligible) at randomization

§ Best overall response according to RECIST v1.1. CR or PR was confirmed with repeat scans ≥ 28 days after initial response

¶ Subjects had post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1

†† Subjects had no response assessment post-baseline

Data cutoff date: 08 August 2023

Source: Powles et al., 2024[4]

Figure 10. Kaplan Meier plot of DOR per RECIST by BICR – EV-302 ITT analysis set

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; EV, enfortumab vedotin; gem, gemcitabine; HR, hazard ratio; pembro, pembrolizumab; plat, platinum-based therapy.
Data cutoff date: 08 August 2023
Source: Astellas data on file, 2023.[50]

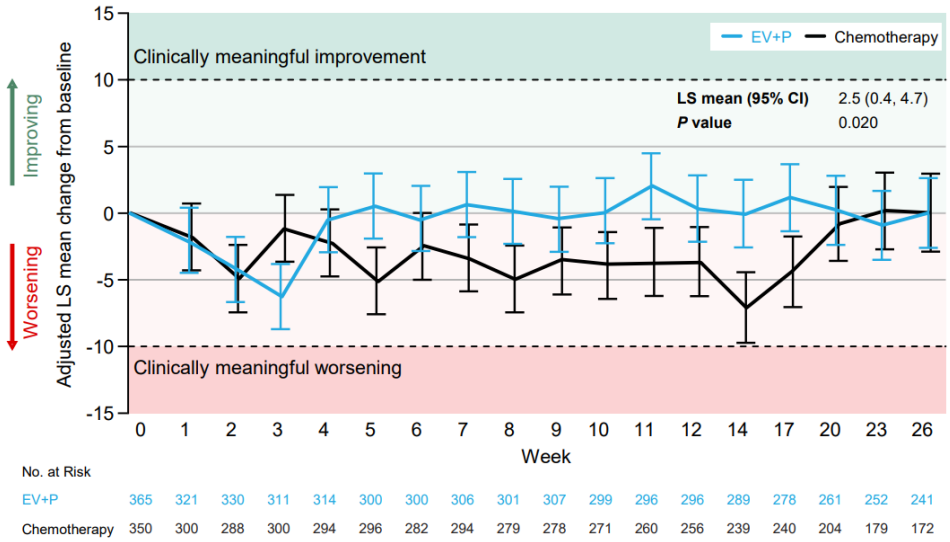
6.1.4.4 Patient reported outcome (PRO)

The humanistic value of EV+P was assessed via PROs using three instruments, the EORTC QLQ-C30, which have been validated in an la/mUC population, the EQ-5D, and the Brief Pain Inventory short form (BPI-SF).[66,80] PRO analyses aimed to evaluate the impact of study treatment on QoL, functioning, and symptoms from the subject perspective. The patient-reported outcome full analysis set (PRO FAS) consisted of 731 patients (n=376 in EV+P arm, n=355 in the Plat+gem arm).

PROs were administered at Cycle 1 Day 1 before study treatment, once weekly for the first 12 weeks, and then once every 3 weeks through the remainder of the study through progression and survival follow-up.[66,80]

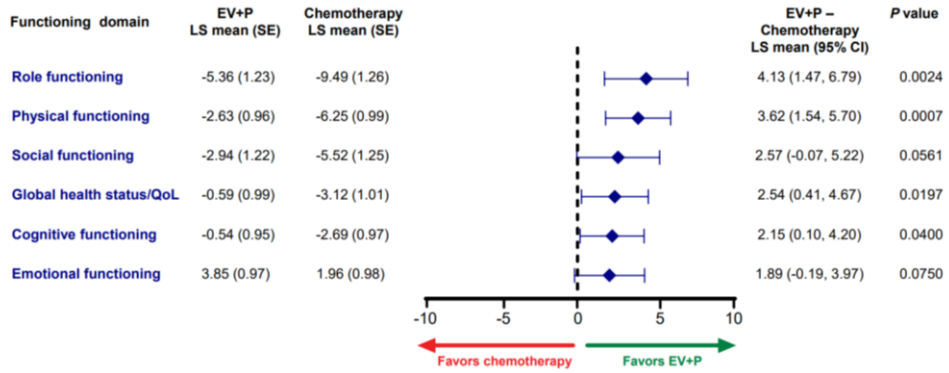
The mean change from baseline to week 26 for the EORTC QLQ-C30 Global Health Status domain, was consistently higher in EV+P arm than Plat+Gem arm (Figure 11). The forest plot showed that all EORTC QLQ-C30 functional domains numerically favoured EV+P over Plat+Gem (Figure 12).[80]

Figure 11. Change in EORTC QLQ-C30 Global Health Status/QoL Score



Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EV+Pembro, enfortumab vedotin in combination with pembrolizumab; Plat+Gem, cisplatin or carboplatin in combination with gemcitabine; PRO FAS, patient-reported outcome full analysis set.
Source: Gupta et al, ASCO poster, 2024 [80]

Figure 12. Change in EORTC QLQ-C30 Functioning Domains (Forest Plot)



Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EV+Pembro, enfortumab vedotin in combination with pembrolizumab; Plat+Gem, cisplatin or carboplatin in combination with gemcitabine; PRO FAS, patient-reported outcome full analysis set.
Source: Gupta et al, ASCO poster, 2024 [80]

The EQ-5D analysis showed that the mean baseline VAS scores were 72.8 in EV+P arm and 69.7 in the Plat+Gem arm. The Health State Index Scores (utility scores) were 0.844 and 0.818, respectively. During the treatment period, both VAS and utility scores remained stable with little to no change from baseline throughout the study period. A detailed description of EQ-5D data collection and result is presented in section 10.

In summary, the PRO results demonstrate the maintenance of QoL during treatment. These findings, layered with the superior efficacy and manageable safety profile, demonstrated patients may benefit from this novel 1L combination without compromising HRQoL.

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Head-to-head study used. Not applicable.

7.1.2 Method of synthesis

Head-to-head study used. Not applicable.

7.1.3 Results from the comparative analysis

Table 17 present the results from the comparative analyses of EV+P vs. Plat+Gem derived from the head-to-head trial: EV-302 (NCT04223856).

Table 17. Results from the comparative analysis of EV+P vs. Plat+Gem for patients with previously untreated la/mUC who are eligible for platinum-based chemotherapy

Outcome measure	EV+P (N=442)	Plat+Gem (N=444)	Result
OS per RECIST (median duration of follow-up 17.2 months)	Median: 31.5 months (95% CI: 25.4, -)	Median: 16.1 months (95% CI: 13.9, 18.3)	HR: 0.468 (95% CI: 0.376, 0.582) p <0.00001
PFS per RECIST by BICR (median duration of follow-up 17.2 months)	Median: 12.5 months (95% CI: 10.4, 16.6)	Median: 6.3 months (95% CI: 6.2, 6.5)	HR: 0.450 (95% CI: 0.377–0.538) p <0.00001
Proportion of subjects who achieving ORR per RECIST by BICR (median duration of follow-up 17.2 months)	296/437 (67.7%) (95% CI: 61.4, 70.4)	196/441 (44.4%) (95% CI:38.3, 47.7)	Stratified OR: 2.64 (95% CI: 2.000, 3.490) p <0.00001
Median DOR per RECIST by BICR (08 August 2023)*	Not reached (95% CI: 20.2, -)	7.0 months (95% CI: 6.2, 10.2)	N/A
DCR per RECIST by BICR (median duration of follow-up 17.2 months)*	[redacted]	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; BPI-SF, Brief Pain Inventory short form; DCR, disease control rate; DOR, duration of response; EV+P, enfortumab vedotin; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; Plat+Gem, platinum-based chemotherapy; RECIST, response Evaluation Criteria in Solid Tumours; TTPP, time to pain progression
*Response evaluable set by BICR includes all subjects in ITT analysis set who had measurable disease at baseline per RECIST v1.1 by BICR.
**Includes all randomized subjects who received any study treatment and completed at least one PRO assessment at baseline. Subjects were analysed according to the treatment arm assigned at randomization

7.1.4 Efficacy – results per outcome measure

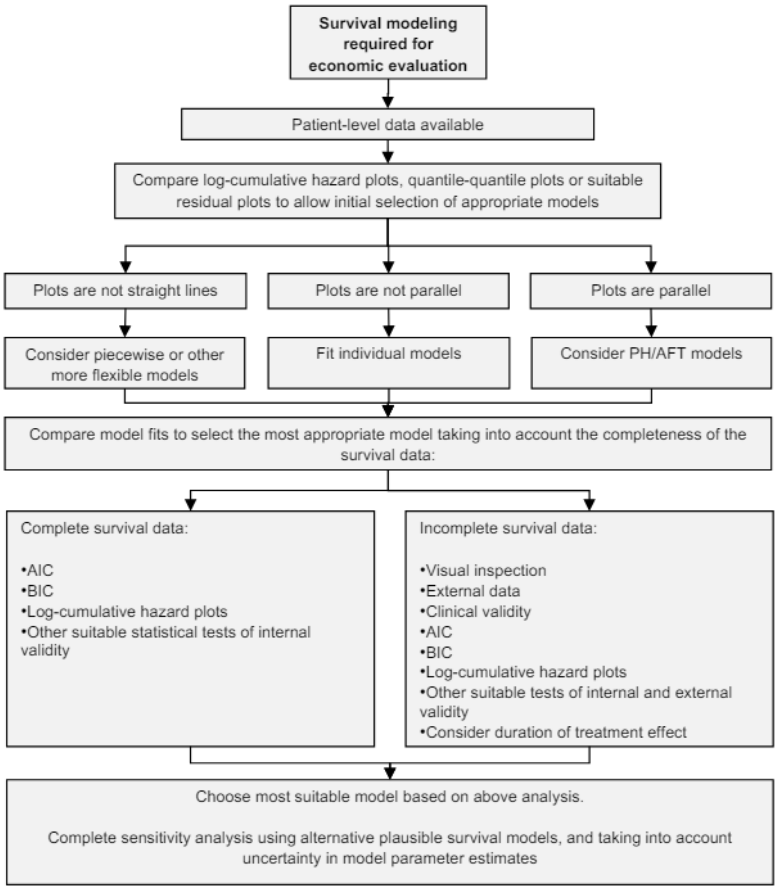
All results per efficacy outcome of interest are summarised in Section 6.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

EV-302 was directly used as head-to-head evidence to compare the clinical efficacy of EV+P and SoC (Plat+Gem followed by avelumab). PFS, OS, and ToT endpoints corresponding to patients treated with EV+P and SoC were derived from patient-level data from the 8 August 2023 data cut of the EV-302 trial. Survival models were chosen based on the NICE DSU technical support document 14, as seen in Figure 13.

Figure 13. Survival model selection process algorithm



8.1.1 Extrapolation of efficacy data

For PFS and OS, parametric curves could be fitted both independently (i.e., separate models for the EV+P arm and SoC arm), and jointly (dependent curves fitted to both

EV+P and SoC arms, with the calculation of a treatment arm coefficient to capture differences between the two).

Each approach has its advantages: the jointly fitted estimates draw on a greater pool of evidence, informed by approximately twice the number of observations, but assumes proportional hazards between the two arms. Independent curve fitting avoids the undue influence of the comparator arm on estimates, and does not rely on the proportional hazard's assumption, but incurs in greater uncertainty associated with sample size. Proportional hazards assessments (log (cumulative hazards) versus log (time)) were conducted for the ITT population of interest.

Seven parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) were fitted to data for each endpoint. Appropriate curve selection was determined according to statistical (AIC and BIC), visual goodness of fit and the clinical plausibility of extrapolations.

8.1.1.1 Extrapolation of OS

The base-case analysis fitted independent parametric models to extrapolate outcomes based on assessment of proportional hazards, see Appendix D. Table 18 summarises assumptions and extrapolation methods for OS. Scenario analyses explored other plausible parametric models.

Table 18. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	EV-302, 8 August 2023 data cut
Model	OS can be extrapolated with independent or dependent curves for EV+P and SoC (Plat+Gem). Both methods address the following curves: Exponential, Weibull, Gompertz, Gamma, Lognormal, Loglogistic, and Generalized Gamma
Assumption of proportional hazards between intervention and comparator	Proportional hazard assumption is violated
Function with best AIC fit	EV+P: Weibull SoC: Log-logistic
Function with best BIC fit	EV+P: Exponential SoC: Log-logistic
Function with best visual fit	EV+P: Log-logistic SoC: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	See Appendix D

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	EV+P: Log-logistic SoC: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 14. Base-case curves for OS (ITT population); log-logistic (EV+P) and log-logistic (SoC)

8.1.1.2 Extrapolation of PFS

The base-case analysis fitted independent parametric models to extrapolate outcomes based on assessment of proportional hazards, see Appendix D. Table 19 summarizes assumptions and extrapolation methods for PFS. Scenario analyses explored other independent curves and a dependent approach.

Table 19. Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	EV-302, 8 August 2023 data cut
Model	PFS can be extrapolated with independent curves for EV+P and SoC (Plat+Gem) or a dependent approach. Both methods address the following curves: Exponential, Weibull, Gompertz, Gamma, Lognormal, Loglogistic, and Generalized Gamma
Assumption of proportional hazards between intervention and comparator	No assumption on proportional hazards. Independent fits were used, as the proportional hazards assumption was violated
Function with best AIC fit	EV+P: Generalised Gamma SoC: Log-logistic
Function with best BIC fit	EV+P: Log-normal SoC: Log-logistic
Function with best visual fit	EV+P: Generalised Gamma SoC: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	See Appendix D
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	EV+P: Generalised Gamma SoC: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 15. Base-case curves for PFS (ITT population); Generalised Gamma (EV+P) and log-logistic (SoC)

8.1.1.3 Extrapolation of ToT

ToT in EV+P could be modelled both separately (ToT for EV and ToT for P) or jointly (ToT for EV+P), the separate approach allowed to capture different treatment durations. Based on EV-302 data, a stopping rule of 24 months was applied to Pembrolizumab.

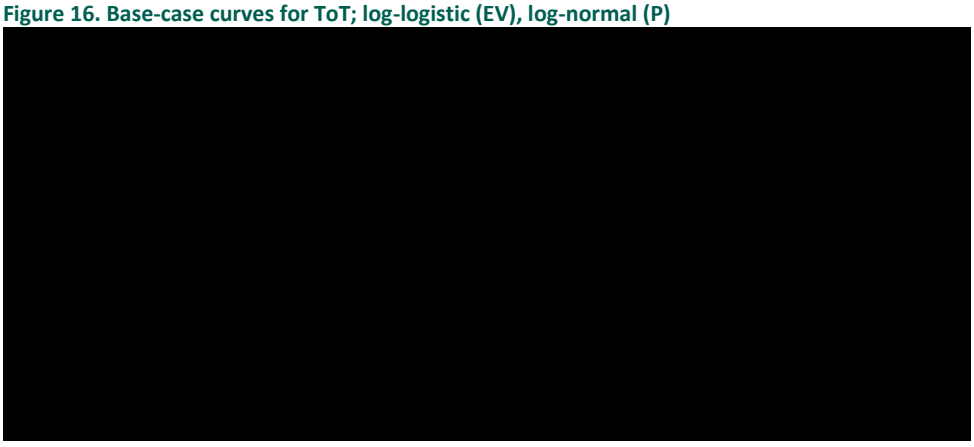
As patients in the SoC arm had a maximum of six treatment cycles of 3-week for Plat+Gem, ToT did not need to be extrapolated. Therefore, ToT for Plat+Gem was based on the KM estimates from the EV-302. ToT for Avelumab maintenance, which could follow treatment with Plat+Gem, was extrapolated using parametric models.

Table 20. Summary of assumptions associated with extrapolation of ToT

Method/approach	Description/assumption
Data input	EV-302, 8 August 2023 data cut
Model	ToT can be extrapolated with independent curves for EV and for P or with a dependent approach EV+P. Both methods address the following curves: Exponential, Weibull, Gompertz, Gamma, Lognormal, Log-logistic, and Generalized Gamma. For Soc, the ToT for Plat+Gem was not extrapolated and was informed directly with KM estimates. ToT for Avelumab maintenance was extrapolated fitting a parametric distribution
Assumption of proportional hazards between intervention and comparator	Independent fits for EV and for P were used to capture different treatment durations.
Function with best AIC fit	EV: Log-logistic, P: Generalised Gamma Avelumab: Gompertz

Method/approach	Description/assumption
Function with best BIC fit	EV: Log-logistic, P: Exponential Avelumab: Gompertz
Function with best visual fit	EV: Log-logistic, P: Log-normal Avelumab: Log-logistic.
Function with best fit according to evaluation of smoothed hazard assumptions	NA
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	EV: Log-logistic, P: Log-normal Avelumab: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	NA
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 16. Base-case curves for ToT; log-logistic (EV), log-normal (P)



8.1.2 Calculation of transition probabilities

Not applicable.

8.2 Presentation of efficacy data from additional documentation

Not applicable.

8.3 Modelling effects of subsequent treatments

No effects were modelled for remaining subsequent treatments.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Table 21 and Table 22 present estimates in the model for the modelled average OS and PFS, respectively.

Table 21. Estimates in the model for PFS

	Modelled average PFS (reference in Excel)	Modelled median PFS (reference in Excel)	Observed median from relevant study
EV+P	XXXXXXXXX	XXXXXXXXX	12.5 months
SoC	XXXXXXXXX	XXXXXXXXX	6.3 months

Notes: Modelled average refers to a time horizon of 30 years
Abbreviations: PFS, progression free survival; EV+P, enfortumab vedotin plus pembrolizumab; SoC, Standard of Care.

Table 22. Estimates in the model for OS

	Modelled average OS (reference in Excel)	Modelled median OS (reference in Excel)	Observed median from relevant study
EV+P	XXXXXXXXX	XXXXXXXXX	31.5 months
SoC	XXXXXXXXX	XXXXXXXXX	16.1 months

Notes: Modelled average refers to a time horizon of 30 years
Abbreviations: OS, overall survival; EV+P, enfortumab vedotin plus pembrolizumab; SoC, Standard of Care.

Table 23 presents the modelled average treatment length for EV, P, Plat+Gem, and Avelumab. Since treatment length for Plat+Gem was entirely captured during the EV-302 trial (following guidelines on max cycles allowed) it was not extrapolated.

Table 23. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Average treatment length [months]	PF [months]	PD [months]
EV+P	XXXXXX XXXXXXXXXX	XXXXX	XXXXX
SoC	XXXXXXXXXX XXXXXXXXXXXXX	XXXXX	XXXXX

Abbreviations: PF, progression free; PD, progressed disease; EV+P, enfortumab vedotin plus pembrolizumab; SoC, Standard of Care; Plat+Gem, platinum-based chemotherapy

9. Safety

9.1 Safety data from the clinical documentation

Safety data were derived by treatment arm using the safety analysis set (SAF) from the EV-302 head-to-head trial. The SAF for these two arms included 873 subjects that received any amount of study treatment. This included 440 subjects that received EV+P and 433 that received Plat+Gem. In this application, safety data (adverse events [AEs]) are presented as treatment-emergent adverse events (TEAEs) (Table 24)

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 26.0 or higher. Laboratory values were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 or higher. Concomitant medications were coded using the WHO Drug Dictionary (version 2019Mar B3 or higher).

This application does not include comparative analyses of safety. Meta-analyses indirect treatment comparisons have not been conducted as a single RCT provides head-to-head evidence of EV+P and Plat+Gem.

Summary of TEAEs

EV+P has a distinct mechanism of action and was administered for a longer duration of treatment (median 9.43 months) compared with Plat+Gem (median 4.14 months). As such, differences in the safety profile between treatment arms were anticipated and exposure-adjusted analyses were conducted.[4,57]

A summary of the AEs is provided in Table 24. TEAEs are displayed both as the subject incidence rate (%) and as the event rate per patient year (E/PY) of exposure.

Table 24. Overview of safety events. (Data cut off: 8 August 2023)

	Subject incidence rate			Exposure-adjusted event rate	
	EV+P (N=440), n (%) EV-302 [4,57]	Plat+Gem (N=433), n (%) EV-302[4,57]	Difference, % (95 % CI)	EV + Pembro PY=385.56 E (E/PY)	Plat + Gem PY=147.82 E (E/PY)
Number of adverse events, n	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	439 (99.8)	427 (98.6)	N/A	7,442 (19.3)	5,034 (34.1)
Number of serious adverse events, n	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	220 (50.0)	169 (39.0)	N/A	440 (1.1)	328 (2.2)
Number of CTCAE grade ≥ 3 events, n	321 (73.0)	341 (78.8)	N/A	854 (2.2)	1,069 (7.2)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	N/A	N/A	N/A	N/A	N/A
Number of adverse reactions, n	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	XXXXXXXXXX	XXXXXXXXXX	N/A	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction*, n (%)	XXXXXXXXXX	XXXXXXXXXX	N/A	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	XXXXXXXXXX	XXXXXXXXXX	N/A	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; E, number of events; EV, enfortumab vedotin; Gem, gemcitabine; P, pembrolizumab; Plat, platinum-based chemotherapy (cisplatin or carboplatin); PY, Patient-years (total duration of exposure in years)

*Due to treatment-emergent adverse event

Data cutoff date: 08 Aug2023, Dictionary: MedDRA v26.0

Source: Powles et al., 2024, Astellas, data on file[4,57]

In general, the percentages of subjects in the EV+P arm and the Plat+Gem arm with any TEAE (99.8% and 98.6%, respectively), Grade 3 to 5 TEAE (73.0% and 78.8%), or TEAE leading to death (4.3% and 3.2%), including fatal events that were considered treatment related by the investigator (0.9% in both arms), were similar in both treatment arms. The percentages of subjects with serious TEAEs (50.0% and 39.0%, respectively) and TEAEs leading to dose interruption (78.9% and 64.4%) or discontinuation (39.8% and 21.5%) were higher in the EV+P arm than in the Plat+Gem arm; however, when assessed as E/PY, the PY exposure-adjusted event rates for these AE categories were either similar between arms or numerically higher for the Plat+Gem arm.[4,57]

A similar percentage of subjects experienced an adverse reaction in the EV+P arm (97.0%) and the Plat+Gem arm (95.6%). Overall, the profile of treatment-related TEAEs observed during combination therapy with EV+P was consistent with the known adverse reactions of EV, P, or both.[57]Serious TEAEs were derived by treatment arm from the EV-302 head-to-head trial. Serious TEAEs reported for ≥ 2% of subjects in either arm are listed in Table 25

Table 25. Serious adverse events in >2% of the SAF population (Data cut off: 8 August 2023)

Adverse events	EV+P (N=440)		Plat+Gem (N=433)	
	Number of patients with serious adverse events (%)	Number of serious adverse events	Number of patients with serious adverse events (%)	Number of serious adverse events
Adverse event, n (%)				
Overall	[redacted]	N/A	[redacted]	N/A
Acute kidney injury	[redacted]	N/A	[redacted]	N/A
Urinary tract infection	[redacted]	N/A	[redacted]	N/A

Abbreviations: EV, enfortumab vedotin; Gem, gemcitabine; P, pembrolizumab; Plat, platinum-based chemotherapy (cisplatin or carboplatin)
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Data cutoff date: 08Aug2023
Source: Astellas, data on file[57]

Overall, [redacted] of subjects in the EV + P arm and [redacted] of subjects in the Plat + Gem arm experienced a serious TEAE. In the EV+P, the most common serious TEAEs were [redacted]. All other serious TEAEs were reported for less than <2% of subjects (in the EV-302 CSR). In the Plat + Gem arm, the most common serious TEAEs was [redacted]. All other serious TEAEs were reported < 2%. Overall, the profile of serious TEAEs reported in both arms was generally consistent with the known adverse reactions of the respective

treatments and/or underlying disease, preexisting comorbidities, and advanced age of the study population.[57] A list of all serious AEs observed in the EV-302 trial is reported in Appendix E.

AEs considered in the model included grade 3+ TEAEs, which occurred in at least 5% of patients in any treatment regimen. Note Grade 2 and Grade 3+ peripheral neuropathy was also included in the model on the advice of clinical experts, who considered the event to be impactful on patient QoL. Peripheral neuropathy is an adverse event category which is comprised of individual adverse events (e.g., peripheral sensory neuropathy, paraesthesia etc.), so although Grade 3+ peripheral neuropathy is above the 5% threshold, it was not initially considered in the model as none of the individual adverse events comprising peripheral neuropathy were above the 5% threshold.

For EV+P and Plat+Gem, the TEAEs were informed by rates reported in the EV-302 trial. The safety reporting period for all AEs in EV-302 was from study Day 1 (pre-dose) through 30 days after the last study treatment. Thus, AE data were not available from EV-302 for patients receiving avelumab maintenance (Note: avelumab maintenance was not considered a study drug but was captured under subsequent anticancer therapy data collection). To account for the cost and quality of life impact of adverse events in patients receiving avelumab maintenance, rates were included from TA788 (derived from Javelin Bladder 100 study) (note: study reported any Grade 3+ AEs in the safety population).[67] AE rates for the ITT population are reported in Table 26.

Table 26. Adverse events used in the health economic model

Adverse events	EV+P	SoC: Plat+Gem	SoC: Avelumab (maintenance)		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Frequency used in economic model for comparator	Source	Justi-fication
Adverse event, n (%)	N/A	N/A	N/A	N/A	
Acute kidney injury	[redacted]	[redacted]	0.0%	EV-302 CSR (ITT)[57] Powles et al. 2020[67] TA788	Grade ≥3 AEs with ≥ 5% incidence in any treat-ment regimen
Anaemia	[redacted]	[redacted]	3.8%		
Fatigue	[redacted]	[redacted]	1.7%		
Hyperglycaemia	[redacted]	[redacted]	0.0%		
Hyponatraemia	[redacted]	[redacted]	0.0%		
Neutropenia	[redacted]	[redacted]	0.0%		
Neutrophil count decreased	[redacted]	[redacted]	0.0%		

Platelet count decreased	[redacted]	[redacted]	0.0%
Rash maculo-papular	[redacted]	[redacted]	0.3%
Thrombocytopenia	[redacted]	[redacted]	0.0%
Urinary tract infection	[redacted]	[redacted]	4.4%
Neuropathy (Grade 2)	[redacted]	[redacted]	0.0%
Peripheral neuropathy (Grade 3+)	[redacted]	[redacted]	0.0%

Abbreviations: AE, adverse event; EV+ P, enfortumab vedotin in combination with pembrolizumab; ITT, intention-to-treat; Plat+Gem, platinum-based chemotherapy in combination with gemcitabine.

Peripheral neuropathy, adverse event of special interest

Peripheral neuropathy was reported for a higher percentage of subjects in EV+P (66.6%), than in Plat+Gem (13.9%) (Table 27), which in part was attributable to longer treatment duration with enfortumab vedotin (7.01 months) in EV+P compared with the Plat+Gem (4.14 months). Subjects in EV+P with peripheral neuropathy had events that were primarily [redacted]

Table 27. Overview of Peripheral Neuropathy (Safety Analysis Set)

	EV+P (N=440) (%)	Plat+Gem (N = 433) (%)
Any peripheral neuropathy	[redacted]	[redacted]
By severity	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Serious	[redacted]	[redacted]
Led to discontinuation of	[redacted]	[redacted]
EV	[redacted]	[redacted]
Pembro	[redacted]	[redacted]
Any study drug	[redacted]	[redacted]

EV: Enfortumab vedotin; Gem: Gemcitabine; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin)
Source: EV-302, data on file (CSR)[57]

Subsequent anticancer treatment

As of the data cutoff, 32.6% of the patients in EV+P arm and none of the patients in th Plat+Gem arm were still receiving treatment; 31.7% of the patients in the EV+P arm and 70.5% of the patients in the comparator arm received subsequent anticancer therapies (Table 28 Among the patients in EV+P who received subsequent therapies, 78.6%

received Plat+Gem as the first subsequent therapy. In EV+P 1.6% and in Plat+Gem 58.5% received PD-1 or PD-L1 inhibitor–containing therapy as the first subsequent systemic therapy, including 143 patients (32.2% total; 135 patients [30.4%] received avelumab) who received maintenance therapy[4].

Table 28. Summary of subsequent therapy (EV-302 ITT analysis set)

	Arm A: EV+P (N=442) (%)	Arm B: Plat+Gem (N=444) (%)
Patients who remained on treatment	144 (32.6)	0
Patients who received subsequent anticancer therapies	140 (31.7)	313 (70.5)
First subsequent systemic therapy	128 (29.0)	294 (66.2)
Platinum-based therapy	110 (24.9)	17 (3.8)
PD-1/PD-L1 inhibitor-containing therapy	7 (1.6)	260 (58.6)
Maintenance therapy*,†	0	143 (32.2)
Avelumab	0	135 (30.4)
Other therapy	7 (1.6)	117 (26.4)

Abbreviations: EV, Enfortumab vedotin; gem, gemcitabine; ITT, intention-to-treat; P, pembrolizumab; plat, platinum-based chemotherapy; PD-1, Programmed Cell Death Protein 1; PD-L1, Programmed Death-Ligand 1
*Included atezolizumab, avelumab, ipilimumab, M 6223, nivolumab, Nktr 255, and pembrolizumab.
†Maintenance therapy was permitted in the trial after platinum-based chemotherapy.
PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
Data cutoff date: 08 August 2023
Source: Powles et al., 2024, supplementary appendix[4]

9.2 Safety data from external literature applied in the health economic model

Not applicable.

10. Documentation of health-related quality of life (HRQoL)

Table 29. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	EV-302 trial	HRQoL data was collected to estimate HSUVs for PF and PD states

Abbreviations: PF; progression free; PD, progressed disease

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The health-related quality of life (HRQoL) of EV+P was assessed in EV-302 using using three instruments, the EORTC QLQ-C30, which have been validated in a la/mUC population, the EQ-5D, and the Brief Pain Inventory short form (BPI-SF). In summary the HRQoL documents showed patients receiving EV+Pembro consistently demonstrated their QoL, functioning, and symptom experience was not compromised compared with patients receiving Plat+Gem.

In this section only the results for EQ-5D-5L will be presented since that's the data DMC prefer for the assessment. For EQ-5D-5L both the utility index and the visual analogue scale (VAS) was used to collect HRQoL.

10.1.2 Data collection

An electronic PRO (ePRO) assessments including the EQ-5D-5L questionnaire were administered at Cycle 1 day 1 before study treatment, once weekly for the first 12 weeks, at week 14, and then once every 3 weeks through the remainder of the study through progression and survival follow-up. In Appendix F more details regarding the data collection of EQ-5D-5L is presented, e.g. baseline characteristics for ITT vs PRO FAS, pattern of missing data, and completion rate per health state.

10.1.3 HRQoL results

The mean change from baseline for the EQ-5D-5L VAS is presented in Figure 17. The PRO full analysis set includes all randomized subjects (ITT) who received any amount of study treatment and completed at least one PRO assessment at baseline. The summary statistics are presented in Table 30.

Figure 17. Mean change from baseline, EQ-5D-5L VAS Score PRO Full Analysis Set

Source:[68]

Table 30. HRQoL EQ-5D-5L summary statistics

	Intervention EV+P		Comparator Plat+Gem		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	NA
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	NA
Week 23	[redacted]	[redacted]	[redacted]	[redacted]	NA
Week 35	[redacted]	[redacted]	[redacted]	[redacted]	NA
Week 47	[redacted]	[redacted]	[redacted]	[redacted]	NA
Week 59	[redacted]	[redacted]	[redacted]	[redacted]	NA
Week 71	[redacted]	[redacted]	[redacted]	[redacted]	NA
Week 83	NA	NA	NA	NA	NA
Week 95	NA	NA	NA	NA	NA
Week 107	NA	NA	NA	NA	NA
Follow-up	NA	NA	NA	NA	NA

Source: EV-302 CSR (Table 12.3.9.3)

10.2 Health state utility values (HSUVs) used in the health economic model

Responses to the EQ-5D can be converted to a utility score, a weighted heath state index, using published population tariffs for the country of interest and these utility scores are used as the QoL input to inform the cost-effectiveness model (CEM). Specifically, utilities by health state are of interest for the CEM as defined by tumour response, where patients' observations are categorized as progressed or non-progressed (i.e., complete response [CR], partial response [PR], or stable disease [SD]). EQ-5D-5L response data (i.e., response to each of the five questions) collected in EV-302 were used to calculate country-specific health state utility values (HSUVs). For Denmark, EQ-5D-5L utilities were calculated using the value set reported by Jensen et al., 2021.[69]

10.2.1 HSUV calculation

Descriptive statistics were used to summarize the observed utility at each visit and change from baseline at post-baseline visits for the patient-reported outcome full analysis set (PRO FAS). The PRO FAS included all randomized subjects who received any

amount of study treatment and completed at least one PRO assessment at baseline. Line plots of observed mean utility and mean changes from baseline were generated for each country to demonstrate average utility trends over time. The relationship between health state (i.e., progression-free or progressed disease) and patient-reported health utility were evaluated through a longitudinal analysis of utility index scores. More specifically, it was evaluated the health utility of patients in the baseline/pre-treatment, pre-progression, and (if available) post-progression periods both pooled and by treatment arm. The pre-treatment health utility was derived from the baseline EQ-5D index score. The pre-progression period health utility was calculated as the average EQ-5D index scores from treatment initiation to first documentation of progressive disease. The post-progression health state utility was derived from assessments after progression.

A mixed model was constructed to estimate the mean EQ-5D-5L scores for each health state and included the following covariates: treatment arm, randomization stratification factors, and baseline scores. Various covariance structures, including (1) unstructured, (2) compound symmetry, and (3) first-order autoregressive were tested and compared based on -2 Log Likelihood information criteria, and the first-order autoregressive was selected as the best fit. The equation used was:

$$CFBij = \beta 0 + \beta hsXhsij + \beta timej + \beta trtXtrti + \beta cisXcisi + \beta pdl1Xpdl1i + \beta livmetXlivmeti + \beta blutilXblutili$$

Where 'hs' is health state (pre-progression vs. post-progression), 'trt' is treatment (EV+P vs. gem+plat), 'cis' is cisplatin eligibility (eligible vs. ineligible), 'pdl1' is PD-L1 expression (high vs. low), 'livmet' is liver metastases (present vs absent), and 'blutil' is baseline utility.

The health state utilities presented in the dossier, and used in the cost-effectiveness model, were generated using the mixed model presented above, and based on progression status. Point estimates and standard errors of HSUVs for Progression free and Progressed disease were based on 1,000 bootstrapped samples with replacement.

10.2.1.1 Mapping

For each population the mean utility values for the heath states were calculated using Danish EQ-5D-5L tariffs. Moreover, the utility values for the progression free state and the progressed disease state have been age adjusted following section 7.3 of the DMC methods guide.

10.2.2 Disutility calculation

Not applicable. The disutility calculations were based on external literature.

10.2.3 HSUV results

The mixed effects model for Danish HSUVs values suggested that within the overall PRO FAS and all subgroups except the cisplatin-eligible subgroup, the treatment coefficient (i.e., treatment with EV + P vs. gemcitabine + platinum chemotherapy) was significant (p

<0.05). The use of treatment-specific utility values in the CEM was explored in a scenario analysis. The coefficient for health state (i.e., pre-progression vs. post-progression) was significant in all populations (p <0.001) supporting modelling of differences in utility values for the progression-free and progressed disease health states in the CEM.

The mean utility values from the mixed effects model are reported by treatment arm and pooled across treatment arms in for the progression free, and post-progression health states (Table 31.).

Table 31. Overview of health state utility values

	Results [SEs]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression free	EV+P: [redacted] Plat+Gem: [redacted] Combined: [redacted]	EQ-5D-5L	DK	Health state utilities were derived from a mixed-effect model.
Progressed disease	EV+P: [redacted] Plat+Gem: [redacted] Combined: [redacted]	EQ-5D-5L	DK	

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

Not applicable. Only used for disutilities.

10.3.2 Data collection

Not applicable. Only used for disutilities.

10.3.3 HRQoL Results

Not applicable. Only used for disutilities.

10.3.4 HSUV and disutility results

To account for disutilities associated with adverse events, existing literature was used to inform decrements in the CEM. For these AEs, durations were calculated as the total number of days that each patient experiences a specific AE, even if that event was experienced more than once. An overview of the literature health state utility values is presented in Table 32.

Table 32. Overview of literature-based health state utility values

Disutilities	Decrement	Duration	QALY decrement	Decrement source	Duration source
Acute kidney injury	0.075	7.0	0.001	TA772[58]	TA772 [58]
Anaemia	0.090	28.0	0.007	Beusterien et al. 2010/TA788[59]	TA581/TA788 [70]
Fatigue	0.073	108.0	0.022	Decrement: Nafees et al. 2008/TA788[59]	TA581/TA788 [70]
Hyperglycemia	[redacted]	[redacted]	[redacted]	Decrement: TA858, assumed as anaemia[61]	Time to resolution hyperglycaemia EV-302
Hyponatraemia	[redacted]	[redacted]	[redacted]	Assume same as hyperglycaemia	Assumed same as hyperglycaemia
Neutropenia	0.090	12.3	0.003	Nafees et al. 2008[59]	TA772 [58]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	Assumed same as neutropenia	Assumed same as neutropenia
Platelet count decreased	[redacted]	[redacted]	[redacted]	Assumed same as thrombocytopenia	Assumed same as thrombocytopenia
Rash maculo-papular	[redacted]	[redacted]	[redacted]	Nafees et al. 2008/TA788, assumed rash[70]	Time to resolution skin disorders EV-302
Thrombocytopenia	0.080	34.0	0.007	TA780/581[60]	TA780/581 [60]
Urinary tract infection	0.009	14.0	0.000	Sullivan et al., 2006 (ICD-9 599)/TA788[70]	TA788 [70]
Neuropathy (Grade 2)	0.330	76.0	0.069	Assumed to be the same as Neuropathy grade 3+	Expert consultation

Peripheral neuropathy (Grade 3+)	0.33	76.0	0.069	Swinburn et al., 2015/TA772[58]	Expert consultation

11. Resource use and associated costs

Costs and resource use vary dependent on the administered treatment and health states. The model includes direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines.[51] Costs included in the model were categorised by type and by health state in which they occur; that is, pre-progression, post-progression, and death costs. Costs related to pre-progression included drug costs (acquisition and administration costs), treatment-specific monitoring costs, healthcare resource use costs associated with the pre-progression state, AE costs. Costs related to post-progression included drug costs (acquisition and administration costs of subsequent treatment), and healthcare resource use costs associated with the post-progression state. All costs were valued in 2024 Danish Krone (DKK).

The following section regarding cost and resource use is presented per health state, containing information regarding drug acquisition costs, disease management costs and AE costs. Drug costs are sourced from Medicinpriser.dk[71] and applied as pharmacy purchasing prices (AIP). Disease management and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2024[72] and DMC catalogue for unit cost.[73] Patient and transportation costs are also based on the DMC catalogue for unit costs.[73] and are presented in a separate section covering all patient- and transportation costs for all health states.

11.1 Medicine costs - intervention and comparator

The dosage for the pharmaceuticals (intervention and comparator) applied in the model are summarized in Table 33.

Table 33. Dosage used in the model

Regimen	Medicine	Dose	Relative dose intensity**	Frequency	Vial sharing
EV+P	Enfortumab vedotin	1.25 mg/kg	XXXXX	Day 1 and 8, every third week	No
	Pembrolizumab	200 mg	XXXXX	Every third week	No

SOC	Gemcitabine	100 mg /m^2	XXXXX	Day 1 and 8, every third week	No
	Cisplatin	70 mg/m^2	XXXXX	Every third week	No
	Gemcitabine	100 mg/m^2	XXXXX	Day 1 and 8, every third week	No
	Carboplatin	450 mg	100%*	Every third week	No
	Avelumab	800 mg	95.1%[81]	Every second week	No

Notes: *No available data on carboplatin RDI, assumed 100%. ** RDI = ADI / IDI x 100%" where IDI is the intended dose intensity per study protocol (i.e., 70 mg/m2/3-week cycle), and ADI is defined as the actual dose per unit of time that a subject received over the entire treatment period. For the purpose of calculating ADI, treatment period is defined as the time from first dose of treatment to Day 21 of last treatment cycle that it was administered, regardless of whether death occurs before the end of cycle
Abbreviations: kg, kilograms; m2, square meter; mg, milligrams; SOC, standard of care

Drug dosing and unit cost for each intervention are summarised in

Table 34 and Table 35, respectively. Drug acquisition costs for the comparators were based on the list prices derived from Medicinpriser.dk. Where multiple formulation sizes are available, the lowest cost per mg was selected. For EV+P, dosing was based on the EV-302 trial protocol, assuming a 1.25 mg/kg dose of EV intravenously on days one and eight and a 200 mg dose of pembrolizumab intravenously on day one of a three-week cycle.[64] Drug costs are assumed to be incurred according to the time on treatment curve and all comparators.

Costs for the SoC arm was calculated by weighting the individual treatment costs based on the proportion of patients receiving one of the two Plat+Gem regimens in EV-302: 1) gemcitabine + cisplatin, 2) gemcitabine + carboplatin. Dosing for gemcitabine, carboplatin, and cisplatin was based on the EV-302 trial and consistent with the EMA labels.[47] Costs for gemcitabine + cisplatin and gemcitabine + carboplatin were weighted by their respective uptake in the EV-302 study, which in the ITT population was 51% and 49%, respectively. Drug dosing for avelumab maintenance was based on the EMA label, assuming an 800 mg dose on day one of a two-week cycle for non-progressors following Plat+Gem. The avelumab maintenance cost was applied after a maximum of six cycles of Plat+Gem and following a treatment-free washout period of five weeks (based on EV-302 data), with the proportion of patients receiving avelumab maintenance being 30% as reported in EV-302.

The average weight (75.89 kg) and BSA (1.88 m^2) were based on the EV-302 trial data[64]. Given the prevalence of weigh/BSA-based dosing among the alternative regimens, it was considered appropriate for the base case to use the method of moments approach to estimate the average dose per treatment by considering the distribution of patient

weight or BSA in the trial (i.e., considers wastage). Total acquisition costs per cycle were calculated based on dosage and administrations per cycle. Costs per cycle were converted to costs per week accounting for the treatment cycle length. Costs were modelled on a weekly basis with the costs of wastage considered in the base case. No wastage was considered when calculating the costs of drugs administered at a fixed dose. We assumed treatment costs to be applied as weekly average costs, to accommodate complex dosing of EV and gemcitabine, to clearly implement stopping rules, and to allow a flexible washout period for avelumab.

Table 34. Medicine costs used in the model

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Source
Enfortumab vedotin	20 mg	1 pcs	4,643.30	Medicinpriser.dk (2024)[71]
	30 mg	1 pcs	6,964.14	Medicinpriser.dk (2024)[71]
Pembrolizumab	25 mg/ml	4 ml	21,574	Medicinpriser.dk (2024)[71]
Gemcitabine	40 mg/ml	25 ml	1,000.00	Medicinpriser.dk (2024)[71]
	10 mg/ml	120 ml	310.00	Medicinpriser.dk (2024)[71]
	10 mg/ml	140 ml	330.00	Medicinpriser.dk (2024)[71]
	10 mg/ml	160 ml	350.00	Medicinpriser.dk (2024)[71]
	10 mg/ml	180 ml	370.00	Medicinpriser.dk (2024)[71]
	10 mg/ml	200 ml	385.00	Medicinpriser.dk (2024)[71]
	10 mg/ml	220 ml	420.00	Medicinpriser.dk (2024)[71]
Cisplatin	1 mg/ml	50 ml	100.00	Medicinpriser.dk (2024)[71]
	1 mg/ml	100 ml	200.00	Medicinpriser.dk (2024)[71]
Carboplatin	10 mg/ml	10 ml	95.68	Medicinpriser.dk (2024)[71]
	10 mg/ml	45 ml	226.00	Medicinpriser.dk (2024)[71]
Avelumab	20 mg/ml	10 ml	6,338.80	Medicinpriser.dk (2024)[71]

Abbreviations: DKK, Danish krone; kg, kilograms; m2, square meter; mg, milligram

Table 35. Drug dosing and total acquisition costs

Regimen	Medicine	Cost per treatment cycle [DKK]	Modelled cost per week [DKK]

EV+P		Enfortumab vedotin	37.600,79	12.533,60
		Pembrolizumab	-	13.274,94
SOC	Gemcitabine + cisplatin (51% in ITT)	Gemcitabine	697,07	329,94
		Cisplatin	292,77	
	Gemcitabine + carboplatin (49% in ITT)	Gemcitabine	697,07	307,69
		Cisplatin	-	
	Avelumab maintenance (30% in ITT)		-	12.048,16

Notes:

Abbreviations: ITT, intention-to-treat; SOC, standard of care.

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

Administration costs (Table 36) were obtained from DRG tariffs 2024.[74] The administration frequency of EV and P were based on the dosing schedule from the EV-302 study protocol (ISN/Protocol 7465-CL-0301).[47] For the SoC, the frequency of healthcare visits per month was based on the CSR.[57] As all drugs in the model are administered IV, the cost per administration were assumed to be the same.

Table 36. Administration costs used in the model

Regimen	Medicine	Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
EV+P*	EV	IV infusion	Day 1 and 8 every 3rd week	1,550.00	11MA98	DRG, 2024[74]
	P	IV infusion	Day 1 every 3rd week	1,550.00	11MA98	DRG, 2024[74]
SoC	Gemcitabine	IV infusion	Day 1 and 8 every 3rd week	1,550.00	11MA98	DRG, 2024[74]
	Cisplatin	IV infusion	Day 1 every 3rd week	1,550.00	11MA98	DRG, 2024[74]

	Carboplatin	IV infusion	Day 1 every 3rd week	1,550.00	11MA98	DRG, 2024[74]
	Avelumab maintenance	IV infusion	Day 2 every 2nd week	1,550.00	11MA98	DRG, 2024[74]

Abbreviations: EV, enfortumab vedotin; IV, intravenous; P, pembrolizumab; SoC, standard of care

11.4 Disease management costs

Drug monitoring costs per treatment cycle were informed by requirements for each agent, as these differ by intervention. Periodic monitoring requirements were based on the EMA and Electronic Medicines Compendium (EMC) prescribing information for medicines and are presented in Table 37. For EV+P, monitoring use is accounted for either as a combination therapy or as monotherapies and is applied dependent on the respective duration of treatment and stopping rules applied. EV monotherapy monitoring was assumed to be the same as for pembrolizumab. All monitoring costs were calculated using ToT for each regimen and were half-cycle corrected.

The unit costs of monitoring were sourced from interaktiv.drg.[74] Drug monitoring costs used in the model are presented in Table 37.

Table 37. Disease management costs used in the model based on treatment cycle

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Blood count	Every 3rd week* Every 2nd week**	1,550.00	DRG: 11MA98 Diagnose code: DC679M Procedure code: ZZ0149W	Interaktiv.drg[74]
Hepatic function	Every 3rd week* Every 2nd week**	0.00	To avoid double counting, it was assumed that this cost was already included in the cost of the item "blood count".	
Adrenal function	Every 3rd week* Every 2nd week**	0.00	To avoid double counting, it was assumed that this cost was already included in the cost of the item "blood count".	
Renal function	Every 3rd week* Every 2nd week**	0.00	To avoid double counting, it was assumed that this cost was already included in the cost of the item "blood count".	

Thyroid function	Every 3rd week* Every 2nd week**	0.00	To avoid double counting, it was assumed that this cost was already included in the cost of the item "blood count".	
CT scan	Every 2nd month* Every 6th week**	2,585.00	DRG: 30PR06 Diagnose code: DC679M Procedure code: UXCD75	Interaktiv.drg[74]

*Applicable to P and EV (both in combination and as monotherapies) as well as gemcitabine + PBC
**Applicable to avelumab (treatment cycle 14 days)
Abbreviations: CT, computed tomography; DRG, diagnosis-related group

Costs associated with additional healthcare resource use whilst in the progression-free and progressed disease health states were accounted for within the CEM. These health state specific costs were assumed to be the same for all treatment arms and applied based on time spent in each health state. The healthcare activity (e.g., type of physician/nurse visit) and frequency of visits per month for each health state was sourced from TA788[70], and are presented in Table 38. The unit costs were sourced from the most recent version of the DMCs 'Katalog for enhedsomkostninger', 2023.[73] and adjusted to 2024 pricing using the net price index excluding energy[75] (Table 38). Based on the monthly frequencies and the unit costs, a total monthly cost per health state was calculated. The monthly costs were converted to weekly costs to align with the model cycle length.

Table 38. Routine care, progression-free and progressed health state (per month)

Activity	PF, frequency per month	PD, frequency per month	Reference	Unit cost [DKK]	Reference
Oncologist follow-up visit	0.88	0.93	TA788[81]	801.10	DMC 2023[73] - First consultation with a specialist
Clinical nurse specialist	0.62	1.00	TA788[81]	453.00	DMC 2023[73] - Nurse hourly rate
Dietician	0.06	0.16	TA788[81]	326.00	DMC 2023[73] - Nutritionist hourly rate
Urologist	0.07	0.04	TA788[81]	801.10	DMC 2023[73] - First consultation with a specialist
District nurse	0.27	0.96	TA788[81]	455.00	DMC 2023[73] - Municipality nurse hourly rate

Abbreviations: GP, general practitioner; PD, progressed disease; PF, progression free; TA, technology appraisal.

11.5 Costs associated with management of adverse events

The costing codes and unit costs of hospitalisation associated with the management of AEs included within the CEM were sourced from interaktiv.drg.[74] The cost of managing AEs were applied once during the first model cycle, aligning with the application of AE utility decrements, as treatment-related AEs were assumed to be associated with treatment initiation instead of occurring on an ongoing basis throughout the entire treatment course. The costs associated with the management of each AE were multiple by the frequency reported in Table 26. The costs of treating AEs are shown in Table 39.

Table 39. Cost associated with management of adverse events

Adverse event	DRG code	Unit cost/DRG tariff[74]
Acute kidney injury	DRG: 11MA01 Action diagnosis: DN179 Secondary diagnosis: DC679M	49,298.00
Anaemia	DRG: 16MA98 Action diagnosis: DD649 Secondary diagnosis: DC679M	2,111.00
Fatigue	DRG: 21MA98 Action diagnosis: DT983D5 Secondary diagnosis: DC679M	1,684.00
Hyperglycaemia	DRG: 23MA03 Action diagnosis: DR739 Secondary diagnosis: DC679M	5,103.00
Hyponatraemia	DRG: 10MA98 Action diagnosis: DE871A Secondary diagnosis: DC679M	1.847,00
Neutropenia	DRG: 16MA98 Action diagnosis: DD709 Secondary diagnosis: DC679M	2,111.00
Neutrophil count decreased	DRG: 16MA98 Action diagnosis: DD709 Secondary diagnosis: DC679M	2,111.00
Rash maculo-papular	DRG: 09MA98 Action diagnosis: DR219 Secondary diagnosis: DC679M	1,625.00
Thrombocytopenia	DRG: 16MA98 Action diagnosis: DD696 Secondary diagnosis: DC679M	2,111.00
Urinary tract infection	DRG: 11MA98 Action diagnosis: DN289	1,550.00

	Secondary diagnosis: DC679M	
Neuropathy (Grade 2)	DRG: 21MA98 Action diagnosis: DT983DD Secondary diagnosis: DC679M	1,684.00
Peripheral neuropathy (Grade 3+)	DRG: 01MA98 Action diagnosis: DG629 Secondary diagnosis: DC679M	1,941.00

Abbreviations: DRG, diagnosis-related group

11.6 Subsequent treatment costs

Following first-line therapy, it was anticipated a proportion of the population would go on to receive subsequent systemic therapy after disease progression. The option to include the cost of subsequent treatments is available in the model, whereby interventions and their respective distributions was informed by EV-302 data using a ≥3% threshold for uptake in either arm of the study.[57] The cost of subsequent therapies for each treatment arm was calculated as a weighted average cost considering the distribution of subsequent treatments received in second line and beyond, treatment costs per cycle (drug acquisition and administration), as well as median treatment duration and patient distributions, which was informed by EV-302 trial data. Dosing for subsequent treatment interventions were either based on the EV-302 trial or consistent with the EMA label for interventions not evaluated in EV-302. Duration of subsequent therapies were based on post-hoc analysis of EV-302.[65] The subsequent treatment unit costs are shown in Table 40.

The distribution of subsequent treatments for each arm was obtained from the EV-302 CSR and IPD post-hoc analysis[57] and is outlined in Table 41.

Table 40. Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment (months)
Enfortumab vedotin	20 mg	1 pcs	4,643.30	100%	XXXXX
	30 mg	1 pcs	6,964.14	100%	XXXXX
Pembrolizumab	25 mg/ml	25 ml	21,573.58	100%	XXXXX
Gemcitabine	40 ml/mg	25 ml	1,000.00	100%	XXXXX
	10 mg/ml	120 ml	310.00	100%	XXXXX
	10 mg/ml	140 ml	330.00	100%	XXXXX
	10 mg/ml	160 ml	350.00	100%	XXXXX
	10 mg/ml	180 ml	370.00	100%	XXXXX
	10 mg/ml	200 ml	385.00	100%	XXXXX
	10 mg/ml	220 ml	420.00	100%	XXXXX
Cisplatin	1 mg/ml	50 ml	100.00	100%	XXXXX
	1 mg/ml	100 ml	200.00	100%	XXXXX
Carboplatin	10 mg/ml	15 ml	95.68	100%	XXXXX
	10 mg/ml	45 ml	226.00	100%	XXXXX
Atezolizumab	840mg	1 vial	20,265.86	100%	XXXXX
	1200mg	1 vial	28,952.64	100%	XXXXX
Docetaxel	20 mg/ml	1 ml	35.00	100%	XXXXX
	80 mg/4ml	4 ml	150.00	100%	XXXXX
	160 mg/8ml	8 ml	309.00	100%	XXXXX
Paclitaxel	6 mg/ml	16.7 ml	110.50	100%	XXXXX
	6 mg/ml	25 ml	1,500.00	100%	XXXXX
	6 mg/ml	50 ml	201.50	100%	XXXXX
Vinflunine	25 mg/ml	2 ml	1,749.00	100%	XXXXX
	25 mg/ml	10 ml	8,746.00	100%	XXXXX

Table 41. Distribution of subsequent treatments

	EV + P, %[57]	SOC,%
Gemcitabine + cisplatin	XXXXX	XXXXX
Gemcitabine + carboplatin	XXXXX	XXXXX
Atezolizumab	XXXXX	XXXXX
Pembrolizumab	XXXXX	XXXXX
Docetaxel	XXXXX	XXXXX
EV	XXXXX	XXXXX
Paclitaxel	XXXXX	XXXXX
Vinflunine	XXXXX	XXXXX

11.7 Patient costs

The unit costs from DMC's catalogue of unit costs were applied in the model, with a patient hour being costed as DKK 205.27, and travel expenses were assumed to be DKK 141.56 per roundtrip, as per DMC's unit cost catalogue adjusted for 2024 pricing.[70,76] The administration duration for EV+P was determined from the 302 study protocol.[47] For SoC, the durations for gemcitabine, cisplatin, and carboplatin were sourced from Rigshospitalet[77], while the duration for avelumab came from Herlev Hospital. [78] Duration of treatment administration (chair time) per hospital visit for each regimen are listed in Table 42.

Table 42. Administration duration per visit

Regimen	Administration duration per visit
EV+P[47]	EV: 30 minutes P: 30 minutes
SoC[62,78]	Gemcitabine: 30 minutes Cisplatin: 120 minutes or carboplatin: 60 minutes Avelumab maintenance (non-progressors): 60 minutes

Abbreviations: EV, enfortumab vedotin; P, pembrolizumab; SoC, standard of care

In the EV+P arm, it was assumed that each visit would take an average of 2 hours patients' time in the PF health state, accounting for additional time spent in the hospital apart for chair time. For Plat+Gem, the average patient time was derived from Rigshospitalet[62] and was assumed to be 4 hours and 45 minutes. Avelumab maintenance therapy was assumed to be administered for a duration of one hour[78]. Furthermore, an additional 0.5 hours was anticipated for related activities.

It was assumed that all treatments within a given arm could be combined during a single hospital visit, with the associated disease management activities (monitoring and AEs) conducted concurrently during the hospital visit. The frequency of transportation (one roundtrip) was assumed to match the frequency of hospital visits. The activity assumption is presented in Table 43.

Patient costs for progressed disease were applied uniformly to both arms. The patient costs associated with hospital visits were calculated using a weighted average of the frequencies of all subsequent treatments in the model. It was assumed that the frequency of transportation matched the frequency of hospital visits, and that each hospital visit averaged four hours. Disease management costs and the management of adverse events were again considered to be included in the regular hospital visits for therapy administration.

Table 43. Patient costs used in the model

Activity	Time spent [hours, minutes]
Hospital visit, EV+P, progression-free	Patient time assumption: 2 hours[57]
Hospital visit: SoC, progression-free	Patient time assumption: Plat+Gem 4 hours and 45 minutes[62] Avelumab maintenance: 1 hour[78] and 30 minutes
Hospital visit: EV+P, progressed disease	Patient time assumption: 4 hours
Hospital visit: SoC, progressed disease*	Patient time assumption: 4 hours

Abbreviations: EV, Enfortumab vedotin; Gem, gemcitabine; P, pembrolizumab; Plat, platinum based chemotherapy (cisplatin or carboplatin), SoC, standard of care

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Palliative care costs were excluded, as they are not typically included in the assessment by DMC.

12. Results

12.1 Base case overview

The base case overview is presented in Table 44 with the results of the base case presented in Table 45.

Table 44. Base case overview

Feature	Description
Comparator	SoC
Type of model	Partitioned survival model
Time horizon	30 years (lifetime)
Treatment line	Subsequent treatments included
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in EV-302. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs, hospital costs, costs of adverse events, patient costs
Dosage of medicine	Based on weight and surface body area
Average time on treatment	EV+P: EV: XXXXX Plat+Gem: XXXXX Avelumab: XXXXX
Parametric function for PFS	Intervention: Generalised gamma Comparator: Log-logistic
Parametric function for OS	Intervention: Log-logistic Comparator: Log-logistic
Inclusion of waste	Yes, no vial sharing
Average time in model health state (months)	PF: EV+P: XXXXX, Plat+Gem: XXXXX PD: EV+P: XXXXX, Plat+Gem: XXXXX

Abbreviations: EV, Enfortumab vedotin; EQ-5D-5L, EuroQoL 5-dimension 5-level; P, pembrolizumab; PD, progressed disease; PF, progression-free; Plat+Gem, platinium-based chemotherapy plus gemcitebine.

12.1.1 Base case results

Table 45 presents the discounted base case results for the first-line treatment of la/mUC with EV+P versus SoC. The comparison indicates a net QALY gain of XXXXX at an incremental cost of DKK XXXXX. Results suggest that EV+P is more effective but also more costly than SoC, with an overall ICER of DKK XXXXX per QALY.

Table 45. Base case results, discounted estimates

	EV+P	SoC	Difference
Drug acquisition costs	XXXXX	XXXXX	XXXXX
Drug administration costs	XXXXX	XXXXX	XXXXX
Adverse event costs	XXXXX	XXXXX	XXXXX
Monitoring costs	XXXXX	XXXXX	XXXXX
Subsequent treatment	XXXXX	XXXXX	XXXXX
Subsequent administration cost	XXXXX	XXXXX	XXXXX
PF and PD health state costs	XXXXX	XXXXX	XXXXX
Patient and transport cost	XXXXX	XXXXX	XXXXX
Total costs	XXXXX	XXXXX	XXXXX
Life years gained (PF)	XXXXX	XXXXX	XXXXX
Life years gained (PD)	XXXXX	XXXXX	XXXXX
Total life years	XXXXX	XXXXX	XXXXX
QALYs (PF)	XXXXX	XXXXX	XXXXX
QALYs (PD)	XXXXX	XXXXX	XXXXX
QALYs (adverse reactions)	XXXXX	XXXXX	XXXXX
Total QALYs	XXXXX	XXXXX	XXXXX
Incremental costs per life year gained	**DKK** XXXXXXX		
Incremental cost per QALY gained (ICER)	**DKK** XXXXXXX		

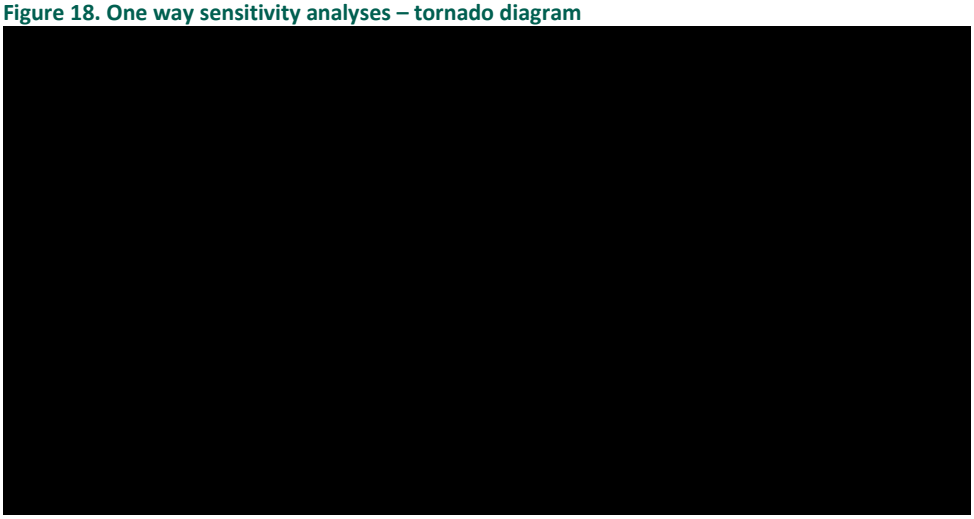
12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available or using standard errors estimated based on ±10% variation around the mean where measures of variance around the base case values were not available. Pairwise one way sensitivity analyses were performed separately for each comparator and are reported for the 10 most influential parameters on the ICER.

OWSA results for EV+P versus SoC are presented in Figure 18 and Table 46. The OWSA showed that the parameters with the greatest influence on the ICER were the proportion of patients receiving avelumab maintenance, the discount rates weight. Overall, the analysis illustrates robustness to univariant analyses.

Figure 18. One way sensitivity analyses – tornado diagram



Abbreviations: ICER, Incremental cost-effectiveness ratio; PF, progression free; EV, enfortumab vedotin; P, pembrolizumab; SoC, standard of care; PBC, platinum-based chemotherapy; PFS, progression free survival; AE, adverse event; HCRU, health care resource use.

Table 46. One way sensitivity analyses

Parameter	Parameter variation		ICER		
	Low value	High value	At low value	At high value	Difference
Proportion of patients receiving avelumab maintenance	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Discount rate - Outcomes	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Weight	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Health state utility values, PF - EV + P	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Time horizon	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Age (at baseline)	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Administration cost, Subsequent Elements of a Chemotherapy Cycle	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Monitoring frequency - Blood count ()	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Discount rate - Cost	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Pre-progression treatment SOC: Gemcitabine + PBC [1], Pembrolizumab	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX

Abbreviations: ICER, Incremental cost-effectiveness ratio; PF, progression free; EV, enfortumab vedotin; P, pembrolizumab; SoC, standard of care; PBC, platinum-based chemotherapy; PFS, progression free survival; AE, adverse event

12.2.1.1 Scenario analysis

Scenario analyses were performed to test the impact of change in key inputs and assumptions on the CE estimates. Table 47 lists the scenarios conducted around the base case analysis presented above. These scenarios included an alternative time horizon, discount rates, extrapolations of OS, PFS and ToT, changes to costs, utilities, and other assumptions.

Given the average age of the patient population, an alternative and plausible time horizon of 20 years was explored. To assess the impact of discounting, more extreme values have been selected and presented in scenarios. Furthermore, alternative parametric curves for OS, PFS, and ToT were explored based on clinical plausibility, AIC/BIC fit, and visual goodness-of-fit curves. As discussed in section 10.2.3, treatment-specific utility values were included in a separate scenario.

The results of the scenario analyses (Table 47) illustrates the robustness of the analysis with ICER results varying from [redacted] per QALY. Based on the EV-302 trial follow-up time, it is expected that different extrapolations impact the results, but generally the scenario analyses confirm the findings in the deterministic base case. The ICER drops noticeably, in the scenarios where a higher proportion of patients are receiving avelumab as maintenance treatment.

Table 47. Scenario analyses for the health economic model

Scenario	Inc. costs	Inc. QALYs	ICER
BASE CASE	[redacted]	[redacted]	[redacted]
Time horizon	[redacted]	[redacted]	[redacted]
20-years	[redacted]	[redacted]	[redacted]
Discount rates	[redacted]	[redacted]	[redacted]
0% for costs, LYs and QALYs	[redacted]	[redacted]	[redacted]
6% for costs, LYs and QALYs	[redacted]	[redacted]	[redacted]
PFS EV+P	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
ToT EV	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
ToT P	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
OS EV+P	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
PFS Plat+Gem	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
OS Plat+Gem	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]

ToT avelumab	XXXXX	XXXXX	XXXXX
Weibull	XXXXX	XXXXX	XXXXX
Costing scenarios	XXXXX	XXXXX	XXXXX
No wastage	XXXXX	XXXXX	XXXXX
Utility scenarios	XXXXX	XXXXX	XXXXX
Treatment dependent progression-free utilities	XXXXX	XXXXX	XXXXX

12.2.2 Probabilistic sensitivity analyses

A probabilistic analysis was conducted to account for the joint uncertainty of the underlying parameter estimates. The choice of distribution (beta, gamma, log-normal, normal and Dirichlet) applied to parameters was selected based on recommendations outlined in Briggs et al. 2008[79]. Standard errors (SEs) were taken directly from source data if reported or calculated from published standard deviations (SD) sample size and/ or 95% confidence interval data. If none were reported SE is estimated as 20% of the default value. The probabilistic base case was run with 1000 iterations following a visual assessment to ensure adequate convergence of mean ICER estimates (Figure 21).

The probabilistic results XXXXX XXXXX XXXXX align well with deterministic results XXXXXXXXXXXXXXX. The scatterplot of all the PSA iterations is presented in Figure 19, while Figure 20 presents the cost-effectiveness acceptability curves (CEAC). The scatterplot confirms that EV+P is more efficacious but also more expensive compared to SoC. The CEAC indicates approximately XXXXX XXXXX XXXXX XXXXX XXXXX XXXXX XXXXX.

Figure 19. Cost-effectiveness scatterplot

Abbreviations: EV, enfortumab vedotin; P, pembrolizumab; QALY, quality adjusted life year; SOC, standard of care

Figure 20. Cost-effectiveness acceptability curves for EV+P and Plat+Gem

Abbreviations: EV, enfortumab vedotin; P, pembrolizumab; QALY, quality adjusted life year; SOC, standard of care; WTP, willingness to pay threshold; PBC, platinum-based chemotherapy

Figure 21. ICER convergence over number of simulations

Abbreviations: ICER, incremental cost effectiveness ratio

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending EV+P in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the DMC guidelines.

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where EV+P is recommended as a standard treatment and the scenario where EV+P is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

The DMC has estimated that each year, approximately 150 patients receive systemic oncological treatment for newly diagnosed advanced urothelial cancer.[24] Of these, in case EV+P were to be introduced, XXXX will receive EV+P in the first year. The share is assumed to grow up to approximately XXXXX XXXXX.

Table 48. Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
EV+P	75	130	130	130	130
Standard of care	75	20	20	20	20
			Non-recommendation		
EV+P	0	0	0	0	0
Standard of care	150	150	150	150	150

Note: 50% to EV+P in the first year and 86% to EV+P in years 2-5 in case the medicine is introduced

Budget impact

Table 49. Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
The medicine under consideration is NOT recommended	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Budget impact of the recommendation	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX

14. List of experts

Not applicable.

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Appendix A. Main characteristics of studies included

Table 50. Main characteristic of studies included

Trial name: EV-302	**NCT number: NCT04223856**
Objective	This study is being conducted to evaluate the combination of enfortumab vedotin + pembrolizumab versus standard of care gemcitabine + platinum-containing chemotherapy, in subjects with previously untreated locally advanced or metastatic urothelial cancer.
Publications – title, author, journal, year	Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, van der Heijden MS. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med. 2024;390(10):875-888.
Study type and design	An Open-label, Randomized, Controlled Phase 3 Study of Enfortumab Vedotin in Combination With Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer
Sample size (n)	Total N = 886 Arm A: EV+P, N = 442 Arm B: Plat+Gem, N = 444
Main inclusion criteria	Histologically documented, unresectable locally advanced or metastatic urothelial carcinoma Measurable disease by investigator assessment according to RECIST v1.1 Participants with prior definitive radiation therapy must have measurable disease per RECIST v1.1 that is outside the radiation field or has demonstrated unequivocal progression since completion of radiation therapy Participants must not have received prior systemic therapy for locally advanced or metastatic urothelial carcinoma with the following exceptions: Participants that received neoadjuvant chemotherapy with recurrence >12 months from completion of therapy are permitted Participants that received adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy are permitted Must be considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, in the investigator's judgment Archival tumor tissue comprising muscle-invasive urothelial carcinoma or a biopsy of metastatic urothelial carcinoma must be provided for PD-L1 testing prior to randomization

	Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2 Adequate hematologic and organ function
Main exclusion criteria	Previously received enfortumab vedotin or other monomethyl auristatin E (MMAE)-based antibody-drug conjugate (ADCs) Received prior treatment with a programmed cell death ligand-1 (PD-(L)-1) inhibitor for any malignancy, including earlier stage urothelial cancer (UC), defined as a PD-1 inhibitor or PD-L1 inhibitor Received prior treatment with an agent directed to another stimulatory or co inhibitory T-cell receptor Received anti-cancer treatment with chemotherapy, biologics, or investigational agents not otherwise prohibited by exclusion criterion 1-3 that is not completed 4 weeks prior to first dose of study treatment Uncontrolled diabetes Estimated life expectancy of less than 12 weeks Active central nervous system (CNS) metastases Ongoing clinically significant toxicity associated with prior treatment that has not resolved to ≤ Grade 1 or returned to baseline Currently receiving systemic antimicrobial treatment for active infection (viral, bacterial, or fungal) at the time of randomization. Routine antimicrobial prophylaxis is permitted. Known active hepatitis B, active hepatitis C, or human immunodeficiency virus (HIV) infection. History of another invasive malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class IV within 6 months prior to randomization Receipt of radiotherapy within 2 weeks prior to randomization Received major surgery (defined as requiring general anesthesia and >24 hour inpatient hospitalization) within 4 weeks prior to randomization Known severe (≥ Grade 3) hypersensitivity to any enfortumab vedotin excipient contained in the drug formulation of enfortumab vedotin Active keratitis or corneal ulcerations History of autoimmune disease that has required systemic treatment in the past 2 years History of idiopathic pulmonary fibrosis, organizing pneumonia, drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

	Prior allogeneic stem cell or solid organ transplant Received a live attenuated vaccine within 30 days prior to randomization
Intervention	Enfortumab vedotin + pembrolizumab. Enfortumab vedotin at a dose of 1.25 mg per kg of body weight IV on days 1 and 8 of every 3-week cycle. Pembrolizumab at a dose of 200 mg IV on day 1 of every 3-week cycle with a maximum of 35 treatment cycle.
Comparator(s)	Gemcitabine + platinum-containing chemotherapy (cisplatin or carboplatin). Chemotherapy was used for a maximum of six 3-week cycles. Gemcitabine as an IV infusion on days 1 and 8 of every 3-week cycle. Cisplatin administered as IV infusion on day 1 of each 3-week cycle, or carboplatin dosed according to local guidelines and administered as IV infusion on day 1 of each 3-week cycle.
Follow-up time	Up to approximately 5 years
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	*Primary endpoints* • progression-free survival (PFS)) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by blinded independent central review (BICR) • overall survival (OS). *Secondary endpoints:* • Objective response rate (ORR) per RECIST v1.1 by BICR • Time to pain progression (TTPP) • Mean change from baseline in worst pain at Week 26 • Duration of PFS per RECIST v1.1 by investigator assessment • ORR per RECIST v1.1 by investigator assessment • Duration of response (DOR) per RECIST v1.1 by BICR • DOR per RECIST v1.1 by investigator assessment • Disease control rate (DCR) per RECIST v1.1 by BICR • DCR per RECIST v1.1 by investigator assessment • Change from baseline in patient reported outcome assessment measured by the EuroQOL Five Dimensions Questionnaire 5L (EQ-5D-5L) • Mean scores in patient reported outcome assessment measured by the EQ-5D-5L

	◦ Change from baseline in patient reported outcome assessment measured by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)
	◦ Mean scores in patient reported outcome assessment measured by EORTC QLQ-C30
	◦ Incidence of adverse events (AEs)
	◦ Incidence of laboratory abnormalities
	◦ Treatment discontinuation rate due to AEs
	Endpoints included in this application:
	• PFS per RECIST v1.1 by BICR
	• OS
	• Clinical response:
	  • ORR per RECIST v1.1 by BICR
	  • DOR per RECIST v1.1 by BICR
	  • DCR per RECIST v1.1 by BICR
	• Patient reported outcomes:
	  • Change from baseline in patient reported outcome assessment measured by the EQ-5D-5L
	  • Mean scores in patient reported outcome assessment measured by the EQ-5D-5L

Method of analysis	The primary analysis of each efficacy endpoint was based on data from subjects in the ITT analysis set or response evaluable analysis set. For primary endpoints of OS and PFS, a log-rank test stratified by randomization stratification factors was used to compare the experimental arm to the control arm. The estimated HR and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model was also presented. The median survival time was estimated using the Kaplan-Meier method and was reported along with the corresponding 95% confidence interval by treatment arm. Similar estimation methods were used for the other time-to-event endpoints. DOR was summarized descriptively by Kaplan-Meier methods for subjects with a confirmed response (complete response or partial response per RECIST v1.1). ORR, DCR, and DOR were analyzed using the response evaluable set. P-values for the comparison of ORR and DCR in the experimental arm and the control arm, using the Cochran Mantel-Haenszel test stratified by randomization stratification factors, were reported. The frequency of AEs and SAEs were categorized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOCL). In addition, summary statistics or listings were provided for the following safety parameters: laboratory values, vital sign measurements, ECGs, and ECOG performance status. Descriptive statistics were provided for antibody drug-conjugate and unconjugated drug (MMAE) concentrations in Arm A at each PK

	sampling time point. The incidence of anti-therapeutic antibodies (ATA) were summarized. Completion and compliance rates along with change from baseline for each domain of the PROs, including EQRTC QLQ-C30, EQ-5D-5L, and BPI-SF were summarized. Cumulative incidence of HRU, including length of stay, hospitalizations, and ER visits were summarized by treatment arm and by cycle. Additionally, TTPP and mean changes from baseline in worst pain at Week 24 were evaluated.
Subgroup analyses	Subgroup analyses of OS, PFS, ORR, DCR, ToT, grade 3+ TEAEs, and HSUVs were explored in populations expected to be of interest to healthcare professionals and payers. All analyses were post-hoc. The subgroups of interest included the following: Cisplatin-eligible Defined as not meeting any of the criteria for cisplatin ineligibility (see below) Cisplatin-ineligible Defined as meeting at least one of the following criteria (EV-302 protocol)[1]: Glomerular filtration rate (GFR) <60 mL/min but >30mL/min, ECOG or World Health Organization (WHO) PS of 2, NCI CTCAE Grade ≥2 audiometric hearing loss, or New York Heart Association (NYHA) Class III heart failure. PD-L1 high (CPS ≥10 based on Dako/Agilent PD-L1 Immunohistochemistry [IHC] 22C3 PharmDx)18 PD-L1 low (CPS <10) Cisplatin-ineligible and high PD-L1 Cisplatin-ineligible and low PD-L1 Avelumab maintenance accessible population This subgroup included patients randomized in EV-302 after regulatory approval of avelumab at the country/regional level as applicable to included study sites. This definition aligned with the analysis population that was requested by the FDA, which defined avelumab availability using regional regulatory approval dates of avelumab maintenance, independent of the EV-302 protocol amendment 4 which clarified the use of avelumab in the trial. This analysis population was flagged in the IPD provided by Seagen. [2] Further, for PFS and OS outcomes only, the control arm was separated into four mutually exclusive subgroups based on eligibility and receipt of avelumab. Subjects randomized to receive gemcitabine + platinum chemotherapy were considered eligible for avelumab if after completion of or discontinuation after at least 3 cycles of platinum-based chemotherapy and a 10-week washout period had no evidence of disease progression as determined by the investigator. For those

who completed or discontinued platinum-based chemotherapy after at least 3 cycles, those who were eligible for avelumab maintenance had not had a progression event and were alive after 91 days from the first day of their last cycle (i.e., no progression event 21 days from the first day of their last cycle [within the last cycle] plus a 10-week washout period) as determined by the investigator. Patients receiving less than 3 cycles were considered ineligible for avelumab maintenance as an investigator would not have been able to evaluate their tumor response prior to the first planned scan, which was scheduled after 9 weeks (i.e., after three 3-week cycles). Patients with non-evaluable or missing scans between the end of platinum-based chemotherapy and the end of the washout period were considered eligible. Based on this definition of avelumab eligibility, the control arm was divided into four subgroups based on eligibility and receipt of avelumab:

Eligible for avelumab & received avelumab maintenance

Patients meeting the post-hoc eligibility definition as defined above and receiving at least one dose of avelumab maintenance

Eligible for avelumab & did not receive avelumab maintenance

Not eligible for avelumab & did not receive avelumab maintenance

Not eligible for avelumab but received avelumab maintenance

Patients who did not meet the post-hoc eligibility definition as defined above but received at least one dose of avelumab maintenance

Given the definition of eligibility was established post-hoc, it was suspected that some patients who did not meet the post-hoc criteria may have been treated with avelumab maintenance and deemed appropriate candidates by the clinician.

A secondary analysis using a 4-week washout period in place of a 10-week washout period was also conducted. These two time periods represent the low end and the high end of the treatment-free interval required prior to randomization in the JAVELIN Bladder 100 trial and were expected to provide the minimum and maximum washout periods used in clinical practice.

Outputs were also generated to summarize the number of patients and percentage of patients for each subgroup based on avelumab eligibility and receipt according to receipt of 3, 4, 5, or 6 cycles of platinum-based chemotherapy. This was conducted to be able to compare the trial use of avelumab against real-world use of avelumab, where 3 cycles would be considered discontinuation and 4-6 cycles would be considered completion of platinum-based chemotherapy.

Time-to-event end points, such as DOR, PFS, and OS, were estimated using the Kaplan-Meier method, with 95% CIs by the complementary log-log transformation. Objective response rate and disease control rate were summarized with 95% CIs using the Clopper-Pearson method.

Grade 3+ treatment-emergent adverse events (TEAEs) were summarized for the seven subgroups of the safety set (i.e., cisplatin-eligible, cisplatin-ineligible, PD-L1 high, PD-L1 low, cisplatin-ineligible and PD-L1 high, cisplatin-ineligible and PD-L1 low, and avelumab

	maintenance accessible). The frequency of AEs and SAEs were categorized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOCL). Completion and compliance rates along with change from baseline for each domain of the PROs, including EQRTC QLQ-C30, EQ-5D-5L, and BPI-SF were summarized.
Other relevant information	N/A

Abbreviations: EV+P, enfortumab vedotin + pembrolizumab; Plat+Gem, platinum-based chemotherapy

Appendix B. Efficacy results per study

Results per study

Results of the EV-302 trial is presented in Table 51, below. All results are based on the latest efficacy data cut from 8th of August 2023. A summary of the proportional hazards testing for OS and PFS in the ITT population is provided in Section D.1.3.

Table 51. Results per study

Results of EV-302 (NCT04223856)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS (median duration of follow-up 17.2 months) ITT analysis set	EV+P	442	31.5 (25.4, -)	N/A	N/A	N/A	HR: 0.468	0.376, 0.582	<0.00001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm. Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization. The p-value was calculated using stratified log-rank test. The p-value threshold for statistical significance is 0.01548. In the	Powles et al., 2024[3]
	Plat+Gem	444	6.1 (13.9, 18.3)								Powles et al., 2024[3]

										absence of confirmation of death, OS was censored at the last date the subject was known to be alive.	
Median PFS per RECIST by BICR (up to approximately 5 years), ITT analysis set	EV+P	442	12.5 (10.4, 16.6)	N/A	N/A	N/A	HR: 0.450	0.377–0.538	<0.00001	The median progression-free survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm. Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization. The p-value was calculated using stratified log-rank test. The p-value threshold for statistical significance is 0.01548.	Powles et al., 2024[3]
	Plat+Gem	444	6.3 (6.2, 6.5)								Powles et al., 2024[3]
Proportion of subjects who achieving ORR per RECIST by BICR (%) (up to approximately	EV+P	437	296 (67.7%) (61.4, 70.4)	N/A	N/A	<0.00001	Stratified OR: 2.64	2.000, 3.490	<0.00001	Clopper-Pearson method used to compute 95% confidence interval for rates. Odds ratio and p-value were estimated using Cochran-Mantel-Haenszel test (CMH) controlling for stratification	Powles et al., 2024[3]
	Plat+Gem	441	196 (44.4%) (38.3, 47.7)								Powles et al., 2024[3]

5 years) response evaluable analysis set by BICR										factors (cisplatin eligibility: eligible or ineligible, PD-L1 expression: low or high, and liver metastases: present or absent) at randomization.	
Median DOR per RECIST by BICR (up to approximately 5 years), response evaluable analysis set by BICR	EV+P	437	- (20.2, -)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using Kaplan Meier methods. Complementary log-log transformation method was used to calculate 95% confidence interval	Powles et al., 2024[3]
	Plat+Gem	441	7.0 (6.2, 10.2)								Powles et al., 2024[3]
DCR per RECIST by BICR (up to approximately 5 years), response evaluable analysis set by BICR	EV+P	437	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	Clopper-Pearson method used to compute 95% confidence interval for rates. Odds ratio and p-value were estimated using Cochran-Mantel-Haenszel test (CMH) controlling for stratification factors (cisplatin eligibility: eligible or ineligible, PD-L1 expression: low or high, and liver metastases: present or absent) at randomization.	Astellas data on file, 2023.[2]
	Plat+Gem	345	[redacted]								Astellas data on file, 2023.[2]

Abbreviations: BICR, blinded independent central review; CR, complete reponse; DCR, disease control rate; DOR, duration of response; EuroQOL Five Dimensions Questionnaire 5L: EQ-5D-5L, EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; Plat+Gem, platinum-based chemotherapy; PFS, progression-free survival; PR, Partial response; RECIST, Response Evaluation Criteria in Solid Tumors

Appendix C. Comparative analysis of efficacy

Not applicable.

Appendix D. Extrapolation

D.1 Extrapolation of OS

D.1.1 Data input

OS was based on the EV-302 study and was extrapolated beyond the follow-up of the study to assess the CE of EV vs SoC over a lifetime horizon.

D.1.2 Model

Standard parametric models were used to extrapolate OS from EV-302 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.1.3 Proportional hazards

To assess proportional hazards two plots are presented, see cumulative hazards in Figure 22 and Schoenfeld residuals plot in Figure 23.

Results of the PH testing for OS did not clearly suggest whether the PH assumption may hold. However, given the different mechanism of actions of EV+P and SOC and the clear violation of the PH assumption for PFS, it was considered that the OS would likely have a similar violation when it was more mature, so independent models were fitted to EV+P and SOC in the base case.

Figure 22. Log cumulative hazard for OS

Figure 23. Schoenfeld residuals plot for OS

D.1.4 Evaluation of statistical fit (AIC and BIC)

The statistical fits are evaluated by AIC and BIC which is presented in Table 52. For EV+P, the Weibull extrapolation had the best statistical fit in terms of AIC, while the exponential extrapolation had the best BIC fit. For SoC, the log-logistic extrapolation entailed the best statical fit in terms of both AIC and BIC.

Table 52. AIC and BIC from independent parametric models – OS (ITT population)

Model	EV+P		SoC: Gemcitabine + PBC	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

D.1.5 Evaluation of visual fit

The visual fit is evaluated for EV+P in Figure 24 and for SoC in Figure 25. For EV+P, it is seen that all extrapolations seem to fit the KM data reasonably, though, the log-normal curve may deviate slightly from the KM data. It is seen that the log-normal extrapolation entails a rather long tail, which may overestimate the OS, while generalised Gompertz, exponential, gamma and Weibull results in pessimistic extrapolations, which may underestimate OS. The log-logistic and generalised gamma extrapolations provide a 'middle of the bunch' extrapolation.

For SoC, all extrapolations seem to fit the KM data reasonably well. The log-normal and log-logistics entail long tails, which could overestimate OS, while Gompertz, Weibull and gamma seem have shorter tails, that could underestimate OS.

Figure 24. EV+P overall survival distributions

Figure 25. SoC overall survival distributions

D.1.6 Evaluation of hazard functions

The smoothed hazard plot for both EV+P and SoC is presented in Figure 26, while the hazard plots for each of the extrapolations are presented for EV+P in Figure 27 and SoC in Figure 28. For EV+P, the Gompertz and log-normal extrapolations seem to have the worst fit in terms of hazard plots. While the worst fit for SoC in terms of hazard plot was Gompertz and Weibull.

Figure 26. OS observed smoothed hazards for both comparators

Figure 27. OS EV+P smoothed hazards distributions

Figure 28. OS SoC smoothed hazards distributions

D.1.7 Validation and discussion of extrapolated curves

Evaluation of the hazards for SOC demonstrated an increasing and then decreasing hazards, whilst the hazards for EV+P were too immature to see declining hazard inflection point. However, based on the declining PFS hazard for EV+P, a declining hazard for EV+P OS is anticipated when more follow-up becomes available. Independently fitted distributions were selected for OS, with log-logistic was selected for both EV+P and for SoC due to the overall best fit. The model selections are summarised in Table 53 and Table 54.

Table 53. Summary table for EV+P curve selection for OS.

Model	AIC[a]	BIC[b]	Fit based on visual inspection	Hazard over time	Median (months)	Mean (months)	Landmark				Model selection
							1 year	2 years	5 years	10 years	
EV-302[2] EV+P KM				Monotonically increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	--
Exponential	[redacted]	[redacted]	All models fit reasonably well to the data up to 24 months.	Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Scenario
Weibull	[redacted]	[redacted]		Increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor prediction (TA788 10 years)
Gompertz	[redacted]	[redacted]	All models fit reasonably	Monotonically increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor prediction (TA788 10 years)

Gamma	[redacted]	[redacted]	well to the data up to 24 months.	Increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5%	Poor prediction (TA788 10 years)
Log-normal	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23%	Poor statistical fit/prediction (TA788)
Log-logistic	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16%	Base case – reasonable AIC/BIC and clinically plausible long-term estimates. Anticipate hazards to be similar to decrease in future based on PFS and SOC OS.
Generalised gamma	[redacted]	[redacted]		Increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3%	Poor prediction (TA788 10 years)
Exponential	[redacted]	[redacted]		Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8%	Scenario

Table 54. Summary table for SoC curve selection for OS.

Model	AIC	BIC	Fit based on visual inspection	Hazard over time	Median (months)	Mean (months)	Landmark				Model selection
							1 year	2 years	5 years	10 years	
EV-302[2] SOC KM				Increasing then decreasing	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	--
Exponential	XXXXX	XXXXX	All models fit reasonably well to the data up to 24 months.	Constant	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	Poor statistical fit/fit to hazards
Weibull	XXXXX	XXXXX		Increasing	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	Poor statistical fit/fit to hazards
Gompertz	XXXXX	XXXXX		Monotonic increasing	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	Poor statistical fit/fit to hazards
Gamma	XXXXX	XXXXX		Increasing	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	Poor statistical fit/fit to hazards
Log-normal	XXXXX	XXXXX		Increasing then decreasing	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	Scenario
Log-logistic	XXXXX	XXXXX		Increasing then decreasing	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	Base case – best fit to hazards, AIC/BIC and

											clinically plausible long-term estimates.
Generalised gamma	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit
Exponential	[redacted]	[redacted]		Increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards

To our knowledge, no RWE studies exist to validate the extrapolation of the EV + P arm as the treatment combination only recently has been approved for this indication by regulatory agencies across the globe. However, 5-year follow-up results were presented from the EV-103 Dose Escalation/Cohort A (DE/A) at ESMO in September 2024[145]. The study is an ongoing phase 1/2B trial evaluating 1L EV+P in patients with la/mUC ineligible for cisplatin-containing chemotherapy and reports results from 45 pts. Median follow-up was 62.1 months, median PFS was 12.7 months (95% CI, 6.11-NR), and median OS was 26.1 months (95% CI, 15.5-NR). 47% of patients who responded to treatment maintained a response at 2-5 years. PFS rate remained at 38.2% at 3-5 years and 41.5% of patients were alive at 5 years[145]. Despite not representing the full ITT population, the data shows that the OS estimates in the model are clinically plausible. A overview of the modelled OS compared to KM estimates from EV-302 and KM estimates from EV-103 DE/A is shown in Table 55.

Table 55. Comparison of modelled OS and KM estimates from EV-302 and EV-103 DE/A

Data source	1 year	2 years	3 years	5 years
EV + P modelled	[redacted]	[redacted]	[redacted]	[redacted]
KM EV-302	78.2%	59.9%	N/a	N/a
KM EV-103 DE/A[145]	83.4%	56.4%	49.1%	41.5%

For the comparator arm we have not been able to identify RWE studies describing the survival of all 1st line la/mUC after implementation of avelumab in clinical practise. Recent RWE studies have focused on patient populations receiving avelumab as maintenance after responding to 1st chemotherapy in clinical practise, but this is not relevant for validation of the ITT population in EV-302 as only 30% received avelumab post-platinum. Prior to the implementation of avelumab, the COBRA study investigated the treatment patterns and prognosis for patients with la/mUC in Denmark 2015–2020. The study found the median OS for the 651 patients receiving first-line treatment to be 12.1 months. The majority, 75% received chemotherapy in 1st Line[146].

D.1.8 Adjustment of background mortality

Yes, based on Danish life tables

D.1.9 Adjustment for treatment switching/cross-over

Not applicable

D.1.10 Waning effect

No waning in the base case, assumed continuation of hazards

D.1.11 Cure-point

No cure point.

D.2 Extrapolation of PFS

D.2.1 Data input

PFS was based on the EV-302 study and was extrapolated beyond the follow-up of the study to assess the CE of EV vs SoC over a lifetime horizon.

D.2.2 Model

Standard parametric models were used to extrapolate PFS from EV-302 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.2.3 Proportional hazards

To assess proportional hazards two plots are presented below, see cumulative hazards in Figure 29 and Schoenfeld residuals plot in Figure 30.

Figure 29. Log cumulative hazard for PFS

Figure 30. Schoenfeld residuals plot for PFS

Results of the PH testing for PFS indicated a violation of the PH assumption based on the Grambsch-Therneau test (p <0.001) and the shape of the above plots, see Table 56. Thus, independent models were fitted to EV+P and SOC in the base case.

Table 56. Test for proportional hazards

Population/ subgroup	Grambsch-Therneau test p-value	Schoenfeld residuals visual inspection	Log cumulative hazards visual inspection
ITT	<0.001	Treatment line falls outside confidence bounds	Overlap at early time points, then curves increasingly separate

D.2.4 Evaluation of statistical fit (AIC and BIC)

The statistical fits are evaluated by AIC and BIC which is presented in Table 57. For EV+P, the generalised gamma extrapolation had the best statistical fit in terms of AIC, while the log-normal extrapolation had the best BIC fit. For SoC, the log-logistic extrapolation entailed the best statical fit in terms of both AIC and BIC.

Table 57. AIC and BIC from independent parametric models – PFS (ITT population)

Model	EV+P		SoC: Plat+Gem	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

D.2.5 Evaluation of visual fit

The visual fit is evaluated for EV+P in Figure 31 and for SoC in Figure 32.

For EV+P, it is seen that all extrapolations seem to fit the KM data reasonably, though, the log-normal curve may deviate slightly from the KM data. It is seen that the Gompertz extrapolation entails a rather long tail, which may overestimate the PFS, while exponential, gamma and Weibull extrapolations resulted in pessimistic extrapolations, which may underestimate the PFS. The log-logistic, log-normal, and generalised gamma extrapolations provide a 'middle of the bunch' extrapolation.

For SoC, all extrapolations seem to fit the KM data reasonably well, with similar extrapolation tails.

Figure 31. EV+P progression free survival distributions

Notes: Calculations in the cost effectiveness model capped PFS with OS

Figure 32. SoC progression free survival distributions

D.2.6 Evaluation of hazard functions

The smoothed hazard plot for both EV+P and SoC is presented in Figure 33, while the hazard plots for each of the extrapolations are presented for EV+P in Figure 34 and SoC in Figure 35. For EV+P, the exponential, Weibull and gamma extrapolations seem to have the worst fit in terms of hazard plots. While the worst fit for SoC in terms of hazard plot was Gompertz, exponential and Weibull.

Figure 33. Observed smoothed hazards

Figure 34. PFS EV+P smoothed hazards distributions

Figure 35. PFS SoC smoothed hazards distributions

D.2.7 Validation and discussion of extrapolated curves

Evaluation of the hazards for EV + P and SOC demonstrated an increasing and then decreasing hazards. Independently fitted distributions were selected for PFS, with log-logistic selected for SOC and generalised gamma for EV+P. The model selections are summarised in Table 58 and Table 59.

Table 58. Summary table for EV+P curve selection for PFS.

Model	AIC	BIC	Fit based on visual inspection	Hazard over time	Median (months)	Mean (months)	Landmark					Model selection
							6 months	1 year	2 years	5 years	10 years	
EV-302[2] EV+P KM				Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	--
Exponential	[redacted]	[redacted]	All distributions fit reasonably well to the data.	Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards.
Weibull	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards.
Gompertz	[redacted]	[redacted]		Decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Scenario – based on expert feedback
Gamma	[redacted]	[redacted]		Increasing then constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards.
Log-normal	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Scenario

Log-logistic	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit
Generalised gamma	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Base case – best fit to hazards, AIC/BIC and clinically plausible long-term estimates.

Table 59. Summary table for SoC curve selection for PFS

Model	AIC	BIC	Fit based on visual inspection	Hazard over time	Median (months)	Mean (months)	Landmark					Model selection
							6 months	1 year	2 years	5 years	10 years	
EV-302[2] SOC KM (includes 30% avelumab)				Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	--
Exponential	[redacted]	[redacted]	Data is mature, so there is little difference between the fit of the distributions.	Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards.
Weibull	[redacted]	[redacted]		Increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards.
Gompertz	[redacted]	[redacted]		Monotonic increasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards.

Gamma	[redacted]	[redacted]		Increasing then constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit/fit to hazards.
Log-normal	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit.
Log-logistic	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Base case – best fit to hazards, AIC/BIC and clinically plausible long-term estimates.
Generalised gamma	[redacted]	[redacted]		Increasing then decreasing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Poor statistical fit.

As for the validation of OS, an overview of the modelled PFS compared to KM estimates from EV-302 and KM estimates from EV-103 DE/A is shown in Table 60.

Table 60. Comparison of modelled PFS and KM estimates from EV-302 and EV-103 DE/A

Data source	1 year	2 years	3 years	5 years
EV + P modelled	[redacted]	[redacted]	[redacted]	[redacted]
KM EV-302	51.0%	38.2%	N/a	N/a
KM EV-103 DE/A[145]	55.0 %	41.1 %	38.2%	38.2%

D.2.8 Adjustment of background mortality

OS was adjusted based on Danish life tables.

D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

D.2.10 Waning effect

No waning in the base case, assumed continuation of hazards

D.2.11 Cure-point

No cure point.

D.3 Extrapolation of ToT

D.3.1 Data input

ToT was based on the EV-302 study and was extrapolated beyond the follow-up of the study to assess the CE of EV vs SoC over a lifetime horizon.

D.3.2 Model

Standard parametric models were used to extrapolate ToT from EV-302 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.3.3 Proportional hazards

Not applicable. Proportional hazards were not tested between Plat+Gem and EV+P since the entire treatment duration for Plat+Gem was captured during the trial. EV and P were modelled separately.

D.3.4 Evaluation of statistical fit (AIC and BIC)

The statistical fits are evaluated by AIC and BIC which is presented in Table 61. For EV, the log-logistic extrapolation had the best statistical fit in terms of AIC and BIC. For P, the generalised gamma extrapolation entailed the best statical fit in terms of both AIC, while the exponential extrapolation had the best fit in terms of BIC. Log-normal entailed a good fit in terms of both AIC and BIC.

For avelumab, the Gompertz extrapolation had the best statical fit in terms of both AIC and BIC, while the log-logistic extrapolation also entailed a good statical fit in both AIC and BIC.

Table 61. AIC and BIC from independent parametric models – ToT (ITT population)

Time on treatment: Goodness of fit						
	EV		Pembrolizumab		Avelumab maintenance	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Gamma	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Log-normal	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Log-logistic	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Generalised gamma	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX

D.3.5 Evaluation of visual fit

The visual fit is evaluated for EV in Figure 36, for P Figure 37 and for avelumab in Figure 38.

For EV, it is seen that all extrapolations seem to fit the KM data reasonably. It is seen that the log-normal entails a rather long tail, which may overestimate the ToT, while gamma and Weibull extrapolations resulted in pessimistic extrapolations, which may underestimate ToT. The log-logistic and generalised gamma extrapolations provide a 'middle of the bunch' extrapolation. For P, it is seen that the log-logistic entails a rather long tail, which may overestimate the ToT, while gamma, generalised gamma and Weibull extrapolations resulted in pessimistic extrapolations, which may underestimate ToT.

For avelumab, the extrapolations based on the Gompertz distribution seems clinically implausible. The generalised gamma, gamma and Weibull seem to entail pessimistic tails, which could underestimate ToT. Remaining extrapolation seemed to entail reasonable fits.

Figure 36. EV time on treatment distributions

Figure 37. P time on treatment distributions

Figure 38. Avelumab time on treatment distributions (ToT 10 years)

D.3.6 Evaluation of hazard functions

Figure 39. Time on treatment hazards to three years, EV (overall safety population)

Figure 40. Time on treatment hazards to three years, pembrolizumab (overall safety population)

Figure 41. Time on treatment hazards to three years, avelumab maintenance after PBC (patients in overall safety population receiving avelumab maintenance)

D.3.7 Validation and discussion of extrapolated curves

For EV+P, as ToT was relatively mature, there was little difference in the tails between the alternative distributions for both EV and pembrolizumab. Based on the hazards over time and the goodness of fit statistics, in the base case the log-logistic was selected for EV and the log-normal was selected for pembrolizumab.

For SoC, the Plat+Gem ToT was solely based on KM data. Therefore, only the avelumab ToT needed to be modelled. The avelumab ToT parametric model selection, the logistic extrapolations seemed to be the best selection overall.

To validate the modelled treatment duration for avelumab two sources were identified: long-term data from the JAVELIN 100 bladder study and the AVENANCE RWE study.

Long-term data from JAVELIN bladder 100 was published in April 2023 and the median follow-up was 38.0 months and 39.6 months, respectively. 19.5% of patients in the avelumab arm remained on treatment after two years and at the time of the data-cut 12.3 % remained on treatment[147].

The AVENANCE study is investigating the efficacy and safety of avelumab 1L maintenance in a real-world population of pts with advanced UC in France. Updated results were presented at ASCO GU 2024 with a median follow-up of 24.2 months. At this point of time, 23.9% of patients remained on treatment[148]. The proportion on treatment at the 2-year follow-up matches well with modelled treatment duration (at year 2).

D.3.8 Adjustment of background mortality

Not applicable.

D.3.9 Adjustment for treatment switching/cross-over

Not applicable.

D.3.10 Waning effect

Not applicable.

D.3.11 Cure-point

Not applicable.

Appendix E. Serious adverse events

All serious AEs are reported in Table 62. In this application, as stated, safety data (AEs) are presented as TEAEs.

Table 62. Serious adverse events

Preferred term	EV+P (N=440), n (%)	Plat+Gem (N=433), n (%)
Overall	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Immune-mediated lung disease	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Dyspnoea	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Immune-mediated enterocolitis	[redacted]	[redacted]
Immune-mediated hepatitis	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Toxic epidermal necrolysis	[redacted]	[redacted]
Urinary tract stoma complication	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]

Blood creatinine increased	[redacted]	[redacted]
Calculus bladder	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]
Enterovesical fistula	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hydronephrosis	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Immune-mediated nephritis	[redacted]	[redacted]
Infectious pleural effusion	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Peripheral motor neuropathy	[redacted]	[redacted]
Peripheral sensorimotor neuropathy	[redacted]	[redacted]
Rash macular	[redacted]	[redacted]
Rash morbilliform	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Seizure	[redacted]	[redacted]

Syncope	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]
Urosepsis	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]
Anaemia of malignant disease	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Aortic aneurysm rupture	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Aspiration	[redacted]	[redacted]
Atrioventricular block complete	[redacted]	[redacted]
Autoimmune hepatitis	[redacted]	[redacted]
Bacteraemia	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]
Bone lesion	[redacted]	[redacted]
Burkitt's lymphoma	[redacted]	[redacted]
Campylobacter gastroenteritis	[redacted]	[redacted]
Cancer pain	[redacted]	[redacted]
Cerebral haemorrhage	[redacted]	[redacted]
Cholangitis sclerosing	[redacted]	[redacted]
Chronic inflammatory demyelinating polyradiculoneuropathy	[redacted]	[redacted]
Chronic lymphocytic leukaemia	[redacted]	[redacted]
Clostridium difficile infection	[redacted]	[redacted]
Colitis ulcerative	[redacted]	[redacted]
Colonic fistula	[redacted]	[redacted]
Condition aggravated	[redacted]	[redacted]

Cystitis	[redacted]	[redacted]
Cytomegalovirus colitis	[redacted]	[redacted]
Death	[redacted]	[redacted]
Delirium	[redacted]	[redacted]
Dermatitis exfoliative	[redacted]	[redacted]
Dermatitis exfoliative generalised	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]
Diabetic hyperglycaemic coma	[redacted]	[redacted]
Disorientation	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]
Duodenal stenosis	[redacted]	[redacted]
Duodenal ulcer	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Eczema	[redacted]	[redacted]
Enterocolitis infectious	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]
Heat stroke	[redacted]	[redacted]
Hypercreatininaemia	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]

Hypovolaemia	[redacted]	[redacted]
Iliac artery occlusion	[redacted]	[redacted]
Immune thrombocytopenia	[redacted]	[redacted]
Immune-mediated encephalitis	[redacted]	[redacted]
Immune-mediated myocarditis	[redacted]	[redacted]
Immune-mediated neuropathy	[redacted]	[redacted]
Inguinal hernia	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
Large intestinal ulcer haemorrhage	[redacted]	[redacted]
Large intestine perforation	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Lung opacity	[redacted]	[redacted]
Lymphoedema	[redacted]	[redacted]
Malignant gastrointestinal obstruction	[redacted]	[redacted]
Metabolic acidosis	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]
Nervous system disorder	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutropenic sepsis	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Oesophageal candidiasis	[redacted]	[redacted]
Oesophagitis	[redacted]	[redacted]

Optic neuritis	[redacted]	[redacted]
Organising pneumonia	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]
Oxygen saturation decreased	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Pancreatitis acute	[redacted]	[redacted]
Partial seizures	[redacted]	[redacted]
Pelvic infection	[redacted]	[redacted]
Performance status decreased	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Pharyngeal dyskinesia	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Postrenal failure	[redacted]	[redacted]
Prostatitis	[redacted]	[redacted]
Prothrombin time prolonged	[redacted]	[redacted]
Pyelonephritis acute	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Rash erythematous	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]
Rectal ulcer haemorrhage	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
SJS-TEN overlap	[redacted]	[redacted]
Sarcoidosis	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]

Small intestinal obstruction	[redacted]	[redacted]
Staphylococcal bacteraemia	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]
Toxic erythema of chemotherapy	[redacted]	[redacted]
Tumour rupture	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
Urinary tract infection staphylococcal	[redacted]	[redacted]
Urinary tract obstruction	[redacted]	[redacted]
Ventricular tachycardia	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Abdominal abscess	[redacted]	[redacted]
Acute generalised exanthematous pustulosis	[redacted]	[redacted]
Acute right ventricular failure	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Cardiogenic shock	[redacted]	[redacted]
Cerebral infarction	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]
Duodenitis	[redacted]	[redacted]

Escherichia infection	[redacted]	[redacted]
Faeces discoloured	[redacted]	[redacted]
Failure to thrive	[redacted]	[redacted]
Gastric haemorrhage	[redacted]	[redacted]
Haemorrhoidal haemorrhage	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]
Hypercalcaemia of malignancy	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Kidney infection	[redacted]	[redacted]
Klebsiella sepsis	[redacted]	[redacted]
Lymphocele	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Metastases to central nervous system	[redacted]	[redacted]
Mobility decreased	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]
Obstructive pancreatitis	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]
Pathological fracture	[redacted]	[redacted]
Pericardial effusion	[redacted]	[redacted]
Perineal abscess	[redacted]	[redacted]
Peritonitis	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Pneumonia haemophilus	[redacted]	[redacted]

Pneumothorax	XXXXX	XXXXX
Respiratory syncytial virus infection	XXXXX	XXXXX
Rhabdomyolysis	XXXXX	XXXXX
Shock	XXXXX	XXXXX
Sinus tachycardia	XXXXX	XXXXX
Small intestinal perforation	XXXXX	XXXXX
Sternal fracture	XXXXX	XXXXX
Stress cardiomyopathy	XXXXX	XXXXX
Supraventricular tachycardia	XXXXX	XXXXX
Thrombocytopenia	XXXXX	XXXXX
Tibia fracture	XXXXX	XXXXX
Toxicity to various agents	XXXXX	XXXXX
Urinary tract infection bacterial	XXXXX	XXXXX
Urinary tract infection pseudomonal	XXXXX	XXXXX
Urinoma	XXXXX	XXXXX
Vaginal haemorrhage	XXXXX	XXXXX
Wound infection	XXXXX	XXXXX

Abbreviations: EV, enfortumab vedotin; Gem, gemcitabine; P, pembrolizumab; Plat, platinum-based chemotherapy (cisplatin or carboplatin)
Preferred terms are sorted by descending order of incidence in the EV+P arm.
Data cutoff date: 08 Aug 2023, Dictionary: MedDRA v26.0
Source: Astellas, data on file.[2]

Appendix F. Health-related quality of life

An electronic PRO (ePRO) assessment device including the EQ-5D-5L questionnaire was administered at Cycle 1 day 1 before study treatment, once weekly for the first 12 weeks, at week 14, and then once every 3 weeks through the remainder of the study through progression and survival follow-up.

On Cycle 1 Day 1, patients completed questionnaires in the clinic up to 24 hours prior to the first dose of study treatment and before any study procedures/assessments are conducted. After Cycle 1 Day 1, questionnaires were completed at home several days prior to a clinic visit. The ePRO device notified subjects to complete the questionnaires at the appropriate time points.

PRO FAS include randomized subjects who have received any amount of study treatment and have completed at least one PRO prior to the first dose of study treatment. In the PRO FAS, there were 376 patients in the EV+P arm and 355 patients in the Plat+Gem arm. Demographic and baseline characteristics of the PRO FAS are provided in Table 63 which is similar to the ITT[2].

Table 63. Demographic and baseline characteristics of the ITT and PRO FAS population

	ITT		PRO FAS*	
	EV+P (N=442)	Plat+Gem (N=444)	EV+P (N=376)	Plat+Gem (N=355)
Male sex, n (%)	344 (77.8)	336 (75.7)		
Age (yrs), median (range)	69.0 (37,87)	69.0 (22,91)	XXXXX	XXXXX
Race, n (%)			XXXXX	XXXXX
White	308 (69.7)	290 (65.3)	XXXXX	XXXXX
Asian	99 (22.4)	92 (20.7)	XXXXX	XXXXX
Geographic location, n (%)			XXXXX	XXXXX
North America	103 (23.3)	85 (19.1)	XXXXX	XXXXX
Europe	172 (38.9)	197 (44.4)	XXXXX	XXXXX
Rest of World	167 (37.8)	162 (36.5)	XXXXX	XXXXX
ECOG PS, n (%)				

0	223 (50.5)	215 (48.4)	[redacted]	[redacted]
1	204 (46.2)	216 (48.6)	[redacted]	[redacted]
2	15 (3.4)	11 (2.5)	[redacted]	[redacted]
Primary tumor location, n (%)			[redacted]	[redacted]
Upper tract	135 (30.5)	104 (23.4)	[redacted]	[redacted]
Lower tract	305 (69.0)	339 (76.4)	[redacted]	[redacted]
Metastatic category, n (%)			[redacted]	[redacted]
Visceral metastases	318 (71.9)	318 (71.6)	[redacted]	[redacted]
Bone	81 (18.3)	102 (23.0)	[redacted]	[redacted]
Liver	100 (22.6)	99 (22.3)	[redacted]	[redacted]
Lung	170 (38.5)	157 (35.4)	[redacted]	[redacted]
Lymph node only disease	103 (23.3)	104 (23.4)	[redacted]	[redacted]

*The PRO FAS include all randomized subjects who have received any amount of study treatment and have completed at least one PRO assessment at baseline.

Table 64 and Table 65 shows the number of subjects reporting HRQoL data via ePRO during the study. Completion rate was defined as the proportion of subjects who completed the instrument in the ITT population.

Table 64. Pattern of missing data and completion for EV+P (ITT)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	442	[redacted]	[redacted]	[redacted]
Week 12	442	[redacted]	[redacted]	[redacted]
Week 23	442	[redacted]	[redacted]	[redacted]
Week 35	442	[redacted]	[redacted]	[redacted]
Week 47	442	[redacted]	[redacted]	[redacted]
Week 59	442	[redacted]	[redacted]	[redacted]
Week 71	442	[redacted]	[redacted]	[redacted]
Week 83	442	[redacted]	[redacted]	[redacted]
Week 95	442	[redacted]	[redacted]	[redacted]
Week 107	442	[redacted]	[redacted]	[redacted]

Notes: The numerator of this rate is used to inform the "Missing" column of this table (Randomized – numerator). The denominator of this rate is used to directly inform the "Expected to complete" column of this table Completion rate is defined as the proportion of subjects who completed the instrument among the ITT analysis set. Used to inform the "completion" column in this table.
Source: Astellas data on file (EV-302 CSR; Table 12.3.9.1[2])

Completion rates were steady at ≥80% in both treatment arms through Week 8, after which rates declined more rapidly in the Plat+Gem arm.

Table 65. Pattern of missing data and completion for SoC (ITT)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)

	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	444	XXXXXXX	XXXXX	XXXXXXX
Week 12	444	XXXXXXX	XXXXX	XXXXXXX
Week 23	444	XXXXXXX	XXXXX	XXXXXXX
Week 35	444	XXXXXXX	XXXXX	XXXXXXX
Week 47	444	XXXXXXX	XXXXX	XXXXXXX
Week 59	444	XXXXXXX	XXXXX	XXXXXXX
Week 71	444	XXXXXXX	XXXXX	XXXXXXX
Week 83	444	XXXXXXX	XXXXX	XXXXXXX
Week 95	444	XXXXXXX	XXXXX	XXXXXXX
Week 107	444	XXXXXXX	XXXXX	XXXXXXX

Notes: The numerator of this rate is used to inform the "Missing" column of this table (Randomized – numerator). The denominator of this rate is used to directly inform the "Expected to complete" column of this table Completion rate is defined as the proportion of subjects who completed the instrument among the ITT analysis set. Used to inform the "completion" column in this table.
Source: Astellas data on file (EV-302 CSR; Table 12.3.9.1[2])

EQ-5D-5L completion rates by health state and treatment arm are summarized in the table below. In both treatment arms, completion rates were higher for patients in the pre-progression health state than the post-progression health state across study visits. In general, for a given health state and study visit, completion rates were typically higher for EV+P than for Gem+Plat. Beyond Week 83, the completion rate for all health states and treatment arms were less than 20%[2]. The completion rate is especially low for Gem+Plat which probably can be explained by the faster disease progression.

Table 66. EV-302 completion rate by health state, overall population

Visit	EV+P		Gem+Plat		Overall	
	Pre-progression	Post-progression	Pre-progression	Post-progression	Pre-progression	Post-progression
Baseline	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX

Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 47	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 71	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 83	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 107	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Completion rate is defined as the proportion of subjects who completed the instrument among the ITT analysis set by health state. Health state (i.e., pre- and post-progression) was determined based on BICR assessment. Patients were assumed to be in pre-progression state until first instance of BICR-confirmed progression. Abbreviations: BICR, blinded independent central review; EV, enfortumab vedotin; ITT, intention-to-treat.

Appendix G. Probabilistic sensitivity analyses

Table 67. Overview of parameters in the PSA

Parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Age (at baseline)	[redacted]	[redacted]	[redacted]	Normal
Proportion of males	[redacted]	[redacted]	[redacted]	Beta
Weight	[redacted]	[redacted]	[redacted]	Lognormal
Body surface area	[redacted]	[redacted]	[redacted]	Lognormal
PFS parametric distributions, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
PFS parametric distributions, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
PFS parametric distributions, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
PFS parametric distributions, SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	Multivariate normal
PFS parametric distributions, SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	Multivariate normal
PFS parametric distributions, SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	Multivariate normal
PFS treatment coefficient, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
PFS HR, SOC: Gemcitabine + PBC vs. EV + P	[redacted]	[redacted]	[redacted]	Lognormal
OS parametric distributions, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
OS parametric distributions, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
OS parametric distributions, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
OS parametric distributions, SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	Multivariate normal

OS parametric distributions, SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	Multivariate normal
OS parametric distributions, SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	Multivariate normal
OS treatment coefficient, EV + P	[redacted]	[redacted]	[redacted]	Multivariate normal
OS HR, SOC: Gemcitabine + PBC vs. EV + P	[redacted]	[redacted]	[redacted]	Lognormal
ToT parametric distributions, EV	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, EV	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, EV	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, Pembrolizumab	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, Pembrolizumab	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, Pembrolizumab	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, Avelumab maintenance	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, Avelumab maintenance	[redacted]	[redacted]	[redacted]	Multivariate normal
ToT parametric distributions, Avelumab maintenance	[redacted]	[redacted]	[redacted]	Multivariate normal
EV + P - Acute kidney injury, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Anaemia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Fatigue, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Hyperglycemia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Hyponatraemia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Neutropenia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Neutrophil count decreased, AE (%)	[redacted]	[redacted]	[redacted]	Beta

EV + P - Rash maculo-papular, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Thrombocytopenia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Urinary tract infection, AE (%)	[redacted]	[redacted]	[redacted]	Beta
EV + P - Neuropathy (Grade 2), AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Acute kidney injury, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Anaemia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Fatigue, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Hyperglycemia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Hyponatraemia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Neutropenia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Neutrophil count decreased, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Platelet count decreased, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Thrombocytopenia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Urinary tract infection, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: Gemcitabine + cisplatin - Neuropathy (Grade 2), AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: avelumab maintenance - Anaemia, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: avelumab maintenance - Fatigue, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: avelumab maintenance - Rash maculo-papular, AE (%)	[redacted]	[redacted]	[redacted]	Beta
SOC: avelumab maintenance - Urinary tract infection, AE (%)	[redacted]	[redacted]	[redacted]	Beta
Health state utility values, PF - EV + P	[redacted]	[redacted]	[redacted]	Beta

Health state utility values, PF - SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	Beta
Health state utility values, PF - Pembrolizumab	[redacted]	[redacted]	[redacted]	Beta
Health state utility values, PF - Placeholder 1	[redacted]	[redacted]	[redacted]	Beta
Health state utility values, PF - Placeholder 2	[redacted]	[redacted]	[redacted]	Beta
Health state utility values, PD	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Acute kidney injury	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Anaemia	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Fatigue	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Hyperglycemia	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Hyponatraemia	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Neutropenia	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Neutrophil count decreased	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Platelet count decreased	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Rash maculo-papular	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Thrombocytopenia	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Urinary tract infection	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities decrement - Neuropathy (Grade 2)	[redacted]	[redacted]	[redacted]	Beta
Adverse event disutilities duration - Acute kidney injury	[redacted]	[redacted]	[redacted]	Lognormal

Adverse event disutilities duration - Anaemia	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Fatigue	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Hyperglycemia	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Hyponatraemia	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Neutropenia	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Neutrophil count decreased	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Platelet count decreased	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Rash maculo-papular	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Thrombocytopenia	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Urinary tract infection	[redacted]	[redacted]	[redacted]	Lognormal
Adverse event disutilities duration - Neuropathy (Grade 2)	[redacted]	[redacted]	[redacted]	Lognormal
Proportion of patients receiving Gemcitabine + cisplatin	[redacted]	[redacted]	[redacted]	Beta
Proportion of patients receiving Gemcitabine + carboplatin	[redacted]	[redacted]	[redacted]	Beta
Proportion of patients receiving avelumab maintenance	[redacted]	[redacted]	[redacted]	Beta
Administration cost, Simple chemotherapy (first attendance)	[redacted]	[redacted]	[redacted]	Gamma
Administration cost, Complex chemotherapy (first attendance)	[redacted]	[redacted]	[redacted]	Gamma
Administration cost, Complex/Prolonged Chemotherapy (First Attendance)	[redacted]	[redacted]	[redacted]	Gamma
Administration cost, Subsequent Elements of a Chemotherapy Cycle	[redacted]	[redacted]	[redacted]	Gamma

Duration of sub tx (months) [1], Gemcitabine + cisplatin	[redacted]	[redacted]	[redacted]	Lognormal
Duration of sub tx (months) [1], Gemcitabine + carboplatin	[redacted]	[redacted]	[redacted]	Lognormal
Duration of sub tx (months) [1], Atezolizumab	[redacted]	[redacted]	[redacted]	Lognormal
Duration of sub tx (months) [1], Pembrolizumab	[redacted]	[redacted]	[redacted]	Lognormal
Duration of sub tx (months) [1], Docetaxel	[redacted]	[redacted]	[redacted]	Lognormal
Duration of sub tx (months) [1], EV	[redacted]	[redacted]	[redacted]	Lognormal
Duration of sub tx (months) [1], Paclitaxel	[redacted]	[redacted]	[redacted]	Lognormal
Pre-progression treatment EV + P [1], Gemcitabine + cisplatin	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment EV + P [1], Gemcitabine + carboplatin	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment EV + P [1], Pembrolizumab	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment SOC: Gemcitabine + PBC [1], Gemcitabine + cisplatin	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment SOC: Gemcitabine + PBC [1], Gemcitabine + carboplatin	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment SOC: Gemcitabine + PBC [1], Pembrolizumab	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment SOC: Gemcitabine + PBC [1], Docetaxel	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment SOC: Gemcitabine + PBC [1], Paclitaxel	[redacted]	[redacted]	[redacted]	Beta
Monitoring frequency - Blood count (EV + P)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Hepatic function (EV + P)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Adrenal function (EV + P)	[redacted]	[redacted]	[redacted]	Gamma

Monitoring frequency - Renal function (EV + P)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Thyroid function (EV + P)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - CT scan (EV + P)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Blood count (EV)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Hepatic function (EV)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Adrenal function (EV)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Renal function (EV)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Thyroid function (EV)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - CT scan (EV)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Blood count (Pembrolizumab)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Hepatic function (Pembrolizumab)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Adrenal function (Pembrolizumab)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Renal function (Pembrolizumab)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Thyroid function (Pembrolizumab)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - CT scan (Pembrolizumab)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Blood count (SOC: Gemcitabine + PBC)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Hepatic function (SOC: Gemcitabine + PBC)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - Renal function (SOC: Gemcitabine + PBC)	[redacted]	[redacted]	[redacted]	Gamma
Monitoring frequency - CT scan (SOC: Gemcitabine + PBC)	[redacted]	[redacted]	[redacted]	Gamma

Monitoring costs, Blood count	[redacted]	[redacted]	[redacted]	Gamma
Monitoring costs, Hepatic function	[redacted]	[redacted]	[redacted]	Gamma
Monitoring costs, Adrenal function	[redacted]	[redacted]	[redacted]	Gamma
Monitoring costs, Renal function	[redacted]	[redacted]	[redacted]	Gamma
Monitoring costs, Thyroid function	[redacted]	[redacted]	[redacted]	Gamma
Monitoring costs, CT scan	[redacted]	[redacted]	[redacted]	Gamma
Monitoring costs, Neurologic function	[redacted]	[redacted]	[redacted]	Gamma
Proportion of patients requiring hospitalisation for adverse events	[redacted]	[redacted]	[redacted]	Beta
Acute kidney injury, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Anaemia, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Fatigue, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Hyperglycemia, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Hyponatraemia, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Neutropenia, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Neutrophil count decreased, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Rash maculo-papular, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Thrombocytopenia, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Urinary tract infection, hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
Neuropathy (Grade 2), hospitalization unit cost	[redacted]	[redacted]	[redacted]	Gamma
PFS HCRU monthly visits, Consultant led oncologist follow-up visit	[redacted]	[redacted]	[redacted]	Gamma
PFS HCRU monthly visits, Clinical nurse specialist	[redacted]	[redacted]	[redacted]	Gamma

PFS HCRU monthly visits, Dietician	[redacted]	[redacted]	[redacted]	Gamma
PFS HCRU monthly visits, GP home consultation	[redacted]	[redacted]	[redacted]	Gamma
PFS HCRU monthly visits, Urologist	[redacted]	[redacted]	[redacted]	Gamma
PFS HCRU monthly visits, District nurse	[redacted]	[redacted]	[redacted]	Gamma
PD HCRU monthly visits, Consultant led oncologist follow-up visit	[redacted]	[redacted]	[redacted]	Gamma
PD HCRU monthly visits, Clinical nurse specialist	[redacted]	[redacted]	[redacted]	Gamma
PD HCRU monthly visits, Dietician	[redacted]	[redacted]	[redacted]	Gamma
PD HCRU monthly visits, GP home consultation	[redacted]	[redacted]	[redacted]	Gamma
PD HCRU monthly visits, Urologist	[redacted]	[redacted]	[redacted]	Gamma
PD HCRU monthly visits, District nurse	[redacted]	[redacted]	[redacted]	Gamma
Consultant led oncologist follow-up visit, HCRU unit cost	[redacted]	[redacted]	[redacted]	Gamma
Clinical nurse specialist, HCRU unit cost	[redacted]	[redacted]	[redacted]	Gamma
Dietician, HCRU unit cost	[redacted]	[redacted]	[redacted]	Gamma
Urologist, HCRU unit cost	[redacted]	[redacted]	[redacted]	Gamma
District nurse, HCRU unit cost	[redacted]	[redacted]	[redacted]	Gamma
Terminal care setting, proportion, One-off total cost (DKK)	[redacted]	[redacted]	[redacted]	Gamma

Appendix H. Literature searches for the clinical assessment

Not applicable

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Objective

An economic SLR was conducted to identify and summarize studies that report costs, health care resource utilization (HCRU), cost-effectiveness, budget impact, HRQoL, and utility outcomes for the treatment of la/mUC patients who have not received prior systemic therapy in the unresectable or metastatic setting. To avoid repetition the economic SLR as a whole (targeting both HRQoL and inputs for the health economic model) is reported below.

I.1.1 Search strategies

I.1.1.1 Information sources

Relevant economic and HRQoL studies were identified by searching the following databases through the Ovid platform: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (Embase), Cochrane Central Register of Controlled Trials (CCTR), EconLit (economic SLR only), and National Health Service Economic Evaluation Database (NHS EED) (economic SLR only) (Table 68).

Database searches were executed on June 3rd, 2024 for the economic SLR and June 24th, 2024 for the HRQoL SLR with predefined search strategies for each SLR.

The population search strategy terms were based on previously published SLRs conducted in the disease area.[4-6] No intervention terms were included in the search strategies in order to capture any potentially relevant treatments in the target population. The study design filters recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) for MEDLINE and Embase, which were judged to yield the highest degree of sensitivity upon internal testing, were used to identify economic studies related to economic evaluation, economic modeling, and cost reporting, with additional search terms for resource utilization, productivity, and HCRU. The filters were also used to identify HRQoL studies, with additional search terms for bladder cancer questionnaires (https://searchfilters.cadth.ca/). Database searches were restricted to English language publications from 2012 to the present.

Table 68. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE	Ovid	2012 and onwards	03.06.2024 (economic SLR) 24.06.2024 (HRQoL SLR)
Embase	Ovid	2012 and onwards	03.06.2024 (economic SLR) 24.06.2024 (HRQoL SLR)
CCTR	Ovid	2012 and onwards	03.06.2024 (economic SLR) 24.06.2024 (HRQoL SLR)
EconLit	Ovid	2012 and onwards	03.06.2024 (economic SLR only)
NHS EED	Ovid	2012 and onwards	03.06.2024 (economic SLR only)

Abbreviations: CCTR, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica database; MEDLINE, Medical Literature Analysis and Retrieval System Online; NHS EED, National Health Service Economic Evaluation Database

For the HRQoL SLR, the International Clinical Trials Registry Platform (ICTRP) search portal of the World Health Organization (WHO) (https://trialsearch.who.int/) was also searched on March 3rd, 2023 using population search terms such as “urothelial cancer” to identify any ongoing or complete clinical trials (registered in the US or the European Union [EU]) without published results, which have reported their findings on that platform only. Clinical trials with HRQoL results available were included for data extraction. Clinical trials initiated from 2012 onward without HRQoL results available yet were not included in the SLR but were presented in a brief summary table. No date restriction was applied to this search.

The main database searches were augmented with searches of specific conference proceedings. Northern Light is a database that contains conference proceedings from 2010 to the present. This database was used to search for studies with information on economic, HCRU, cost, and HRQoL outcomes from the past two iterations of the six conferences reported in Table 69.

Table 69. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
American Association for Cancer Research (AACR)	www.aacr.org	2012 and onwards	03.06.2024
American Society of Clinical Oncology (ASCO), including Annual Meeting and Genitourinary Cancers Symposium	www.ASCO.org		03.06.2024
American Urological Association (AUA)	www.auanet.org		03.06.2024
European Society for Medical Oncology (ESMO)	www.esmo.org		03.06.2024
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	www.ispor.org		03.06.2024
Society of Urologic Oncology (SUO)	www.suonet.org		03.06.2024

In addition, HTA reports published in English were assessed across various agencies for additional outcome data relevant to both SLRs. Relevant reports were identified by manually hand-searching the websites of HTA agencies of interest in January 2023. Searches involved keyword searching using population terms (e.g., “transitional cell carcinoma”, “urothelial”, “bladder”, or “first-line”) and applied a date restriction from 2012 onwards. The agencies searched included are listed in Table 70.

Table 70. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
UK: National Institute for Health and Care Excellence (NICE) or Scottish Medicines Consortium (SMC)	www.nice.org.uk	Reports from 2012 and onwards are included.	12.06.2024
US: Institute for Clinical and Economic Review (ICER)	www.ICER.org		12.06.2024
Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	www.CADTH.ca		12.06.2024
Germany: German Federal Joint Committee (GBA) or Institute for Quality and Efficiency in Healthcare (IQWiG)	www.iqwig.de/en/		12.06.2024
France: Haute Autorité de Santé (HAS)	www.has-sante.fr		12.06.2024
Australia: Pharmaceutical Benefits Advisory Committee (PBAC)	www.pbs.gov.au		12.06.2024

Finally, the above searches were supplemented with hand searches of the bibliographies of recent relevant SLRs and pooled analyses of clinical trials (i.e., published since 2020) that were flagged during citation screening in each SLR. These references served only as secondary sources to ensure that all key primary studies were identified and to assess the consistency between the data reported in publications and the data reported in these additional sources.

I.1.2 Search strings

The search strings for the economic and HRQoL SLRs are reported below, respectively.

Economic systematic literature review

Table 71. Economic search strategy for Embase (Embase 1974 to 31 May 2024; Search executed: 3 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	111740
2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	58389
3		bladder cancer/	64001
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	155089
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	7048367
6		(or/1-4) and 5	85011
7	CADTH filters for economic studies	Economics/	245419
8		Cost/	64560
9		exp Health Economics/	1075833
10		Budget/	34733
11		budget*.ti,ab,kw.	49653
12		(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.	328529
13		(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	567765
14		(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.	303500
15		(value adj2 (money or monetary)).ti,ab,kw.	4293

16		Statistical Model/	177523
17		economic model*.ab,kw.	6567
18		Probability/	155101
19		markov.ti,ab,kw.	38640
20		monte carlo method/	53751
21		monte carlo.ti,ab,kw.	64849
22		Decision Theory/	1870
23		Decision Tree/	24599
24		(decision* adj2 (tree* or analy* or model*)).ti,ab,kw.	56601
25		or/7-24	2095567
26	Additional search terms for resource utilization and productivity	Health care utilization/	100802
27		Productivity/	52049
28		Caregiver Burden/	11444
29		Hospital admission/	297845
30		Length of Stay/	290323
31		(resource utilization or resource utilisation).mp.	30206
32		(patient admission or hospital admission* or hospital visit* or outpatient admission* or outpatient visit* or inpatient admission* or inpatient visit* or emergency admission* or emergency visit*).mp.	357892
33		(productivity cost or societal cost or opportunity cost).mp.	4186
34		(absenteeism or presenteeism).mp.	25016
35		(work and loss).mp.	88182
36		(caregiver burden or caregiver time or travel time).mp.	19147
37		or/26-36	878577

38	Combined CADTH and resource utilization/ productivity terms	25 or 37	2793177
39	Limits	((energy or oxygen) adj cost).ti,ab.	5228
40		((energy or oxygen) adj expenditure).ti,ab.	38681
41		letter.pt.	1323739
42		Conference proceeding.pt.	0
43		Conference abstract.pt.	5170151
44		editorial.pt.	807718
45		review.pt.	3232714
46		note.pt.	987675
47		or/39-46	11552103
48		38 not 47	1818836
49		exp animal/	31878936
50		exp human/	26616803
51		49 not (49 and 50)	5262133
52		48 not 51	1751561
53	Combined criteria	6 and 52	2480
54	Language restriction	limit 53 to English language	2372
55	Limits	limit 54 to yr=”2012-current”	1960

Table 72. Economic search strategy for MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to 30 May 2024; Search executed: 3 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	64751
2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	70092
3		bladder cancer/	64738
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	97780
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	4951045
6		(or/1-4) and 5	45502
7	CADTH filters for economic studies	exp "Costs and Cost Analysis"/	270815
8		Economics, Nursing/	4013
9		Economics, Medical/	9280
10		Economics, Pharmaceutical/	3137
11		exp Economics, Hospital/	25856
12		Economics, Dental/	1922
13		exp "Fees and Charges"/	31454
14		exp Budgets/	14217
15		budget*.ti,ab,kf.	38068
16		(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	296589
17		(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or	408518

		expenses or financial or finance or finances or financed).ab. /freq=2	
18		(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	226086
19		(value adj2 (money or monetary)).ti,ab,kf.	3208
20		exp models, economic/	16345
21		economic model*.ab,kf.	4470
22		markov chains/	16186
23		markov.ti,ab,kf.	30865
24		monte carlo method/	32904
25		monte carlo.ti,ab,kf.	63260
26		exp Decision Theory/	13673
27		(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	43029
28		or/7-27	942470
29	Additional search terms for resource utilization and productivity	Health Resources/	14821
30		Length of Stay/	104884
31		Patient Admission/	26266
32		(patient admission or hospital admission* or hospital visit* or outpatient admission* or outpatient visit* or inpatient admission* or inpatient visit* or emergency admission* or emergency visit*).mp.	96776
33		(productivity cost or societal cost or opportunity cost).mp.	2344
34		(absenteeism or presenteeism).mp.	15158
35		(work and loss).mp.	56407
36		(caregiver burden or caregiver time or travel time).mp.	9635
37		(resource utilisation or resource utilization).mp.	16658
38		or/29-37	299597
39	Combined CADTH and resource utilization/	28 or 38	1191782

	productivity terms		
40	Limits	(metabolic adj cost).ti,ab.	1797
41		((energy or oxygen) adj cost).ti,ab.	4947
42		((energy or oxygen) adj expenditure).ti,ab.	30151
43		Comment/	1036347
44		Report/ or letter/	1260160
45		Editorial/	693171
46		(comment or editorial or posters or News or Newspaper article or meeting abstracts or lectures or interview or historical article or handbooks or guidelines or guidebooks or essays or editorial or clinical conference or catalogs).pt.	2126030
47		or/40-46	2892511
48		39 not 47	1104976
49		exp animal/	27229854
50		exp human/	22003137
51		49 not (49 and 50)	5226717
52		48 not 51	1060776
53	Combined criteria	6 and 52	1072
54	Language restriction	limit 53 to English language	1027
55	Limits	limit 54 to yr=”2012-current”	777

Table 73. Economic search strategy for Cochrane Register of Controlled Trials (EBM Reviews - Cochrane Central Register of Controlled Trials April 2024; Search executed: 3 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	2338
2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	2518
3		bladder cancer/	2338

4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	6311
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	613950
6		(or/1-4) and 5	4513
7	Language restriction	limit 6 to English language	4317
8	Limits	limit 7 to yr=”2012-current”	3277

Table 74. Economic search strategy for EconLit (Econlit 1886 to 27 May 2024; Search executed: 3 June 2024)

No.	Criteria	Strings	Hits
1	Population	(transitional cell carcinoma or bladder tumor or urogenital tract tumor).ab,ti.	2
2		(bladder cancer).ab,ti.	14
3		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).ab,ti	17
4		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").ab,ti.	106902
5		(or/1-3) and 4	2
6	Limits	limit 5 to yr="2012-current"	1

Table 75. Economic search strategy for the NHS Economic Evaluation database (EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016; Search executed: 3 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	36

2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	39
3		bladder cancer/	36
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	50
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	5910
6		(or/1-4) and 5	20
7	Language restriction	limit 6 to English language	20
8	Limits	limit 7 to yr="2012-current"	5

Table 76. Economic search strategy for the Northern Light database (Northern Light Life Sciences Conference Abstracts 2010 – 2024 Week 21; Search executed: 3 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	14681
2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	14681
3		bladder cancer/	14681
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	22246
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	546120
6		(or/1-4) and 5	10407
7	Limits	"International Society for Pharmacoeconomics and Outcomes Research".cf.	48751

8	Combined criteria	6 and 7	107
9	Limits	limit 8 to yr=”2021-current”	65

Health-related quality of life systematic literature review

Table 77. HRQoL search strategy for Embase (Embase 1974 to 21 June 2024; Search executed: 24 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	112051
2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	58557
3		bladder cancer/	64189
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	155530
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	7074083
6		(or/1-4) and 5	85299
7	CADTH filters for HRQoL studies with additional search terms for bladder cancer questionnaires	socioeconomics/	168041
8		exp Quality of Life/	702279
9		quality of life.ti,kw.	184831
10		((instrument or instruments) adj3 quality of life).ab.	5643
11		Quality-Adjusted Life Year/	37786
12		quality adjusted life.ti,ab,kw.	28164
13		(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.	47866
14		disability adjusted life.ti,ab,kw.	7355
15		daly*.ti,ab,kw.	7191

16	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	52073
17	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.	3109
18	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.	1074
19	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.	12888
20	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	72
21	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.	545
22	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.	41965
23	(hye or hyes).ti,ab,kw.	196
24	((health* adj2 year* adj2 equivalent*) or (HALY* or "years of healthy life" or YHL or "years of potential life lost" or YPLL or YHLL)).ti,ab,kw.	1949
25	(pqol or qls).ti,ab,kw.	780
26	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.	930
27	nottingham health profile*.ti,ab,kw.	1703
28	nottingham health profile/	683
29	sickness impact profile.ti,ab,kw.	1301
30	sickness impact profile/	2407
31	health status indicator/	3586
32	(health adj3 (utilit* or status or index)).ti,ab,kw.	135011

33	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight or coefficient* or rated or rating* or state* or status)).ti,ab,kw.	28469
34	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.	20411
35	disutilit*.ti,ab,kw.	1374
36	rosser.ti,ab,kw.	144
37	willingness to pay.ti,ab,kw.	14233
38	standard gamble*.ti,ab,kw.	1238
39	(time trade off or time tradeoff).ti,ab,kw.	2501
40	tto.ti,ab,kw.	2373
41	(hui or hui1 or hui2 or hui3).ti,ab,kw.	3354
42	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual or "Euroqol 5D-3L" or "Euroqol 5D-5L" or EQ5D5L or EQ5D3L or EQ-5D-5L or EQ-5D-3L).ti,ab,kw.	41502
43	duke health profile.ti,ab,kw.	121
44	functional status questionnaire.ti,ab,kw.	182
45	dartmouth coop functional health assessment*.ti,ab,kw.	14
46	(15D or "15 D" or 15dimension or "15 dimension").ti,ab,kw.	7950
47	or/17-46	280779
48	(QLQ-C30 or QLQC30 or QLQ C30).ti,ab,kw.	12394
49	(QLQ-BLM30 or QLQBLM30 or QLQ BLM30).ti,ab,kw.	87
50	(bladder utility symptom scale$ or BUSS).ti,ab,kw.	1300
51	(VAS or visual analog$ scale$).ti,ab,kw.	158716
52	(DCE or discrete choice experiment$).ti,ab,kw.	15015
53	Functional Assessment of Cancer Therapy General/	1088
54	(fact g or fact-g or functional assessment of cancer therapy-general or functional assessment of cancer therapy general or fact Bl or fact-Bl or functional assessment of cancer therapy-bladder or functional assessment of cancer therapy bladder or fact blsi-18 or fact-blsi-18 or fblsi-18 or	2819

		nfblsi-18 or functional assessment of cancer therapy bladder symptom index-18 or functional assessment of cancer therapy-bladder symptom index-18 or fact taxane or fact-taxane or functional assessment of cancer therapy taxane or functional assessment of cancer therapy-taxane).mp.	
55		or/48-54	189230
56		47 or 55	446823
57	Limits	letter.pt.	1326614
58		editorial.pt.	809936
59		review.pt.	3240288
60		note.pt.	990305
61		Conference proceeding.pt.	0
62		Conference abstract.pt.	5191115
63		or/57-62	11558258
64		56 not 63	301145
65		exp animal/	31966650
66		exp human/	26695223
67		65 not (65 and 66)	5271427
68		64 not 67	283155
69	Combined criteria	6 and 68	462
70	Language restriction	limit 69 to English language	439
71	Limits	limit 70 to yr=2012-current	364

Table 78. HRQoL search strategy for MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to 21 June 2024; Search executed: 24 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	64913

2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	70262
3		bladder cancer/	64901
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	98035
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	4968151
6		(or/1-4) and 5	45637
7	CADTH filters for HRQoL studies with additional search terms for bladder cancer questionnaires	Value of Life/	5827
8		Quality of Life/	289935
9		quality of life.ti,kf.	126209
10		((instrument or instruments) adj3 quality of life).ab.	4080
11		Quality-Adjusted Life Years/	16521
12		quality adjusted life.ti,ab,kf.	18780
13		(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	30726
14		disability adjusted life.ti,ab,kf.	6262
15		daly*.ti,ab,kf.	5640
16		(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	32119
17		(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	2784
18		(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	655

19	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	8172
20	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	42
21	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	468
22	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	26254
23	(hye or hyes).ti,ab,kf.	78
24	(health* adj2 year* adj2 equivalent*) or (HALY* or "years of healthy life" or YHL or "years of potential life lost" or YPLL or YHLL).ti,ab,kw.	1780
25	(pqol or qls).ti,ab,kf.	484
26	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	761
27	nottingham health profile*.ti,ab,kf.	1264
28	sickness impact profile.ti,ab,kf.	1102
29	exp health status indicators/	348016
30	(health adj3 (utilit* or status or index)).ti,ab,kw.	103136
31	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight or coefficient* or rated or rating* or state* or status)).ti,ab,kw.	17940
32	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	15510
33	disutilit*.ti,ab,kf.	685
34	rosser.ti,ab,kf.	112
35	willingness to pay.ti,ab,kf.	9564
36	standard gamble*.ti,ab,kf.	925
37	(time trade off or time tradeoff).ti,ab,kf.	1727
38	tto.ti,ab,kf.	1505

39		(hui or hui1 or hui2 or hui3).ti,ab,kf.	2114
40		(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual or "Euroqol 5D-3L" or "Euroqol 5D-5L" or EQ5D5L or EQ5D3L or EQ-5D-5L or EQ-5D-3L).ti,ab,kw.	24838
41		duke health profile.ti,ab,kf.	94
42		functional status questionnaire.ti,ab,kf.	134
43		dartmouth coop functional health assessment*.ti,ab,kf.	14
44		(15D or "15 D" or 15dimension or "15 dimension").ti,ab,kf.	6365
45		or/7-44	803539
46		(QLQ-C30 or QLQC30 or QLQ C30).ti,ab,kf.	5967
47		(QLQ-BLM30 or QLQBLM30 or QLQ BLM30).ti,ab,kw.	35
48		(bladder utility symptom scale$ or BUSS).ti,ab,kw.	876
49		(VAS or visual analog$ scale$).ti,ab,kf.	106064
50		(DCE or discrete choice experiment$).ti,ab,kf.	10400
51		(fact g or fact-g or functional assessment of cancer therapy-general or functional assessment of cancer therapy general or fact Bl or fact-Bl or functional assessment of cancer therapy-bladder or functional assessment of cancer therapy bladder or fact blsi-18 or fact-blsi-18 or fblsi-18 or nfblsi-18 or functional assessment of cancer therapy bladder symptom index-18 or functional assessment of cancer therapy-bladder symptom index-18 or fact taxane or fact-taxane or functional assessment of cancer therapy taxane or functional assessment of cancer therapy-taxane).mp.	1273
52		or/46-51	124171
53		45 or 52	899161
54	Limits	report/ or letter/	1263516
55		editorial.pt.	695525
56		review.pt.	3340098
57		(comment or editorial or posters or News or Newspaper article or meeting abstracts or lectures or interview or historical article or handbooks or guidelines or guidebooks or essays or editorial or clinical conference or catalogs).pt.	2129463

58		or/54-57	6148511
59		53 not 58	768288
60		exp animal/	27284073
61		exp human/	22050314
62		60 not (60 and 61)	5233759
63		59 not 62	743492
64	Combined criteria	6 and 63	796
65	Language restriction	limit 64 to English language	707
66	Limits	limit 65 to yr=2012-current	547

Table 79. HRQoL search strategy for Cochrane Register of Controlled Trials (EBM Reviews - Cochrane Central Register of Controlled Trials May 2024; Search executed: 24 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	2344
2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	2526
3		bladder cancer/	2344
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	6339
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	618365
6		(or/1-4) and 5	4531
7	Language restriction	limit 6 to English language	4335
8	Limits	limit 7 to yr =2012-current	3295

Table 80. HRQoL search strategy for the Northern Light database (Northern Light Life Sciences Conference Abstracts 2010 – 2024 Week 24; Search executed: 24 June 2024)

No.	Criteria	Strings	Hits
1	Population	exp Urinary Bladder Neoplasms/	14791
2		transitional cell carcinoma/ or bladder tumor/ or urogenital tract tumor/	14791
3		bladder cancer/	14791
4		((bladder or transitional or urothelial or urogenital) adj2 (cancer$ or malign$ or tumo?r$ or neoplas$ or carcino$ or adenocarcino$)).mp.	22437
5		("stage iiib" or "stage iiic" or "stage iii b" or "stage iii c" or "stage iv" or metast* or disseminat* or spread* or migration* or advanced or progress* or invasive or aggressive or unresect* or "not operable" or inoperable or untreatable or "not treatable" or secondary or recurrent or incurable or "not curable").mp.	550321
6		(or/1-4) and 5	10535
7	Limits	"International Society for Pharmacoeconomics and Outcomes Research".cf.	48751
8		American Association for Cancer Research.cf.	73039
9		American Society of Clinical Oncology.cf.	84939
10		European Society for Medical Oncology.cf.	22763
11		American Urological Association.cf.	35179
12		Society of Urologic Oncology.cf.	2474
13		or/7-12	267145
14	Combined criteria	6 and 13	6851
15	Limits	limit 14 to yr="2021-current"	2510

Table 81. Economic studies search strategy for Health Technology Assessment bodies

HTA body	Website	Examples of search terms
National Institute of Health Care Excellence (NICE; England)	https://www.nice.org.uk/guidance/published?type=ta	Urothelial Bladder Transitional cell carcinoma First-line Date filter: January 2012 – Current
Scottish Medicines Consortium (SMC; Scotland)	https://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory	
Institute for Clinical and Economic Review (ICER; US)	https://icer.org/explore-our-research/assessments/	
Canadian Agency for Drugs and Technologies in Health (CADTH; Canada)	https://www.cadth.ca/search?s=health%20technology%20review&op=OR&f%5B0%5D=project_line%3A108244	
Gemeinsamer Bundesausschuss (G-BA; Germany)	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/	
Institute for Quality and Efficiency in Healthcare (IQWiG; Germany)	https://www.iqwig.de/projekte/projekte-und-ergebnisse/#searchQuery=query=*&page=1&rows=10&sortBy=score&sortOrder=desc&facet.filter.language=de	
Pharmaceutical Benefits Advisory Committee (PBAC; Australia) - Outpatient	http://www.pbs.gov.au/info/industry/listing/participants/pbac	
Medical Services Advisory Committee (MSAC: Australia) - Outpatient	http://www.msac.gov.au/	
French National Authority for Health (HAS; France)	https://www.has-sante.fr/jcms/fc_2875171/en/resultat-de-recherche?tmpParam=&opSearch=&portal=prd1_2986155&types=technologies&FACET_THEME=c_64654%2Fc_64675&FACET_THEME=c_64654%2Fc_64675%2Fc_1151690	

Abbreviations: HTA, Health Technology Assessment.

I.1.2.1 Eligibility criteria

Study eligibility criteria were defined in terms of population, interventions, comparators, outcomes, and study design (PICOS) structure outlined in For both SLRs, only studies published in English were included, and only studies published in or after 2012 were eligible for inclusion. This year was chosen as the cut-off to ensure included studies would be reflective of the rapidly evolving treatment landscape and in order to still capture studies evaluating both PD-L1/PD-1 inhibitors (atezolizumab first approved for treatment of UC in 2016[9]).

Table 82 (economic studies) and Table 83 (HRQoL studies), which guided the identification and selection of studies relevant for the SLRs. The population, intervention, and comparator eligibility criteria were the same across both SLRs, whereas the outcomes and study design criteria were specific to each SLR.

The target population for the SLRs included adult (≥18 years) patients with Ia/mUC (stages IIIA-B and IVA-B) who have not received prior systemic therapy in the Ia/mUC setting, based on the populations recruited in Cohort K of EV-103 (Ia/mUC patients ineligible for 1L cisplatin) and EV-302 (Ia/mUC patients who are eligible for 1L platinum chemotherapy). Subgroups of interest included patients who are cisplatin-eligible, those who are cisplatin-ineligible, those treated with cisplatin, and those treated with carboplatin.

The interventions/comparators of interest included all treatments currently licensed and/or recommended for 1L Ia/mUC in the US or Europe.[7,8] This included EV, EV + pembrolizumab, platinum-based chemotherapy, gemcitabine-based chemotherapy (as monotherapy or combination therapy with paclitaxel), ddMVAC with growth factor support, atezolizumab, pembrolizumab, ifosfamide + doxorubicin + gemcitabine, avelumab as maintenance therapy (in patients who did not progress on 1L platinum-containing chemotherapy), placebo or best supportive care (BSC), and no intervention. Specific regimens in development for the target population (alone or in combination with other agents) were also of interest. These included bempegaldesleukin, disitamab vedotin (RC48-ADC), F520, lenvatinib, nivolumab, tremelimumab, ipilimumab, durvalumab, and toripalimab.

The economic SLR captured cost of illness studies, economic evaluations including cost-effectiveness analyses (CEA), cost-utility analyses (CUA), cost-benefit analyses (CBA), cost-consequence studies, cost-minimization analyses (CMA), and budget impact analyses (BIA), along with clinical trials or observational studies (prospective or retrospective) with relevant outcomes. Outcomes of interest for HCRU/cost studies included HCRU and costs associated with treating Ia/mUC, outcomes of interest for cost-effectiveness studies include comparisons of benefits and costs between intervention and comparators (e.g., incremental costs, incremental cost-effectiveness ratios [ICERs], quality-adjusted life years [QALYs], life years [LYs], any other measure of effectiveness reported together with costs), and outcomes of interest for budget impact studies include comparisons of budget impact between scenarios with and without a new intervention.

The HRQoL SLR captured RCTs, non-RCTs, single-arm trials, observational studies (prospective and retrospective), and HRQoL instrument application/validation studies. Outcomes of interest included generic patient-reported outcome (PRO) measures (e.g.,

EuroQoL-five dimensions [EQ-5D], Short Form-36 [SF-36], SF-12, SF-6D, and brief pain inventory [BPI]), disease-specific PRO measures (e.g., European Organization for Research and Treatment of Cancer Quality of Life-Core 30 [EORTC QLQ-C30], EORTC QLQ-Muscle Invasive Bladder Cancer 30 [EORTC QLQ-BLM30], Functional Assessment of Cancer Therapy – General [FACT-G], FACT-Bladder [FACT-BI], NCCN/FACT-Bladder Symptom Index-18 [NFBlSI-18]), FACT-Taxane, and utilities/disutilities.

For both SLRs, only studies published in English were included, and only studies published in or after 2012 were eligible for inclusion. This year was chosen as the cut-off to ensure included studies would be reflective of the rapidly evolving treatment landscape and in order to still capture studies evaluating both PD-L1/PD-1 inhibitors (atezolizumab first approved for treatment of UC in 2016[9]).

Table 82: Eligibility criteria for the economic systematic literature review

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adult (≥18 years) patients with la/mUC who have not received prior systemic therapy in the locally advanced or metastatic setting[a] Subgroups of interest: • Patients who are cisplatin-eligible • Patients who are cisplatin-ineligible • Patients who are treated with 1L cisplatin-containing therapies • Patients who are treated with 1L carboplatin-containing therapies	--

Interventions/ Comparators[b]	• Regimens approved in any of the above populations/subgroups:
	• Enfortumab vedotin
	• Enfortumab vedotin + pembrolizumab
	• Platinum-based chemotherapy
	  ○ Gemcitabine + cisplatin
	  ○ Gemcitabine + cisplatin + paclitaxel
		Non-pharmacological treatments
		
		Surgery, radiotherapy (alone or in combination), neoadjuvant or adjuvant regimens

	○ Gemcitabine + carboplatin ○ ddMVAC with growth factor • Atezolizumab • Pembrolizumab • Gemcitabine • Gemcitabine + paclitaxel • Ifosfamide + doxorubicin + gemcitabine • Avelumab (maintenance)[c] • Placebo or best supportive care • No intervention • Regimens in development for the target population, which may include (alone or in combination with other agents): • Bempegaldesleukin • Disitamab vedotin • F520 • Lenvatinib • Nivolumab • Tremelimumab • Ipilimumab • Durvalumab • Toripalimab	
Outcomes	**Costs/HCRU studies** Costs associated with treating la/mUC • Total healthcare costs, direct costs (e.g., drug-related, AEs, inpatient/outpatient services, hospitalizations), indirect/societal costs (e.g., absenteeism, presenteeism, productivity loss, out-of-pocket costs, caregiver burden) • Healthcare resource use (e.g., hospitalizations,	No outcomes of interest

	physician visits, length of hospitalization, health system use, medication use) or productivity **Cost-effectiveness/budget impact studies** • Comparison of benefits and costs between intervention and comparators (e.g., incremental costs, ICERs, QALYs, LYs, any other measure of effectiveness reported together with costs) • Comparison of budget impact between scenarios with and without a new intervention	

Study design	• Cost of illness studies
	• Economic evaluations, including:
	  ○ Cost-effectiveness analyses
	  ○ Cost-utility analyses
	  ○ Cost-benefit analyses
	  ○ Cost-consequence studies
	  ○ Cost-minimization analyses
	  ○ Budget impact analyses
	• Clinical trials or observational studies (prospective, retrospective) with relevant outcomes, e.g., resource use
		• Cross-sectional studies
		• Phase I trials
		• Dose-finding/dose-escalation trials
		• Pooled analyses of clinical trials[d]
		• Case reports, case studies, studies with <10 patients in target population
		• Editorials, narrative reviews, erratum, commentary
		• Systematic literature reviews[d]

Language	Studies published in English	Studies published in a language other than English
Time	Studies published from 2012 onwards	Studies published prior to 2012

Notes: a) Relevant studies in 2L+ populations were excluded but flagged during screening; If there was insufficient evidence in the 1L population, the identified 2L+ studies were additionally included in the evidence base; **b)** Components of the listed regimens, as monotherapy or in combination with other treatments, were of interest; **c)** Avelumab maintenance therapy only in patients who did not progress on first-line platinum-containing chemotherapy; **d)** Relevant systematic literature reviews and pooled analyses of clinical trials were excluded but used to confirm relevant citations were included. **Abbreviations:** 1L, first-line; 2L, second-line; AE, adverse event; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; la/mUC, locally advanced or metastatic urothelial carcinoma; LY, life year; QALY, quality-adjusted life year.

Table 83: Eligibility criteria for the health-related quality of life systematic literature review

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adult (≥18 years) patients with la/mUC who have not received prior systemic therapy in the locally advanced or metastatic setting[a] *Subgroups of interest:* • Patients who are cisplatin-eligible • Patients who are cisplatin-ineligible • Patients who are treated with 1L cisplatin-containing therapies • Patients who are treated with 1L carboplatin-containing therapies	--

Interventions/ Comparators[b]	Approved regimens in any of the above populations/subgroups:
	• Enfortumab vedotin
	• Enfortumab vedotin + pembrolizumab
	• Platinum-based chemotherapy
	  ○ Gemcitabine + cisplatin
	  ○ Gemcitabine + cisplatin + paclitaxel
	  ○ Gemcitabine + carboplatin
	  ○ ddMVAC with growth factor
	• Atezolizumab
	• Pembrolizumab
	• Gemcitabine
	• Gemcitabine + paclitaxel
	• Ifosfamide + doxorubicin + gemcitabine
	• Avelumab (maintenance)[c]
		Non-pharmacological treatments
		
		Surgery, radiotherapy (alone or in combination), neoadjuvant or adjuvant regimens

	• Placebo or best supportive care • No intervention Regimens in development for the target population (alone or in combination with other agents): • Bempegaldesleukin • Disitamab vedotin • F520 • Lenvatinib • Nivolumab • Durvalumab • Tremelimumab • Ipilimumab • Toripalimab	

Outcomes	Global and subscale scores of the following outcomes:
	• Generic patient-reported outcome measures, such as:
	  ○ EQ-5D
	  ○ SF-36/SF-12/SF-6D
	  ○ BPI
	• Disease-specific patient-reported outcome measures, such as:
	  ○ EORTC QLQ-C30
	  ○ EORTC QLQ-BLM30
	  ○ FACT-G
	  ○ FACT-BI
	  ○ NCCN-FACT-BISI-18
	  ○ FACT-Taxane
	
	Utilities/disutilities[d]
		No patient-reported outcomes or utilities

Study design	• Randomized controlled trials • Non-randomized controlled trials • Single-arm studies	• Phase I trials • Cross-sectional studies • Pooled analyses of clinical trials[e] • Case reports or series

	• Observational studies (prospective, retrospective) • Health-related quality of life instrument application/validation studies	• Editorials • Systematic literature review[e]
Language	Studies published in English	Studies published in a language other than English
Time	Studies published from 2012 onwards	Studies published prior to 2012

Notes: a) Relevant studies in 2L+ populations were excluded but flagged during screening; If there was insufficient evidence in the 1L population, the identified 2L+ studies were additionally included in the evidence base; **b)** Components of the listed regimens, as monotherapy or in combination with other treatments, were also of interest; **c)** Avelumab maintenance therapy only in patients who did not progress on first-line platinum-containing chemotherapy; **d)** Utilities from cost-utility analyses were cross-checked from the economic SLR and HTA submissions; **e)** Relevant systematic literature reviews and pooled analyses of clinical trials were excluded but used to confirm relevant citations were included. **Abbreviations:** 1L, first-line; 2L, second-line; BPI, brief pain inventory; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQoL 5 dimensions; FACT-Bl, Functional Assessment of Cancer Therapy – Bladder; NCCN/FACT-FBlSI-18, National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy – Bladder Symptom Index-18; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-Taxane, Functional Assessment of Cancer Therapy – Taxane; la/mUC, locally advanced or metastatic urothelial carcinoma; QLQ-BLM30, Quality of Life Questionnaire-Muscle Invasive Bladder Cancer 30; QLQ-C30, Quality of Life Questionnaire-Core 30; SF, Short Form.

I.1.3 Systematic selection of studies

I.1.3.1.1 Study selection processes – economic SLR

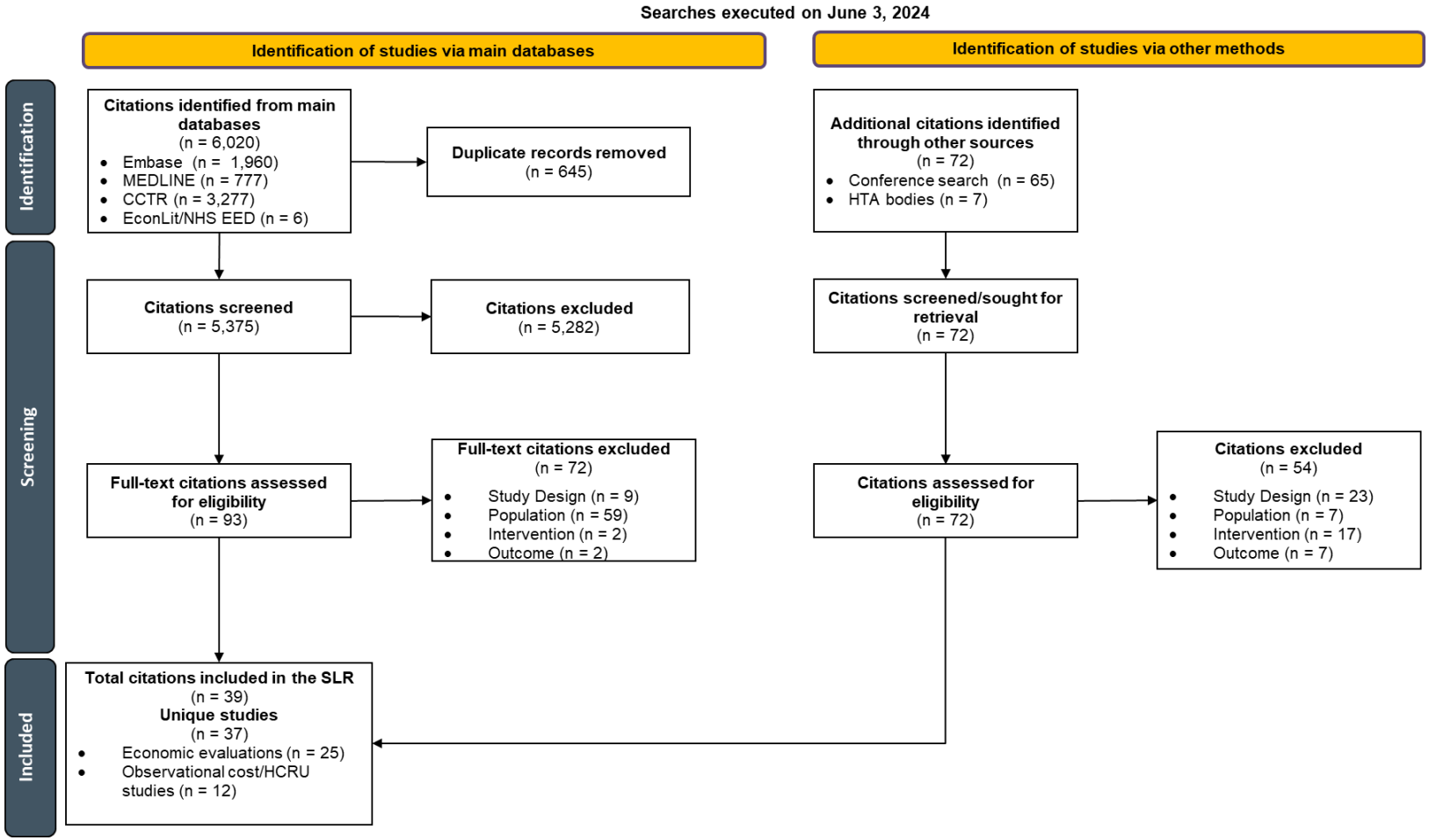
Global economic studies SLR

A total of 6,020 publications were identified from Embase, MEDLINE, CCTR, NHS EED, and EconLit databases. After removing 6,45 duplicates from the bibliographic databases, the titles/abstracts of 5,375 unique citations were screened against the pre-defined PICOS criteria (For both SLRs, only studies published in English were included, and only studies published in or after 2012 were eligible for inclusion. This year was chosen as the cut-off to ensure included studies would be reflective of the rapidly evolving treatment landscape and in order to still capture studies evaluating both PD-L1/PD-1 inhibitors (atezolizumab first approved for treatment of UC in 20169).

Table 82). Of these, 93 citations were reviewed at the full-text stage and 72 were excluded. Grey literature searches of a pre-specified conference proceeding (ISPOR), HTA body websites, and reference checks of relevant SLRs resulted in the identification of 18 additional records for inclusion. Ultimately, a total of 39 citations representing 37 unique studies were included in the final evidence base and are detailed in the following sections, including 25 economic evaluations (n=20 CEAs or CUAs; n=2 BIAs; n=3 both CUA and BIA) and 12 observational cost and HCRU studies. Out of the 25 economic evaluations, 18 were publications (either peer-reviewed full-text articles [n=11][10-16] or conference posters [n=7][17-21]) and seven were HTA submissions. For the 12 cost and HCRU studies, eight were full-text publications and four was a conference abstract.

The PRISMA flow diagram for the study selection process used in the economic SLR is presented in Figure 42**.** Table 84 presents a summary of the included publications. A list of publications excluded during full-text screening, with exclusion reasons are reported in Table 85.

Figure 42. Study selection flow diagram for economic studies



Abbreviations: CCTR, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica database; HCRU, health-care resource utilization; HTA, health technology assessment; MEDLINE, Medline Literature Analysis and Retrieval System Online; NHS EED, National Health Service Economic Evaluation Database; SLR, systematic literature review.

Economic SLR – included publications, global SLR

Table 84. List of studies included in the economic systematic literature review, global SLR

Study ID	First author, year	Title	Publication type
Aly 2019	Aly, 2019[22]	Overall survival, costs, and healthcare resource use by line of therapy in medicare patients with newly diagnosed metastatic urothelial carcinoma	Full text
Bilen 2023a	Bilen, 2023[23]	Clinical and economic outcomes in patients with metastatic urothelial carcinoma receiving first-line systemic treatment (the impact uc i study)	Full text
Bilen 2023b	Bilen, 2023[24]	Healthcare resource utilization (hcru) and costs in patients with metastatic urothelial cancer (muc) who received first-line (1l) treatment: Results from impact uc ii	Conference abstract
Bilen 2021	Bilen, 2021[23]	Treatment pattern and healthcare resource utilization (hru) in patients with metastatic urothelial carcinoma (muc) among medicare fee-for-service (ffs) beneficiaries- results from impact uc	Conference abstract
CADTH 2020	CADTH 2020[25]	Avelumab (Bavencio) for Urothelial Carcinoma	Health technology assessment
CADTH 2019	CADTH 2019[26]	Keytruda Metastatic Urothelial Carcinoma (first line)	Health technology assessment
Chang 2021	Chang, 2021[27]	Cost-effectiveness analysis of avelumab plus best supportive care (bsc) vs bsc alone as a first-line (1l) maintenance treatment for patients with locally advanced or metastatic urothelial carcinoma in taiwan	Conference poster
Critchlow 2024	Critchlow, 2024[28]	Cost-effectiveness analysis for avelumab first-line maintenance treatment of advanced urothelial carcinoma in scotland	Full text
Critchlow 2021	Critchlow, 2021[18]	Modeling health-related outcomes with avelumab as a first-line maintenance treatment following chemotherapy vs. Best supportive care (bsc) for patients with locally advanced or metastatic urothelial cancer in the uk	Conference poster

Flannery 2018	Flannery, 2018[29]	Survival rates and health care costs for patients with advanced bladder cancer treated and untreated with chemotherapy	Full text
Grivas 2019	Grivas, 2019[30]	Healthcare resource utilization and costs of adverse events among patients with metastatic urothelial cancer in USA	Full text
Hale 2021	Hale, 2021[10]	Cost-effectiveness of pembrolizumab versus carboplatin-based chemotherapy as first-line treatment of pd-l1-positive locally advanced or metastatic urothelial carcinoma ineligible for cisplatin-based therapy in the united states	Full text
Karttunen 2021	Karttunen, 2021[19]	Cost-effectiveness of avelumab as first-line maintenance treatment for locally advanced or metastatic urothelial carcinoma in finland	Conference poster
Kearney 2023a	Kearney, 2023[31]	Treatment patterns, healthcare resource utilization (hcru), and associated costs in patients with newly diagnosed metastatic urothelial carcinoma (muc): A real-world analysis of german claims data	Conference poster
Kearney 2023b	Kearney, 2023[32]	Healthcare resource utilization (hcru) and related direct healthcare costs for patients with metastatic urothelial cancer (muc): Findings from a retrospective observational cohort study in a clinical practice setting in italy	Conference poster
Lai 2023	Lai, 2023[33]	Budget impact analysis of pembrolizumab plus enfortumab vedotin as first-line treatment of cisplatin-ineligible locally advanced or metastatic urothelial carcinoma in USA	Conference poster
Lin 2022	Lin, 2022[11]	Avelumab maintenance treatment after first-line chemotherapy in advanced urothelial carcinoma-a cost-effectiveness analysis	Full text
Liu 2023	Liu, 2023[34]	Association between oncology clinical pathway utilization and toxicity and cost outcomes in patients with metastatic solid tumors	Full text
Liu 2022	Liu, 2022[12]	Atezolizumab plus platinum-based chemotherapy as first-line therapy for metastatic urothelial cancer: A cost-effectiveness analysis	Full text
Morgans 2021	Morgans, 2021[35]	Real-world burden of illness and unmet need in locally advanced or metastatic urothelial carcinoma following discontinuation of pd-1/l1 inhibitor therapy: A medicare claims database analysis	Full text
NICE TA788 (2022)	NICE 2022[36]	Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy	Health technology assessment

NICE TA739 (2021)	NICE 2021[37]	Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable	Health technology assessment
Niegisch 2024	Niegisch, 2024[38]	Healthcare resource utilization and associated costs in patients with metastatic urothelial carcinoma: A real-world analysis using german claims data	Full text
Norgaard 2023	Norgaard, 2023[39]	Treatment patterns, survival, and healthcare utilisation and costs in patients with locally advanced and metastatic bladder cancer in denmark 2015-2020	Full text
Patterson 2019	Patterson, 2019[13]	Cost-effectiveness of pembrolizumab for patients with advanced, unresectable, or metastatic urothelial cancer ineligible for cisplatin-based therapy	Full text
PBAC 2021	PBAC 2021[40]	Public Summary Document (March 2021 PBAC Meeting) - AVELUMAB, Solution concentrate for I.V. infusion 200 mg in 10 mL, Bavencio®	Health technology assessment
Peng 2021	Peng, 2021[14]	Cost-effectiveness of avelumab maintenance therapy for advanced or metastatic urothelial carcinoma in the united states	Full text
Plessala 2022	Plessala, 2022[20]	Cost-effectiveness analysis of avelumab plus best supportive care (bsc) as first-line maintenance treatment in locally advanced or metastatic urothelial carcinoma (la/muc) in france	Conference poster
Porte 2024	Porte, 2024[41]	Cost-effectiveness of avelumab first-line maintenance therapy for adult patients with locally advanced or metastatic urothelial carcinoma in france	Full text
Qin 2021	Qin, 2021[14]	Cost-effectiveness of atezolizumab plus chemotherapy as first-line therapy for metastatic urothelial cancer	Full text
Russell 2022	Russell, 2022[21]	Budget impact analysis of avelumab + best supportive care (bsc) as first-line maintenance treatment in patients with locally advanced or metastatic urothelial carcinoma (la/muc) in ireland	Conference poster
Sarfaty 2021	Sarfaty, 2021[42]	The cost of enfortumab vedotin wastage due to vial size-a real-world analysis	Full text
SMC 2018	SMC 2018[43]	Pembrolizumab 25mg/mL concentrate for solution for infusion and 50mg powder for concentrate for solution for infusion (Keytruda®)	Health technology assessment

SMC 2021	SMC 2021[44]	Avelumab 20mg/mL concentrate for solution for infusion (Bavencio®)	Health technology assessment
Su 2023	Su, 2023[45]	A cost-effectiveness analysis of avelumab plus best supportive care versus best supportive care alone as first-line maintenance treatment for patients with locally advanced or metastatic urothelial carcinoma in taiwan	Full text
Tsai 2021	Tsai, 2021[17]	Budget impact analysis of avelumab plus best supportive care (bsc) vs bsc alone as first-line (1l) maintenance treatment in patients with locally advanced (la) or metastatic urothelial carcinoma (muc) in taiwan	Conference poster
Xie 2022	Xie, 2022[15]	Cost-effectiveness of avelumab maintenance therapy plus best supportive care vs. Best supportive care alone for advanced or metastatic urothelial carcinoma	Full text
Yang 2024	Yang, 2024[46]	Cost-effectiveness of immune checkpoint inhibitors in treating metastatic urothelial cancer	Full text
Zhang 2022	Zhang, 2022[16]	Atezolizumab with chemotherapy in first-line treatment for metastatic urothelial cancer: A cost-effectiveness analysis	Full text

Abbreviations: *CADTH, Canadian Agency for Drugs and Technologies in Health; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium.*

I.1.4 Excluded fulltext references

Table 85. List of studies excluded from the economic systematic literature review following full-text review, global SLR

First author, year	Title	Journal	Exclusion reason	Exclusion subreason
Ahern, 2021	Retrospective analysis of hospital admissions due to immune checkpoint inhibitor-induced immune-related adverse events (irae)	Asia-Pacific Journal of Clinical Oncology	Study design	Case report/case series (studies with <10 patients in the target population)
Aly, 2020	The real-world lifetime economic burden of urothelial carcinoma by stage at diagnosis	Journal of Clinical Pathways : The Foundation of Value-based Care	Intervention	Other (specify): Mixed interventions; outcomes not stratified for population of interest
Amano, 2015	Association between early palliative care referrals, inpatient hospice utilization, and aggressiveness of care at the end of life	Journal of Palliative Medicine	Population	Other (specify): Mixed disease population, no separable outcomes
Bakitas, 2015	Early versus delayed initiation of concurrent palliative oncology care: Patient outcomes in the enable iii randomized controlled trial	Journal of clinical oncology	Intervention	Not specified in the inclusion criteria
Bhanvadia, 2021	Financial toxicity among patients with prostate, bladder, and kidney cancer: A systematic review and call to action	European Urology Oncology	Study design	Relevant systematic review, pooled analysis

Bosch-Compte, 2023	Prognostic factors in oncological patients with solid tumours requiring intensive care unit admission	Oncology Letters	Population	Other (specify): Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the genitourinary cancers
Burstein, 2023	Comparing end-of-life care of hematologic malignancy versus solid tumor patients in a tertiary care center	European Journal of Haematology	Population	Other (specify): Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the genitourinary cancers
Cai, 2021	Contemporary trends on expenditure of hospital care on total cancer and its subtypes in china during 2008-2017	Chinese Journal of Cancer Research	Population	Line of therapy not reported or unknown
Carreras, 2023	Use of drugs in clinical practice and the associated cost of cancer treatment in adult patients with solid tumors: A 10-year retrospective cohort study	Current Oncology	Population	Line of therapy not reported or unknown
Cerni, 2023	Does geography play a role in the receipt of end-of-life care for advanced cancer patients? Evidence from an australian local health district population-based study	Journal of Palliative Medicine	Population	Other (specify): Mixed tumor types; "genitourinary" cancers comprised ICD-10 codes C51-67
Contieri, 2024	The financial burden of guideline-recommended cancer medications for metastatic urothelial carcinoma	European Urology Focus.	Study design	Review, letter, expert opinion, editorials, erratum, commentary

Costa, 2023	Health outcomes and budget impact projection of anti-pd-(l)1s in cancer care in portugal	Frontiers in public health	Population	Line of therapy not reported or unknown
Chini, 2021	Homcology: Home chemotherapy delivery in a simultaneous care project for frail advanced cancer patients	Supportive Care in Cancer	Population	Other (specify): frail patients with advanced disease
Cox, 2020	Effects of bladder cancer on uk healthcare costs and patient health-related quality of life: Evidence from the boxit trial	Clinical Genitourinary Cancer	Population	Line of therapy not reported or unknown
de Oliveira, 2020	High-cost patients and preventable spending: A population-based study	JNCCN Journal of the National Comprehensive Cancer Network	Population	Other (specify): Mixed disease population, no separable outcomes
Dinan, 2021	Real-world systemic therapy utilization in medicare patients with locally advanced or metastatic urothelial carcinoma diagnosed between 2008 and 2012	Journal of Geriatric Oncology	Outcomes	Not specified in the inclusion criteria: Treatment pattern
Fletcher, 2020	The impact of underinsurance on bladder cancer diagnosis, survival, and care delivery for individuals under the age of 65 years	Cancer	Population	Line of therapy not reported or unknown
Garcia 2013	Medical costs of cancer attributable to work in the basque country (spain) in 2008	Gaceta Sanitaria	Population	Line of therapy not reported or unknown
Gasperoni, 2023	The role of clinical trials in the sustainability of the italian national health service cancer drug expenditure	European Journal of Hospital Pharmacy	Population	Other (specify): Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell

				carcinoma comprised any of the genitourinary cancers
Gerace 2017	Cost of illness of urothelial bladder cancer in italy	ClinicoEconomics and Outcomes Research	Population	Other (specify): Mixed line of therapy
Ghoshal et al, 2023	A novel nurse-coordinated home care model for palliative care in advanced cancer: A pilot interventional study from suburban mumbai	Progress in Palliative Care	Population	Other (specify): Mixed tumor types; no subgroup outcomes reported for bladder cancer patients; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the bladder cancers
Gitlin et al, 2023	Time duration and health care resource use during cancer diagnoses in the united states: A large claims database analysis	Journal of Managed Care and Specialty Pharmacy	Population	Other (specify): Mixed tumor types; unclear whether 1L la/murothelial carcinoma or transitional cell carcinoma comprised any of the genitourinary cancers
Glisch, 2020	Immune checkpoint inhibitor use near the end of life: A single-center retrospective study	Journal of Palliative Medicine	Population	Other (specify): Mixed disease population, no separable outcomes
Gordan, 2019	Cost differential of immuno-oncology therapy delivered at community versus hospital clinics	American Journal of Managed Care	Population	Line of therapy not reported or unknown
Grumberg, 2024	Clinical benefit of anti-pd-(l)1 immunotherapies in advanced cancer in france: A population-based estimate from 2014 to 2021	ESMO Open	Study design	Relevant systematic review, pooled analysis

Gulten and Banu, 2021	Retrospective evaluation of cancer patients in intensive care unit	Kuwait Medical Journal	Population	Other (specify): No stratified outcomes reporting for bladder cancer. "Urological cancers" reported as both prostate and bladder cancers.
Hanson, 2021	Pre-post evaluation of collaborative oncology palliative care for patients with stage iv cancer	Journal of Pain and Symptom Management	Population	Other (specify): Mixed disease population, no separable outcomes
Hawari, 2016	Predictors of icu admission in patients with cancer and the related characteristics and outcomes: A 5-year registry-based study	Critical Care Medicine	Population	Other (specify): Mixed disease population, no separable outcomes
Heijnsdijk, 2019	Cost-effectiveness of surveillance schedules in older adults with non-muscle-invasive bladder cancer	BJU International	Population	Line of therapy not reported or unknown
Hounsome, 2017	End of life care for urological cancer patients	Journal of Clinical Urology	Population	Line of therapy not reported or unknown
Isikber, 2020	Evaluation of the frequency of patients with cancer presenting to an emergency department	Revista da Associacao Medica Brasileira	Population	Other (specify): Mixed disease population, no separable outcomes
Joyce, 2024	A seer-medicare based quality score for patients with metastatic upper tract urothelial carcinoma	Clinical Genitourinary Cancer	Population	Line of therapy not reported or unknown

Kalinich, 2021	Prediction of severe immune-related adverse events requiring hospital admission in patients on immune checkpoint inhibitors: Study of a population level insurance claims database from the USA	Journal for ImmunoTherapy of Cancer	Population	Other (specify): Mixed population for tx lines; outcomes not stratified for pop. of interest
Khaki, 2021	Cost-effectiveness analysis of neoadjuvant immune checkpoint inhibition vs. Cisplatin-based chemotherapy in muscle invasive bladder cancer	Urologic Oncology: Seminars and Original Investigations	Population	Not 1L
Korkes, 2022	Stage-related cost of treatment of bladder cancer in brazil	PharmacoEconomics - Open	Population	Line of therapy not reported or unknown
Lambert, 2023	Impact of cancer-related virtual visits on travel distance, travel time, and carbon dioxide (co<inf>2</inf>) emissions during the covid-19 pandemic in manitoba, canada	Current Oncology	Population	Other (specify): Mixed tumor types; unclear whether "male genitourinary" comprised 1L la/m urothelial carcinoma or transitional cell carcinoma
Lee, 2020	Humanistic and economic burden of non-muscle invasive bladder cancer: Results of two systematic literature reviews	Clinicoeconomics & Outcomes Research	Study design	Relevant systematic review, pooled analysis
Lee, 2015	Emergency visits among end-of-life cancer patients in taiwan: A nationwide population-based study cancer palliative care	BMC Palliative Care	Population	Not urothelial carcinoma or transitional cell carcinoma
Lillini, 2023	Out-of-pocket costs sustained in the last 12 months by cancer patients: An italian survey-based study on individual expenses between 2017 and 2018	European Journal of Health Economics	Population	Other (specify): Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell

				carcinoma comprised any of the genitourinary cancers
Mantz, 2023	Recent trends in medicare payments for outpatient cancer care at the end of life	International Journal of Radiation Oncology Biology Physics	Population	Other (specify): Mixed tumor types; no subgroup outcomes reported for bladder cancer patients; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the bladder cancers
Matson, 2023	The use of hospital services by patients with muscle invasive bladder cancer in the last year of life: Identifying the areas to improve care	Cureus	Population	Line of therapy not reported or unknown
McCaffrey, 2023	Treatment patterns and out-of-hospital healthcare resource utilisation by patients with advanced cancer living with pain: An analysis from the stop cancer pain trial	PLoS ONE	Population	Other (specify): Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the genitourinary cancers
Medina, 2023	Experiences of a multiethnic cohort of patients enrolled in a financial reimbursement program for cancer clinical trials	JCO Oncology Practice	Population	Other (specify): Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the genitourinary cancers
Michaeli, 2022	Socio-economic burden of disease: Survivorship costs for bladder cancer	Journal of Cancer Policy	Population	Line of therapy not reported or unknown

Morgans, 2022	Clinical and patient-reported outcomes of advanced urothelial carcinoma following discontinuation of pd-1/l1 inhibitor therapy	Clinical Genitourinary Cancer	Outcomes	Not specified in the inclusion criteria: Relevant for HRQoL SLR. Efficacy/safety; Not sure if caregiver hours is an outcome of interest
Mossanen, 2014	The burden of bladder cancer care: Direct and indirect costs	Current Opinion in Urology	Study design	Review, letter, expert opinion, editorials, erratum, commentary
Nadeem, 2016	Cost differential of chemotherapy for solid tumors	Journal of Oncology Practice	Population	Line of therapy not reported or unknown
Pekala, 2021	The centralization of bladder cancer care and its implications for patient travel distance	Urologic Oncology: Seminars and Original Investigations	Population	Other (specify): Mixed interventions; outcomes not stratified for population of interest
Pichler and Steyrer, 2021	Cost-effectiveness analysis of the use of immunotherapy in metastatic solid tumors in austria by applying the esmo-magnitude of clinical benefit scale (esmo-mcbs) version 1.1	ESMO Open	Population	Line of therapy not reported or unknown
Rachev, 2021	Budget projections and clinical impact of an immuno-oncology class of treatments: Experience in four eu markets	Journal of Cancer Policy	Population	Other (specify): Mixed disease population, no separable outcomes
Rashidian, 2018	Epidemiology and hospitalization cost of bladder cancer in kerman province, southeastern iran	Iranian Journal of Public Health	Population	Line of therapy not reported or unknown

Reddy, 2022	Cost of cancer management by stage at diagnosis among medicare beneficiaries	Current Medical Research and Opinion	Population	Line of therapy not reported or unknown
Sadik, 2014	Attributes of cancer patients admitted to the emergency department in one year	World Journal of Emergency Medicine	Population	Other (specify): Mixed population for tx lines; outcomes not stratified for pop. of interest
Sattar, 2019	Health status, emergency department visits, and oncologists' feedback: An analysis of secondary endpoints from a randomized phase ii geriatric assessment trial	Journal of Geriatric Oncology	Population	Other (specify): Mixed population for tx lines; outcomes not stratified for pop. of interest
Scholar, 2017	Improving cancer patient emergency room utilization: A new jersey state assessment	Cancer Epidemiology	Population	Other (specify): Mixed population for tx lines; outcomes not stratified for pop. of interest
Shaz, 2020	Characteristics and outcomes of patients with solid tumors receiving chemotherapy in the intensive care unit	Supportive Care in Cancer	Population	Other (specify): Mixed disease population, no separable outcomes
Siech, 2024	Use of inpatient palliative care in metastatic urethral cancer	Urologic Oncology: Seminars and Original Investigations	Population	Line of therapy not reported or unknown
Singh, 2024	Hospitalizations and re-hospitalizations at the end-of-life among cancer patients; a retrospective register data study	BMC Palliative Care	Population	Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the urothelial cancer patients

Sloan, 2020	The cost to medicare of bladder cancer care	European Urology Oncology	Population	Line of therapy not reported or unknown
Stauder, 2024	Emergency department visits before cancer diagnosis among women at mayo clinic	Mayo Clinic Proceedings: Innovations, Quality and Outcomes	Population	Other (specify): Mixed tumor types; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the kidney/bladder cancers
Svatek, 2014	The economics of bladder cancer: Costs and considerations of caring for this disease	European Urology	Study design	Meta-analysis, indirect treatment comparison, systematic review, pooled analysis (not relevant)
Tiu, 2014	Active surveillance for low-risk bladder cancer	Urologic Oncology	Study design	Review, letter, expert opinion, editorials, erratum, commentary
Toffart, 2023	Icu admission for solid cancer patients treated with immune checkpoint inhibitors	Annals of Intensive Care	Population	Other (specify): Mixed tumor types; no subgroup outcomes reported for bladder cancer patients; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the bladder cancers
Verma, 2018	A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors	Journal for Immunotherapy of Cancer	Study design	Relevant systematic review, pooled analysis

Vogler, 2016	Cancer drugs in 16 european countries, australia, and new zealand: A cross-country price comparison study	The Lancet Oncology	Population	Other (specify): Mixed population for tx lines; outcomes not stratified for pop. of interest
Walsh, 2023	Hospitalization due to adverse drug events in older adults with cancer: A retrospective analysis	Journal of Geriatric Oncology	Population	Other (specify): Mixed tumor types; no subgroup outcomes reported for bladder cancer patients; unclear whether 1L la/m urothelial carcinoma or transitional cell carcinoma comprised any of the bladder cancers
Wang, 2017	Variations among physicians in hospice referrals of patients with advanced cancer	Journal of Oncology Practice	Population	Other (specify): Only reported as "genitourinary"
Westergren, 2019	A nationwide, population based analysis of patients with organ confined, muscle invasive bladder cancer not receiving curative intent therapy in sweden from 1997 to 2014	Journal of Urology	Population	Line of therapy not reported or unknown
Wirtz, 2023	Health care resource utilization, quality metrics, and costs of bladder cancer within the oncology care model	American Journal of Managed Care	Population	Line of therapy not reported or unknown
Zhang, 2017	The intensive palliative care unit: Changing outcomes for hospitalized cancer patients in an academic medical center	Journal of Palliative Medicine	Population	Other (specify): No typology reported beyond "genitourinary"

Zhang, 2013	Comparison of surveillance strategies for low-risk bladder cancer patients	Medical decision making: an international journal of the Society for Medical Decision Making	Population	Line of therapy not reported or unknown

I.1.5 Local adaptation economic SLR

To inform this submission for EV+P indicated for first line treatment of adult patients with la/mUC in Denmark who are eligible for platinum-containing chemotherapy, the global SLR has been adapted to exclude all studies not relevant in a Danish setting. For this reason, only studies examining EV+P versus Plat+Gem among cisplatin eligible adult patients (or mixed cisplatin eligible populations) are included.

Only one of the identified sources from the global SLR were deemed eligible for inclusion in the local adaptation (TA 788); TA788 was also identified as part of the TLR done specifically for this submission (see below). All other sources from the global SLR were omitted as inputs in the health economic model.

Targeted literature review – economic studies

In addition to the SLR, a targeted literature review (TLR) was carried to identify and collect relevant inputs for the health economic model. The TLR was conducted pragmatically, focusing solely on inputs not informed by SmPC, cost sources, etc. The search was conducted on May 16th, 2024 (Table 86). Two literature inputs were used in the health economic model.

Table 86. List of studies included in the economic review, TLR

Source name/database	Location/source	Search strategy	Date of search
NICE	Technology appraisal guidance: Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy TA788: www.nice.org.uk	Hand search	16.05.2024
Rigshospitalet (n.d)	www.rigshospitalet.dk/undersoegelse-og-behandling/find-undersoegelse-og-behandling/Sider/Cisplatin-og-Gemcitabin---Behandling-af-kraeft-i-blaeren-med--2875866.aspx	Hand search	16.05.2024

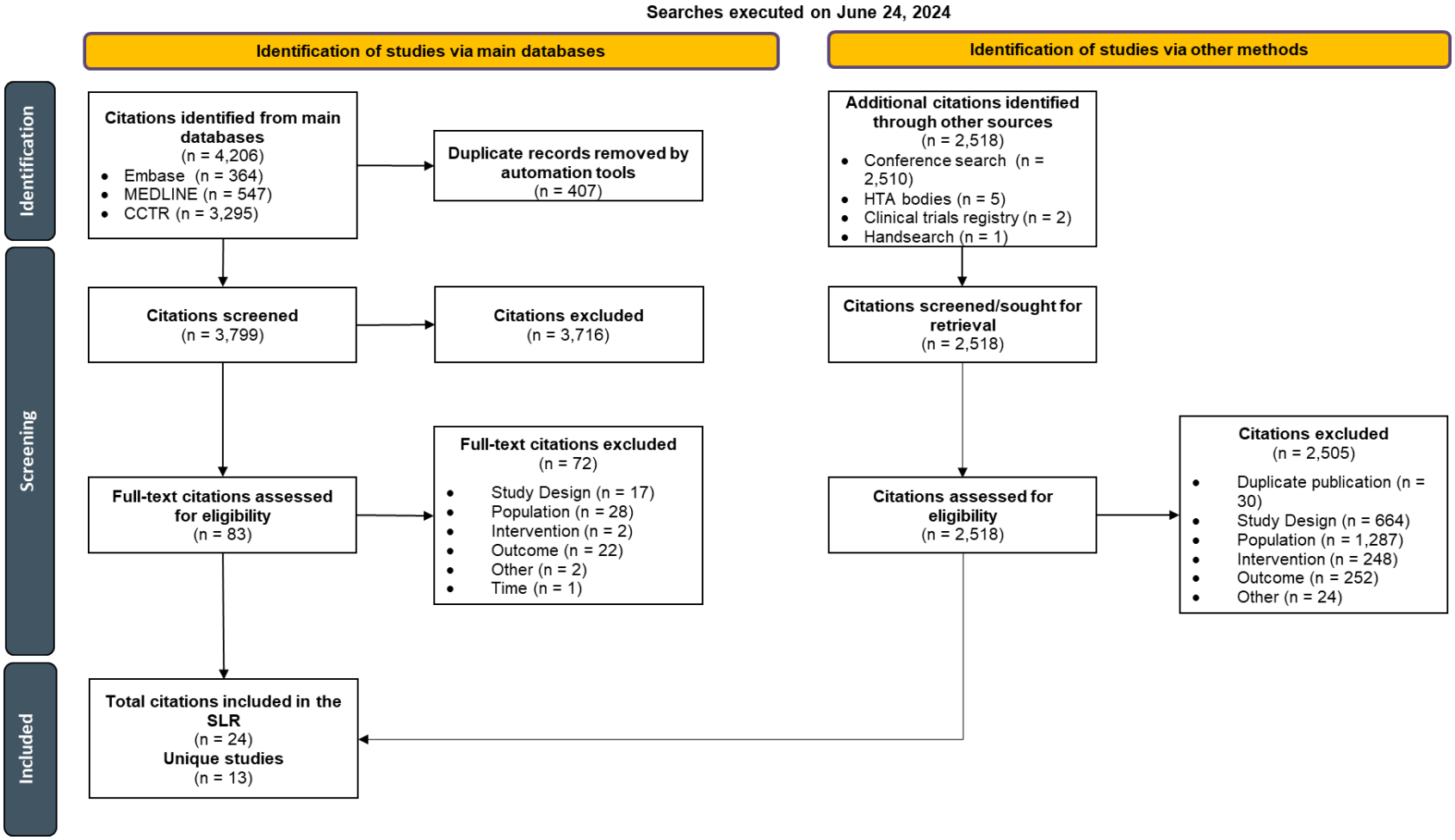
I.1.6 Study selection processes – health-related quality of life

Global SLR health-related quality of life

A total of 4206citations were identified from Embase, MEDLINE, and CCTR databases. After removing 407 duplicates, the titles/abstracts of 3,799unique citations were screened against the pre-defined PICOS criteria (Table 83). Of these, 83 citations were reviewed at the full-text stage and 72 were excluded. Grey literature searches of pre-specified conference proceedings (AACR, ASCO, AUA, ESMO, EUA, ISPOR, and SUO), clinical trials registries (ICTRP), HTA body websites, hand searches, and reference checks of relevant SLRs resulted in the identification of 13 additional records for inclusion. Ultimately, a total of 24 citations representing 13 unique studies were included in the final evidence base and are detailed in the following sections. Out of the 24 HRQoL citations, 16 were publications (either peer-reviewed full-text articles [n=11] or conference materials [n=5]), five were HTA submissions (all of which were also captured in the economic SLR), and three were clinical trial registries.

The PRISMA flow diagram for the study selection process used in the HRQoL SLR is presented in Figure 43. Table 90 presents a summary of the included publications. A list of publications excluded during full-text screening, with exclusion reasons. The list of clinical trials initiated from 2012 onward without HRQoL results available yet are presented in Table 91.

Figure 43. Study selection flow diagram for health-related quality of life studies



Abbreviations: CCTR, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica database; HTA, health technology assessment; MEDLINE, Medline Literature Analysis and Retrieval System Online; SLR, systematic literature review

Health-related quality of life SLR – included and excluded publication, global SLR

Table 87. List of studies included in the health-related quality of life systematic literature review, global SLR

Study ID	First author, year	Title	Publication type
An 2024	An, 2024[47]	Gemcitabine/nab-paclitaxel vs gemcitabine/carboplatin for advanced urothelial carcinoma	Full text
CheckMate 901	van der Heijden, 2024[48]	Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma	Full text
DANUBE	AstraZeneca, 2015[49]	Study of MEDI4736 (Durvalumab) With or Without Tremelimumab Versus Standard of Care Chemotherapy in Urothelial Cancer	Clinical trials registry
EORTC Study 30986	De Santis, 2012[50]	Randomized phase ii/iii trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: Eortc study 30986	Full text
EV-103	Milowsky, 2024[51]	Patient-reported outcomes in patients with advanced urothelial cancer who are ineligible for cisplatin and treated with first-line enfortumab vedotin alone or with pembrolizumab	Full-text
EV-302	Gupta, 2024 [52]	Patient-reported outcomes (pros) from a randomized, phase 3 trial of enfortumab vedotin plus pembrolizumab (ev+p) versus platinum-based chemotherapy (pbc) in previously untreated locally advanced or metastatic urothelial cancer (la/muc)	Conference slides
	Powles, 2024[53]	Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer	Full-text

Hasaligil 2022	Hasaligil, 2022[54]	Health-related quality of life (hrqol) by line of treatment, treatment history, and disease status in patients with metastatic urothelial carcinoma (muc) in eu-4 and the united kingdom: Results from a disease specific programme	Conference poster
IMvigor130	Bamias, 2023[55]	Atezolizumab monotherapy versus chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (imvigor130): Final overall survival analysis from a randomised, controlled, phase 3 study	Full text
	NICE, 2021[37]	Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable	Health technology assessment
JAVELIN Bladder 100	Grivas, 2024[56]	Avelumab first-line maintenance (1lm) for advanced urothelial carcinoma (auc): Long-term patient-reported outcomes (pros) in the phase 3 javelin bladder 100 trial	Conference poster
	Grivas, 2022[57]	Patient-reported outcomes from javelin bladder 100: Avelumab first-line maintenance plus best supportive care versus best supportive care alone for advanced urothelial carcinoma	Full text
	Grumberg, 2024[58]	Clinical benefit of anti-pd-(l)1 immunotherapies in advanced cancer in france: A population-based estimate from 2014 to 2021	Full text
	Kapetanakis, 2021[59]	Health state utility values of patients with locally advanced or metastatic urothelial carcinoma- analysis based on the javelin bladder 100 trial	Conference poster
	Peipert, 2024[60]	Reliability, validity, and change thresholds of the nccn/fact bladder symptom index (nfblsi-18) in patients with advanced urothelial cancer	Full text
	Pfizer, 2015[61]	A Phase 3, Multicenter, Multinational, Randomized, Open-label, Parallel-arm Study of Avelumab (msb0010718c) Plus Best Supportive Care versus Best Supportive Care Alone as a Maintenance Treatment in	Clinical trials registry

		Patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease did not Progress After Completion of First-line Platinum-containing Chemotherapy	
	NICE, 2022[36]	Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy	Health technology assessment
	SMC, 2021[44]	Avelumab 20mg/mL concentrate for solution for infusion (Bavencio®)	Health technology assessment
	PBAC, 2021[40]	Public Summary Document (March 2021 PBAC Meeting) - Avelumab, Solution concentrate for I.V. infusion 200 mg in 10 mL, Bavencio®	Health technology assessment
KEYNOTE-052	Morales-Barrera, 2022[62]	Health-related quality of life (hrqol) for patients with advanced/metastatic urothelial carcinoma (uc) enrolled in keynote-052 who are potentially platinum ineligible	Conference poster
	SMC, 2018[43]	Pembrolizumab 25mg/mL concentrate for solution for infusion and 50mg powder for concentrate for solution for infusion (Keytruda®)	Health technology assessment
KEYNOTE-361	Merck Sharp & Dohme, 2016[63]	A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab With or Without Platinum-Based Combination Chemotherapy Versus Chemotherapy in Subjects With Advanced or Metastatic Urothelial Carcinoma	Clinical trials registry
Taarnhoj 2021	Taarnhoj, 2021[64]	Patient-reported outcomes, health-related quality of life, and clinical outcomes for urothelial cancer patients receiving chemo-or immunotherapy: A real-life experience	Full text

VINGEM	Holmsten, 2020[65]	Vinflunine/gemcitabine versus carboplatin/gemcitabine as first-line treatment in cisplatin-ineligible patients with advanced urothelial carcinoma: A randomised phase ii trial (vingem)	Full text

Abbreviations: NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium.

Table 88. List of studies excluded from the health-related quality of life systematic literature review following full-text review

First author, year	Title	Journal	Exclusion reason	Exclusion subreason
Aly, 2020	Medical oncology referral and systemic therapy of patients with advanced stage urothelial carcinoma	Journal of Comparative Effectiveness Research	Population	Line of therapy not reported or unknown
Balar, 2017	First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (keynote-052): A multicentre, single-arm, phase 2 study	The lancet	Outcomes	Not specified in the inclusion criteria
Balar, 2022	Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: Results from keynote-045 and keynote-052 after up to 5 years of follow-up	Annals of oncology: official journal of the European society for medical oncology	Outcomes	Not specified in the inclusion criteria
Beeren, 2023	Health-related quality of life during the first 4 years after non-muscle-invasive bladder cancer diagnosis: Results of a large multicentre prospective cohort	European Urology Oncology.	Population	Not locally advanced or metastatic

Bergerot, 2021	Discrepancies between genitourinary cancer patients' and clinicians' characterization of the eastern cooperative oncology group performance status	Cancer	Study design	Cross-sectional studies, Phase I trials, dose-finding/dose-escalation trials
Bessa, 2020	Unmet needs in sexual health in bladder cancer patients: A systematic review of the evidence	BMC Urology	Study design	Relevant systematic review, pooled analysis
Caloudas, 2024	Patient-centered development of a bladder cancer survivorship care plan	Supportive Care in Cancer	Study design	Other (specify): Qualitative study (open-ended surveys/interviews of patients regarding their preferences & coping)
Chaballout, 2023	Assessing utilities for muscle-invasive bladder cancer-related health states	Urologic Oncology: Seminars and Original Investigations	Population	Healthy subjects
Chung, 2019	Assessment of quality of life, information, and supportive care needs in patients with muscle and non-muscle invasive bladder cancer across the illness trajectory	Supportive Care in Cancer	Study design	Cross-sectional studies, Phase I trials, dose-finding/dose-escalation trials
Cox, 2020	Effects of bladder cancer on UK healthcare costs and patient health-related quality of life: Evidence from the boxit trial	Clinical Genitourinary Cancer	Population	Not locally advanced or metastatic
De Santis, 2016	Vinflunine-gemcitabine versus vinflunine-carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: Results of an international randomized phase ii trial (jasint1)	Annals of oncology: official journal of the European	Outcomes	Not specified in the inclusion criteria

		society for medical oncology		
Degboe, 2019	Validity and performance of the functional assessment of cancer therapy-bladder (fact-bl) among advanced urothelial cancer patients	Supportive Care in Cancer	Population	Not 1L
Di Costanzo. 2023	Analysis of health-related quality of life reporting in phase iii rcts of advanced genitourinary tumors	Cancers	Study design	Relevant systematic review, pooled analysis
Efficace, 2021	Patient-reported outcomes as independent prognostic factors for survival in oncology: Systematic review and meta-analysis	Value in Health	Study design	Relevant systematic review, pooled analysis
Galsky, 2020	Atezolizumab with or without chemotherapy in metastatic urothelial cancer (imvigor130): A multicentre, randomised, placebo-controlled phase 3 trial	Lancet (London, England)	Outcomes	Not specified in the inclusion criteria
Ghoshal	A novel nurse-coordinated home care model for palliative care in advanced cancer: A pilot interventional study from suburban mumbai	Progress in Palliative Care	Population	Other (specify): Mixed cancer population without la/mUC-specific reporting
Grande	Atezolizumab plus chemotherapy versus placebo plus chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (imvigor130): Final overall survival analysis results from a randomised, controlled, phase 3 study	The lancet	Outcome	Not specified in the inclusion criteria
Grande	Overall survival by response to first-line induction treatment with atezolizumab plus platinum-based chemotherapy or placebo plus platinum-based chemotherapy for metastatic urothelial carcinoma	European urology open science	Outcome	Not specified in the inclusion criteria

Grivas	Avelumab first-line maintenance therapy for advanced urothelial carcinoma: Comprehensive clinical subgroup analyses from the javelin bladder 100 phase 3 trial	European urology	Outcome	Not specified in the inclusion criteria
Guo	Literature analysis of cutaneous adverse reactions induced by tislelizumab	Cutaneous & Ocular Toxicology	Study design	Case report/case series (studies with <10 patients in the target population)
Hall, 2019	Patient-reported outcomes for cancer patients receiving checkpoint inhibitors: Opportunities for palliative care-a systematic review	Journal of Pain and Symptom Management	Study design	Relevant systematic review, pooled analysis
Izumi, 2019	Gemcitabine plus cisplatin split versus gemcitabine plus carboplatin for advanced urothelial cancer with cisplatin-unfit renal function	In vivo (Athens, Greece)	Outcomes	Not specified in the inclusion criteria
Jensen, 2013	Measuring priority symptoms in advanced bladder cancer: Development and initial validation of a brief symptom index	Journal of Supportive Oncology	Population	Line of therapy not reported or unknown
Kent, 2014	The importance of symptom surveillance during follow-up care of leukemia, bladder, and colorectal cancer survivors	Supportive Care in Cancer	Study design	Cross-sectional studies, Phase I trials, dose-finding/dose-escalation trials
Krege, 2014	Prospective randomized double-blind multicentre phase ii study comparing gemcitabine and cisplatin plus sorafenib chemotherapy with gemcitabine and cisplatin plus placebo in locally advanced and/or metastasized urothelial cancer: Suse (auo-ab 31/05)	BJU international	Outcomes	Not specified in the inclusion criteria

Kypriotakis, 2016	The longitudinal relationship between quality of life and survival in advanced stage cancer	Psycho-Oncology	Population	Other (Specify): Mixed cancer population without la/mUC-specific reporting
Lee, 2023	Avelumab first-line maintenance plus best supportive care (bsc) vs. Bsc alone for advanced urothelial carcinoma: Javelin bladder 100 Asian subgroup analysis	Urologic oncology	Outcome	Not specified in the inclusion criteria
Machingura, 2022	Clustering of eortc qlq-c30 health-related quality of life scales across several cancer types: Validation study	European Journal of Cancer	Population	Other (specify): Mixed cancer types/disease stages/treatment statuses, without outcomes stratified for population of interest
Matsubara, 2024	Pembrolizumab with or without lenvatinib as first-line therapy for patients with advanced urothelial carcinoma (leap-011): A phase 3, randomized, double-blind trial	European urology	Outcome	Not specified in the inclusion criteria
Miller, 2016	A phase ii study of the central European society of anticancer-drug research (cesar) group: Results of an open-label study of gemcitabine plus cisplatin with or without concomitant or sequential gefitinib in patients with advanced or metastatic transitional cell carcinoma of the urothelium	Urologia internationalis	Outcomes	Not specified in the inclusion criteria
Mina, 2019	Life quality evaluation in patients with bladder cancer: A systematic review	Actas Urologicas Espanolas	Other	Non-English publication

Minato, 2023	Efficacy and tolerability of enfortumab vedotin for metastatic urothelial carcinoma: Early experience in the real world	Anticancer Research	Population	Not 1L
Miyake, 2024	Dysgeusia in patients with advanced urothelial carcinoma receiving enfortumab vedotin, platinum-based chemotherapy, or immune check point inhibitors: Time-course assessment using chemotherapy-induced taste alteration scale	Journal of Chemotherapy.	Population	Other (specify): Mixed line of therapy, no separable outcomes for 1L
Morgans, 2022	Clinical and patient-reported outcomes of advanced urothelial carcinoma following discontinuation of pd-1/l1 inhibitor therapy	Clinical Genitourinary Cancer	Population	Not 1L
Necchi, 2024	Derazantinib alone and with atezolizumab in metastatic urothelial carcinoma with activating fgfr aberrations	JNCI cancer spectrum	Outcome	Not specified in the inclusion criteria
Nishijima, 2019	Patient-reported outcomes with pd-1/pd-l1 inhibitors for advanced cancer: A meta-analysis	Oncologist	Study design	Relevant systematic review, pooled analysis
O'Donnell, 2023	Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer	Journal of clinical oncology	Outcome	Not specified in the inclusion criteria
O'Donnell, 2019	Patient-reported outcomes and inflammatory biomarkers in patients with locally advanced/metastatic urothelial carcinoma treated with durvalumab in phase 1/2 dose-escalation study 1108	Cancer	Population	Not 1L

Ohyama, 2019	Nivolumab in patients with unresectable locally advanced or metastatic urothelial carcinoma: Checkmate 275 2-year global and japanese patient population analyses	International Journal of Clinical Oncology	Population	Not 1L
Pearman, 2018	Validity and usefulness of a single-item measure of patient-reported bother from side effects of cancer therapy	Cancer	Study design	Cross-sectional studies, Phase I trials, dose-finding/dose-escalation trials
Perlis, 2018	The bladder utility symptom scale: A novel patient reported outcome instrument for bladder cancer	Journal of Urology	Population	Line of therapy not reported or unknown
Pickard, 2016	Using patient-reported outcomes to compare relative burden of cancer: Eq-5d and functional assessment of cancer therapy-general in eleven types of cancer	Clinical Therapeutics	Population	Line of therapy not reported or unknown
Powles, 2023	Avelumab first-line maintenance for advanced urothelial carcinoma: Results from the javelin bladder 100 trial after ≥2 years of follow-up	Journal of clinical oncology	Outcome	Not specified in the inclusion criteria
Powles, 2021	Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (keynote-361): A randomised, open-label, phase 3 trial	The lancet	Outcomes	Not specified in the inclusion criteria
Powles, 2016	A multicentre, international, randomised, open-label phase 3 trial of avelumab + best supportive care (bsc) vs bsc alone as maintenance therapy after first-line platinum-based chemotherapy in patients with advanced urothelial cancer (javelin bladder 100)	Annals of oncology	Other	Conference abstract/proceedings
Powles, 2020	Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma	New England journal of medicine	Outcomes	Not specified in the inclusion criteria

Powles, 2020	Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (danube): A randomised, open-label, multicentre, phase 3 trial	The lancet	Outcomes	Not specified in the inclusion criteria
Qian, 2024	The clinical effect of gratitude extension-construction theory nursing program on bladder cancer patients with fear of cancer recurrence	Frontiers in oncology	Population	Line of therapy not reported or unknown
Ripping, 2022	Validation and reliability of the dutch version of the eortc qlq-blm30 module for assessing the health-related quality of life of patients with muscle invasive bladder cancer	Health & Quality of Life Outcomes	Population	Other (specify): Mixed LoT and intervention, without outcomes stratified for population of interest
Rosenberg, 2021	Randomized phase iii trial of gemcitabine and cisplatin with bevacizumab or placebo in patients with advanced urothelial carcinoma: Results of calgb 90601 (alliance)	Journal of clinical oncology	Outcomes	Not specified in the inclusion criteria
Sanghera, 2022	Challenges in using recommended quality of life measures to assess fluctuating health: A think-aloud study to understand how recall and timing of assessment influence patient responses	Patient	Study design	Case report/case series
Schneidewind, 2023	Prospective evaluation of health-related quality of life in patients with metastatic urothelial carcinoma undergoing immunotherapy with pembrolizumab: Symptom burden can predict survival	Urologia Internationalis	Population	Other (specify): Mixed LoT population, no separable outcomes
Schwartz, 2020	Capturing patient experience: Does quality-of-life appraisal entail a new class of measurement?	Journal of Patientreported Outcomes	Population	Other (specify): Mixed LoT population, no separable outcomes

Singer, 2013	Quality of life in patients with muscle invasive and non-muscle invasive bladder cancer	Supportive Care in Cancer	Population	Other (specify): Mixed LoT and intervention, no separable outcomes
Smith, 2018	Impact of bladder cancer on health-related quality of life	BJU International	Population	Other (specify): Mixed LoT and intervention, no separable outcomes
Sparano, 2019	Inclusion of older patients with cancer in randomised controlled trials with patient-reported outcomes: A systematic review	BMJ supportive & palliative care	Study design	Meta-analysis, indirect treatment comparison, systematic review, pooled analysis (not relevant)
Sternberg, 2013	Larotaxel with cisplatin in the first-line treatment of locally advanced/metastatic urothelial tract or bladder cancer: A randomized, active-controlled, phase iii trial (cilab)	Oncology	Outcomes	Not specified in the inclusion criteria
Taarnhoj, 2023	The iblad study: Patient-reported outcomes in bladder cancer during oncological treatment: A multicenter national randomized controlled trial	Journal of patient-reported outcomes	Population	Line of therapy not reported or unknown
Taarnhoj, 2020	Patient reported symptoms associated with quality of life during chemo- or immunotherapy for bladder cancer patients with advanced disease	Cancer Medicine	Study design	Relevant systematic review, pooled analysis
Taarnhoj, 2019	Quality of life in bladder cancer patients receiving medical oncological treatment; a systematic review of the literature	Health & Quality of Life Outcomes	Study design	Relevant systematic review, pooled analysis
Taarnhoj, 2020	Electronic reporting of patient-reported outcomes in a fragile and comorbid population during cancer therapy - a feasibility study	Health and Quality of Life Outcomes	Population	Other (specify): Mixed LoT population, no separable outcomes

Thalen-Lindstrom, 2013	Anxiety and depression in oncology patients; a longitudinal study of a screening, assessment and psychosocial support intervention	Acta Oncologica	Population	Other (specify): Mixed LoT and intervention, no separable outcomes
Tomita, 2022	Avelumab first-line maintenance plus best supportive care (bsc) vs bsc alone for advanced urothelial carcinoma: Javelin bladder 100 japanese subgroup analysis	International journal of clinical oncology	Outcomes	Not specified in the inclusion criteria
Tsai, 2021	Determinants and dynamic changes of generic quality of life in human bladder cancer patients	Journal of Clinical Medicine	Population	Other (specify): Mixed LoT and intervention, no separable outcomes
Tsai, 2022	Dynamic changes of quality of life in muscle-invasive bladder cancer survivors	BMC Urology	Intervention	Not specified in the inclusion criteria
Van Hemelrijck, 2019	Patient-reported outcomes in randomised clinical trials of bladder cancer: An updated systematic review	BMC Urology	Study design	Relevant systematic review, pooled analysis
von der Maase, 2023	Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase iii study	Journal of clinical oncology	Time	Study published prior to 2012
Wang, 2024	Combination of hyperthermia and intravesical chemotherapy for the treatment of pt1 stage bladder cancer: A retrospectively clinical study	Asia-Pacific Journal of Clinical Oncology	Population	Not 1L
Yanez, 2013	The fact-g7: A rapid version of the functional assessment of cancer therapy-general (fact-g) for monitoring symptoms and concerns in oncology practice and research	Annals of Oncology	Population	Other (specify): Mixed disease population, no separable outcome

Yu, 2019	Health-related quality of life around the time of diagnosis in patients with bladder cancer	BJU International	Population	Line of therapy not reported or unknown

Abbreviations: 1L, first-line; LoT, line of therapy.

Table 89. List of clinical trials initiated from 2012 onward without health-related quality of life results available yet

Study ID	Study start date	Title	Estimated primary completion date
Bristol-Myers Squibb, 2017	March 24, 2017	A Phase 3, Open-label, Randomized Study of Nivolumab Combined With Ipilimumab, or With Standard of Care Chemotherapy, Versus Standard of Care Chemotherapy in Participants With Previously Untreated Unresectable or Metastatic Urothelial Cancer	June 15, 2023
Consorzio Oncotech, 2019	February 6, 2019	Avelumab as Single Agent in Metastatic or Locally Advanced Urothelial Cancer in Patients Unfit for Cisplatin	January 2021
Merck Sharp & Dohme, 2019	May 6, 2019	A Phase 3, Randomized, Double-blind Study to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Lenvatinib (E7080/MK-7902) Versus Pembrolizumab and Placebo as First Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression (LEAP-011)	October 31, 2023

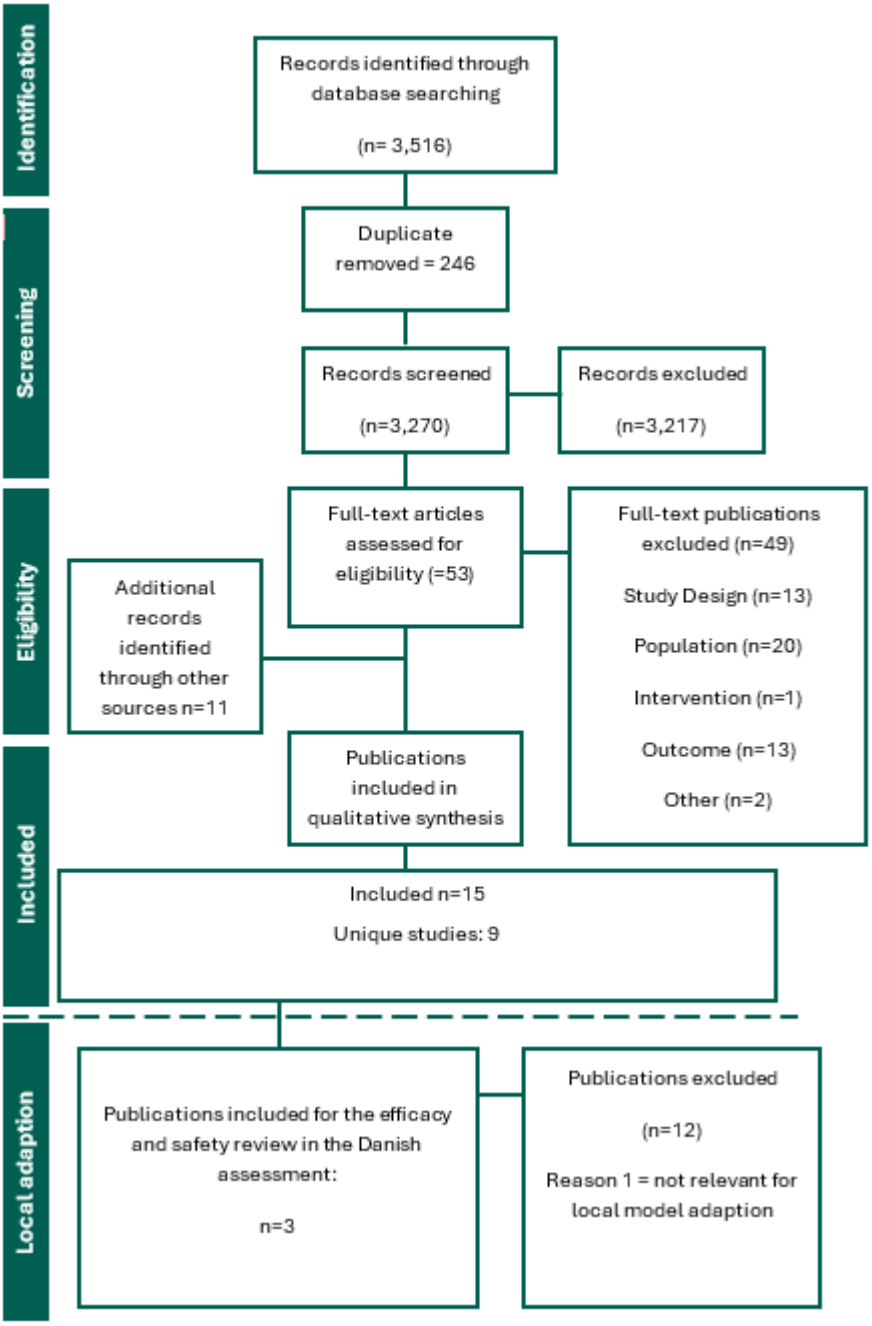
Notes: Results are based on the search date of March 3rd, 2023.

Local adaptation health-related quality of life SLR

To inform this submission for EV+P indicated for first line treatment of adult patients with la/mUC in Denmark who are eligible for platinum-containing chemotherapy, the global SLR has been adapted to exclude all studies not relevant in a Danish setting. For this reason, only studies examining EV+P versus Plat+Gem among cisplatin eligible adult patients (or mixed cisplatin eligible populations) are included.

The study selection process is detailed in the PRISMA flow-chart presented in Figure 44

Figure 44. Study selection flow diagram for health-related quality of life, local adaptation



Health-related quality of life SLR review – included and excluded publication, local adaptation

Table 90. List of studies included in the health-related quality of life systematic literature review, local adaptation

Study ID	First author, year	Title	Publication type
IMvigor130	NICE, 2021[37]	Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable	Health technology assessment
JAVELIN Bladder 100	NICE, 2022[36]*	Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy.	Health technology assessment
	SMC, 2018[43]	Pembrolizumab 25mg/mL concentrate for solution for infusion and 50mg powder for concentrate for solution for infusion (Keytruda®)	Health technology assessment

*Three publications were deemed relevant for inputs from the technical appraisal: 1) Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, Bramham-Jones S. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010 May 18;8:50. doi: 10.1186/1477-7525-8-50. PMID: 20482804; PMCID: PMC2890699. 2) Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006 Jul-Aug;26(4):410-20. doi: 10.1177/0272989X06290495. PMID: 16855129; PMCID: PMC2634296. 3) Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008 Oct 21;6:84. doi: 10.1186/1477-7525-6-84. PMID: 18939982; PMCID: PMC2579282.

Table 91. List of studies excluded in the health-related quality of life systematic literature review, local adaptation

Study ID	First author, year	Title	Publication type
DANUBE	AstraZeneca, 2015[49]	Study of MEDI4736 (Durvalumab) With or Without Tremelimumab Versus Standard of Care Chemotherapy in Urothelial Cancer	Clinical trials registry
EORTC Study 30986	De Santis, 2012[50]	Randomized phase ii/iii trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: Eortc study 30986	Full text
Hasaligil 2022	Hasaligil, 2022[54]	Health-related quality of life (hrqol) by line of treatment, treatment history, and disease status in patients with metastatic urothelial carcinoma (muc) in eu-4 and the united kingdom: Results from a disease specific programme	Conference poster
JAVELIN Bladder 100	Grivas, 2022[57]	Patient-reported outcomes from javelin bladder 100: Avelumab first-line maintenance plus best supportive care versus best supportive care alone for advanced urothelial carcinoma	Full text
	Kapetanakis, 2021[59]	Health state utility values of patients with locally advanced or metastatic urothelial carcinoma- analysis based on the javelin bladder 100 trial	Conference poster
	Pfizer, 2015[61]	A Phase 3, Multicenter, Multinational, Randomized, Open-label, Parallel-arm Study of Avelumab (msb0010718c) Plus Best Supportive Care versus Best Supportive Care Alone as a Maintenance Treatment in Patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease did not Progress After Completion of First-line Platinum-containing Chemotherapy	Clinical trials registry
	PBAC, 2021[40]	Public Summary Document (March 2021 PBAC Meeting) - Avelumab, Solution concentrate for I.V. infusion 200 mg in 10 mL, Bavencio®	Health technology assessment

KEYNOTE-052	Morales-Barrera, 2022[62]	Health-related quality of life (hrqol) for patients with advanced/metastatic urothelial carcinoma (uc) enrolled in keynote-052 who are potentially platinum ineligible	Conference poster
KEYNOTE-361	Merck Sharp & Dohme, 2016[63]	A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab With or Without Platinum-Based Combination Chemotherapy Versus Chemotherapy in Subjects With Advanced or Metastatic Urothelial Carcinoma	Clinical trials registry
Taarnhoj 2021	Taarnhoj, 2021[64]	Patient-reported outcomes, health-related quality of life, and clinical outcomes for urothelial cancer patients receiving chemo-or immunotherapy: A real-life experience	Full text
VINGEM	Holmsten, 2020[65]	Vinflunine/gemcitabine versus carboplatin/gemcitabine as first-line treatment in cisplatin-ineligible patients with advanced urothelial carcinoma: A randomised phase ii trial (vingem)	Full text

Targeted literature review – health-related quality of life

In additional to the global SLR, a TLR was carried out to identify and collect HRQoL, and utility outcomes to inform the health economic model. This was done by targeting technical appraisals published by NICE (Table 92).

Table 92. Sources included in the targeted literature search

Source name/database	Location/source	Search strategy	Date of search
NICE	National Institute for Health and Care Excellence, NICE TA772: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies. (2022)	Hand search	24/07/2024
	National Institute for Health and Care Excellence, NICE TA581: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (2019)		
	National Institute for Health and Care Excellence, NICE TA858: Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma. (2023)		

I.1.7 Quality assessment and generalizability of estimates

Study quality of included cost and HCRU studies, along with single-arm and observational studies were assessed using the Newcastle-Ottawa scale.[66] This instrument was used to evaluate study quality based on 1) study group and selection, 2) comparability of the groups within studies, and 3) the ascertainment of either the exposure or outcomes of interest for case-control or cohort studies. Ranking of the study quality was conducted by using a 'star system' in which a study could be given a maximum of one star for each numbered item within the "Selection" and "Exposure" categories and a maximum of two stars for the "Comparability" category. The quality was summarized by adding the number of stars, where a higher number corresponded to better quality. While the maximum score a study can receive was nine, the denominator for each category was the total number of criteria applicable to a particular design

The Cochrane Collaboration's Risk of Bias (RoB) tool (Version 2) was used to assess risk of bias in included clinical trials (e.g., reporting HRQoL) (Appendix H).[67] This instrument was used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The risk of bias instrument can be used to assign summary assessments of within-study bias, low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high risk of bias (high risk of bias for one or more key domains).

Overall, the studies were deemed to have an adequate level of quality. Based on the Cochrane RoB tool, RCTs were generally judged to be at low risk of bias in most domains or some concerns and high risk of bias in a few domains. Based on the NOS, Taarnhoj 2021 scored a five-star rating out of a possible of six points due to the study being a single cohort, suggesting a low risk of bias.[64]

I.1.8 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

An economic SLR was conducted to identify and summarize studies that report costs, health care resource utilization (HCRU), cost-effectiveness, budget impact, HRQoL, and utility outcomes for the treatment of la/mUC patients who have not received prior systemic therapy in the locally advanced or metastatic setting. To avoid repetition the economic SLR as a whole (targeting both HRQoL and inputs for the health economic model) is in Appendix I.

Appendix K. Appendix references

1. Seagen Inc. EV-302 protocol: An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer, 2022.
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Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk