Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [ID6332]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [ID6332]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Astellas:**
   a. Full submission
      i. New data cut clinical addendum
      ii. New data cut economic addendum
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Action Bladder Cancer UK – written by patient expert, Jeannie Rigby
   b. Fight Bladder Cancer – endorsed by patient expert, Melanie Costin and by clinical expert, Robert Huddart

4. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts:**
   a. Jeannie Rigby – patient expert, nominated by Action Bladder Cancer UK
   b. Melanie Costin – patient expert, nominated by Fight Bladder Cancer
   c. Syed Hussain – clinical expert, nominated by Astellas (company) and MSD
   d. Robert Huddart – clinical expert, nominated by Fight Bladder Cancer

7. **Additional analysis documents**
   a. Company response to additional analysis on severity
   b. EAG critique of company response

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy: ID6332

Document B
Company evidence submission

November 2024

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ID6332 Document B_Final_CIC_redacted_15112024	2	**No**	15 November 2024

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List of abbreviations

1L, 2L	first-line, second line
ADC	antibody-drug-conjugate
AE	adverse event
AFT	accelerated failure time
AIC	Akaike information criterion
AUC	area under the curve
BC	bladder cancer
BIC	Bayesian information criterion
BICR	blinded independent central review
BIM	budget impact model
BSA	body surface area
BSC	best supportive care
CEM	cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CrCL	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CSR	clinical study report
DOR	duration of response
DoT	duration of treatment
DSU	Decision Support Unit
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQol-5 Dimensions-3 Level
ESMO	European Society for Medical Oncology
EV	enfortumab vedotin
FAS	full analysis set
FDA	(U.S.) Food and Drug Administration
GP	general practitioner
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
IMD	Index of Multiple Deprivation
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
IQR	interquartile range
IV	intravenous
KM	Kaplan-Meier

La/mUC	locally advanced/metastatic urothelial cancer
MIBC	muscle invasive bladder cancer
MMAE	microtubule-disrupting agent monomethyl auristatin E
Mo	months
mUC	metastatic urothelial carcinoma
NCCN	National Comprehensive Cancer Network
NMIBC	non-muscle invasive bladder cancer
ORR	objective response rate
OS	overall survival
P	pembrolizumab
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PH	proportional hazards
PR	partial response
PROs	patient-reported outcomes
PS	performance status
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
QALY	quality-adjusted life year
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	quality of life
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SD	standard deviation
SLR	systematic literature review
SmPC	Summary of product characteristics
TA	technology appraisal
TEAE	treatment emergent adverse event
TNM	tumour, node, metastasis
TRAE	treatment-related adverse event
ToT	time on treatment
TSD	Technical Support Document
u/mUC	unresectable or metastatic urothelial carcinoma
UC	urothelial carcinoma
UTUC	upper tract urothelial carcinoma
VAS	visual analogue score
VAT	value added tax

B.1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission covers enfortumab vedotin (EV's) full Great Britain (GB) marketing authorisation for this indication, namely "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".[1] This is also the population covered by the pivotal EV-302 phase 3 trial of EV in combination with pembrolizumab (EV+P).[2]

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.	As NICE scope.	Note: the pivotal trial (EV-302) population was described as 'locally advanced or metastatic' urothelial cancer (UC), whereas the wording in the licensed indication and the NICE scope is 'unresectable or metastatic' UC. However, as noted by the EMA (EPAR p. 110[3]) unresectable disease was an inclusion criterion for the trial (see Section 2.3.1, Table 8). There is therefore no misalignment between the trial population and the licensed indication or the scope.
Intervention	Enfortumab vedotin in combination with pembrolizumab.	As NICE scope: Enfortumab vedotin (EV; Padcev®) in combination with pembrolizumab (P; Keytruda®). The combination is referred to in this document as EV+P.	As NICE scope.
Comparator(s)	For people whom cisplatin-based chemotherapy is suitable: • Gemcitabine plus cisplatin • Methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF]) For people whom cisplatin-based chemotherapy is unsuitable:	For people whom cisplatin-based chemotherapy is suitable: • Gemcitabine + cisplatin For people whom cisplatin-based chemotherapy is unsuitable: • Gemcitabine + carboplatin	**MVAC** is not considered a relevant comparator as it is now rarely used in clinical practice (only ~2% of 1L pts in UK receive it according to recent market research data[4] (Section 1.3.5.1 and Appendix T). **Atezolizumab** was proposed by NICE as a comparator for patients who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%, in line with its licensed indication.[5] However, market research data indicate that it is now infrequently used in 1L treatment (8-10% of

	• Gemcitabine plus carboplatin • Atezolizumab (people whose tumours express PD-L1 at a level of 5% or more)		all patients and 3% of platinum-eligible patients; Section 1.3.5.1 and Appendix T). This is in line with clinical advice which indicates that carboplatin + gemcitabine (followed by avelumab maintenance in eligible patients) is now preferred over atezolizumab in patients who are eligible for carboplatin but not cisplatin (see Appendix P). Furthermore, an overview of systemic treatment for UC in the UK by a group of expert clinicians (Jones et al. 2024)[6] notes that "subsequent results from randomised trials have cast doubt on the relative efficacy of 1L ICI [immune checkpoint inhibitor] monotherapy treatment. As a result, 1L ICI treatment may be considered for patients who are unsuitable for or unwilling to receive platinum-based chemotherapy and who have a PDL1-positive tumour". Thus, atezolizumab is not now considered by these clinical experts as an option for displacing platinum-based chemotherapy, but rather as an option for those who will not receive platinum-based chemotherapy. They note that ESMO guidelines (2022) state that carboplatin-based chemotherapy followed by avelumab maintenance is preferred over 1L ICIs in cisplatin-ineligible patients.[7] This is further supported by scoping consultation comments from the British Uro-Oncology Group and Fight Bladder Cancer (see * below this table).

			In view of the above, the Company does not consider atezolizumab to be a relevant comparator.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As NICE scope (Note: Response rates are presented in the submission but are not used in the economic model)	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People for whom cisplatin containing chemotherapy is unsuitable • People whose tumours express PD-L1	Analyses will be presented for platinum-eligible patients as a whole, reflecting the ITT population of the EV-302 trial and the licensed indication for EV+P. In addition, subgroup analyses will be presented for cisplatin-eligible and cisplatin-ineligible subgroups since the comparator treatment is defined based on cisplatin-eligibility.	The Company do not believe that subgroup analysis based on PD-L1 status is relevant. This is because EV+P significantly improved relative outcomes regardless of PD-L1 status (see Section 2.6.2 and 2.6.3). PD-L1 status did not impact absolute outcomes either for platinum-containing chemotherapy, nor for EV + P OS (see Appendix E). Although there is some indication of PD-L1 status influencing EV+P PFS, any such effect is highly uncertain. Lastly, the licensed indication for EV+P covers all eligible patients and does not differentiate by PD-L1 status.[1]
Special considerations including issues related to equity or equality	None specified	Decisions on the funding of treatments for bladder cancer (which accounts for 90-95% of UC cases at diagnosis[8]) disproportionately affect people living with the consequences of socioeconomic deprivation. In England, the European age-standardised incidence rate/100,000 in the most deprived Index of	Socioeconomic status (IMD quintile) has not been included in the economic modelling. However, the disproportionate impact on people with greater socioeconomic deprivation may be relevant to NICE's decision making given that reducing health inequalities is a priority under the NHS England Core20PLUS5 programme.[10]

		Multiple Deprivation (IMD) quintile was 10.5 in females and 32.3 in males, compared with 7.1 in females and 26.2 in males the least deprived quintile (2013-2017, as reported by Cancer Research UK).[9] Cancer Research UK estimated that there are 980 more cases/year than there would be if every quintile had the same age-specific crude incidence rates as the least deprived quintile.	

*** Further comments on the relevance of atezolizumab as a comparator**

The following comments were made during the NICE scoping consultation, supporting the Company's position that atezolizumab is not a relevant comparator in the appraisal.

British Uro-Oncology Group: "Patients not suitable for cisplatin based chemotherapy are usually treated with carboplatin based combinations in England. The use of immunotherapy (atezolizumab) is reserved for patients who have PD-L1 positive tumours and usually chemotherapy is used in preference unless the patient is unsuitable for both cisplatin and carboplatin."

Fight Bladder Cancer: "In the UK, patients unsuitable for cisplatin-based chemotherapy typically receive carboplatin-based combinations, with immunotherapy (atezolizumab) designated for those with PD-L1 positive tumours, preferring chemotherapy unless the patient is unsuitable for both cisplatin and carboplatin."

1.2 Description of the technology being evaluated

A summary of the technology being evaluated is provided in Table 2. The EMA SmPC is provided in Appendix C, together with the EPAR (MHRA SmPC and UK Public Assessment Report not yet available; see Table 2).

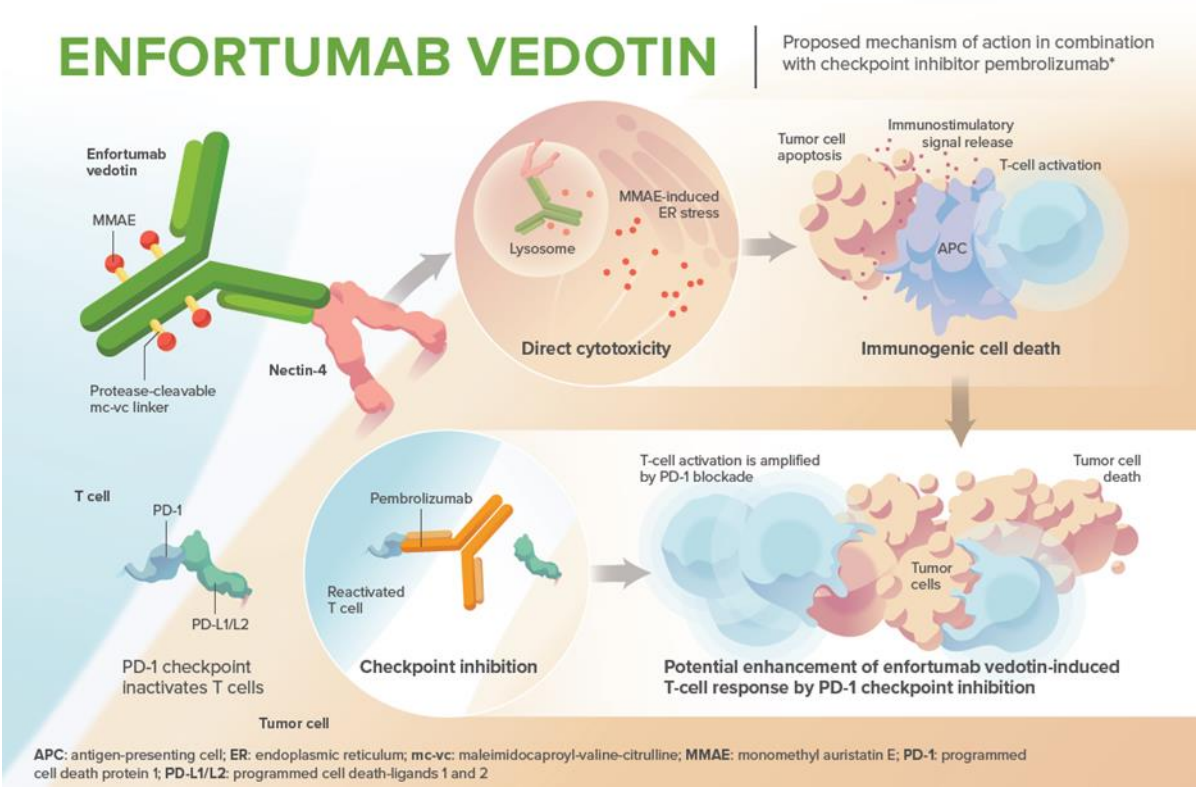
Table 2. Technology being evaluated

UK approved name and brand name	Enfortumab vedotin (EV; Padcev®) in combination with pembrolizumab (P; Keytruda®) The combination is referred to in the dossier as EV+P.
Mechanism of action	Enfortumab vedotin is an antibody drug conjugate (ADC) targeting Nectin-4, an adhesion protein located on the surface of urothelial cancer cells.[1] It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE), via a linking molecule that is broken by protease enzymes. Nonclinical data suggest that the anticancer activity of EV is due to binding of the ADC to Nectin-4-expressing cells, followed by internalisation of the ADC Nectin-4 complex into the cell, and the release of MMAE. Release of MMAE disrupts the microtubule network within the cell, inducing cell cycle arrest and apoptosis, and immunogenic cell death[1] (i.e. the release of signals that activate the immune system and ultimately a T-cell response[11]). In addition, MMAE released from cells targeted by EV can diffuse into nearby cells resulting in cytotoxic cell death[1] ('bystander effect'). Pembrolizumab (P) is a PD-1 inhibitor immunotherapy agent approved in a range of oncology indications which potentiates T-cell responses, including anti-tumour responses, through blockade of programmed cell death protein 1 (PD-1) binding to programmed cell death-ligands 1 and 2 (PD-L1 and PD-L2).[12] Both EV and P have individually been associated with a survival benefit in patients with previously treated locally advanced/metastatic urothelial cancer (UC).[1,2,12] Combination of EV with PD-1 inhibitors such as pembrolizumab results in enhanced anti-tumour activity in vivo, consistent with the complementary mechanisms of the two agents.[1,13] The proposed mechanism of action of the EV+P combination is shown in Figure 1.
Marketing authorisation/CE mark status	EMA marketing authorisation for EV in combination with P in the indication described below was granted on 28 August 2024,[14] and approval was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) on 8 October 2024 via the International Recognition Route (Type II variation).[15] EV and P as monotherapies already have

<table>
<tr><td></td><td>marketing authorisations in some settings within unresectable/metastatic UC (u/mUC; see below).</td></tr>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</td><td>The GB licensed indication for the combination of EV with P is: 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.[1]
EV and P as monotherapies already have licensed indications within u/mUC:
EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.[1]
P as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.[12]
P as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.[12]</td></tr>
<tr><td>Method of administration and dosage</td><td>When given in combination with pembrolizumab, the recommended dose of EV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.[1]
The recommended dose of P in combination with EV in this indication is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered P after EV when given on the same day.
Recommended dose reductions of EV for adverse reactions are:[1]
<table>
<tr><td></td><td>Dose level</td></tr>
<tr><td>Starting dose</td><td>1.25 mg/kg up to 125 mg</td></tr>
<tr><td>First dose reduction</td><td>1.0 mg/kg up to 100 mg</td></tr>
<tr><td>Second dose reduction</td><td>0.75 mg/kg up to 75 mg</td></tr>
<tr><td>Third dose reduction</td><td>0.5 mg/kg up to 50 mg</td></tr>
</table></td></tr>
<tr><td>Additional tests or investigations</td><td>No additional tests or investigations are required for treatment with EV+P. The licensed indication for the combination is not restricted by PD-L1 status, and therefore PD-L1 testing is not required. Patients are routinely assessed for eligibility for platinum-based chemotherapy as part of current clinical practice.</td></tr>
</table>

List price and average cost of a course of treatment	Enfortumab vedotin is available in two different concentrations, with list prices per vial as follows: • 20mg powder for concentrate for solution for infusion vials: £578.00 • 30mg powder for concentrate for solution for infusion vials: £867.00[16] The list price for pembrolizumab is: • 100mg/4ml concentrate for solution for infusion vials: £2,630.00[16] Predicted mean treatment duration in the cost-effectiveness model (see Section 3.3.4.1) is [redacted] months for EV and [redacted] months for P.
Patient access scheme (if applicable)	NHS England have confirmed that the simple discount Patient Access Scheme (PAS) proposal for enfortumab vedotin (Padcev) may be considered by NICE as part of the appraisal.

ADC, antibody drug conjugate; CPS, combined positive score; EMA, European Medicines Agency; EV, enfortumab vedotin; MHRA, Medicines and Healthcare products Regulatory Agency; GB, Great Britain; MMAE, monomethyl auristatin E; P, pembrolizumab; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; u/mUC, unresectable/metastatic urothelial carcinoma; UC, urothelial carcinoma



Source: Seagen data on file, 2022

Figure 1. EV+P: proposed mechanism of action

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Definition and classification of UC

Urothelial carcinoma (UC, also known as transitional cell carcinoma) is a cancer that begins in the urothelial cells lining the urinary tract.[17]

- Bladder cancer (BC) makes up 90-95% of UC cases at diagnosis.[8] Approximately 90% of BC cases in the UK are due to UC.[18]
- Upper tract urothelial carcinoma (UTUC) affects the ureters and renal pelvis, and accounts for 5-10% of UC cases.[8] However, it accounts for a higher proportion of u/mUC cases (approximately 20-30%) as it is typically more advanced at diagnosis than BC.[6,8] Almost all cancers of ureters and renal pelvis are UC; other histologies are rare.[8]

UC is characterised clinically by the extent of invasion and is termed non-muscle invasive, muscle invasive, or metastatic.[18,19] UC that has spread to the pelvic or nearby lymph nodes and/or to the wall of the pelvis or abdomen and is not resectable is referred to as unresectable or locally advanced disease.[18,20] Metastatic UC (mUC) denotes spread to the lymph nodes outside of the pelvis (M1a), or distant metastasis (M1b).

1.3.2 Epidemiology and risk factors

BC is the eleventh most common cancer in the UK, and the 9th most common cause of cancer death.[9] There were approximately 10,190 new cases of UC (all stages, including both BC and UTUC) in England in 2021, and 4652 deaths.[21] A further 1087 cases (2020) and 621 deaths (2022) were reported in Wales (bladder cancer + 'urinary tract excluding bladder').[22]

The majority of BC cases (64% in England in 2018) are diagnosed at stages 1 or 2, with only 9% diagnosed at stage 4 (a further 16% had unknown stage at diagnosis).[23] The number of new cases of u/mUC each year, including newly diagnosed patients and those who have progressed to u/mUC after being diagnosed

with earlier stages, is approximately 3,024 (see Budget Impact document for details of the number of patients expected to be treated with EV+P).

- The incidence of UC increases markedly with age: 56% of BC cases in the UK were diagnosed in people aged ≥75 years in 2016-2018[9] and BC is rarely diagnosed in persons aged <40 years.[24] The peak incidence of UTUC is 70-90 years of age.[8]
- Incidence is significantly higher in males than females,[9] with males accounting for 75% of BC diagnoses and 65% of UTUC diagnoses in England in 2021.[21]
- The main preventable risk factors for BC are smoking (estimated to account for ~50% of cases) and occupational exposure to aromatic amines or ionising radiation.[18,25]

There is an association between BC incidence and socioeconomic deprivation. In England, the European age-standardised incidence rate/100,000 in the most deprived Index of Multiple Deprivation (IMD) quintile was 10.5 in females and 32.3 in males, compared with 7.1 in females and 26.2 in males the least deprived quintile (2013-2017, as reported by Cancer Research UK).[9] Cancer Research UK calculated that there are an estimated 980 more cases/year than there would be if every quintile had the same age-specific crude incidence rates as the least deprived quintile.

1.3.3 Clinical presentation and burden

Painless haematuria (blood in the urine) is the most common presentation of BC at diagnosis.[24,25] Urinary symptoms (frequent, urgent or painful urination) and flank pain can also occur.[24,25] UTUC commonly presents with haematuria, and flank pain due to clot or tumour tissue obstruction may also occur.[8]

Patients with UC may experience urinary symptoms (e.g. frequent urination, pain during urination, incomplete emptying/difficulty emptying the bladder), lower back or abdominal pain, fatigue and malaise.[18] Patients with metastatic UC can also experience, weight loss, anorexia, and pain specific to the site of metastasis (e.g. bone pain).[8,25,26] Due to the risk factors for UC and its concentration in older individuals, patients often have comorbid medical conditions that must be taken into account during management.[24]

U/mUC has a significant impact on patients' physical, mental and social quality of life.[27] Pain associated with u/mUC affects physical and daily activities, social activities, emotional wellbeing and overall health-related quality of life (HRQoL).[26] Patients who have previously undergone bladder resection are living with surgical effects such as urostomy, internal urine pouch or reconstructed neobladder.[18]

Metastatic UC is also associated with a high economic burden driven by medical costs such as hospitalisations, emergency room (ER) visits, and end-of-life care.[28]

1.3.4 Prognosis and unmet need

The prognosis for recurrent or metastatic UC is poor.[29] Five-year relative survival in BC as estimated by the National Cancer Institute in the US is approximately 39.5% for regional disease and only 8.8% for metastatic disease.[30] One-year overall survival for individuals diagnosed with BC in England in 2016-2020 was 64.4% for those diagnosed with stage 3 and 29.2% for those diagnosed at stage 4.[31] However, only about 30% of patients with advanced UC currently receive 1L treatment in the UK.[6,32]

There is a significant unmet need for new, more effective treatment options in u/mUC than current standard-of-care with platinum-based chemotherapy, which is associated with modest survival outcomes. Survival is typically 9-26 months after platinum-based treatment of distant BC recurrence in patients who underwent radical treatment of earlier-stage disease.[29] In a cohort of 216 patients receiving 1L chemotherapy for locally advanced or metastatic UC at an English centre (of whom 44% received cisplatin and 48% carboplatin-based treatment), median OS was 16.2 months (IQR: 10.6–28.3 months).[20]

1.3.5 Clinical pathway of care and position of EV+P

1.3.5.1 Current treatment of u/m UC: treatment pattern data

The treatment landscape for u/mUC has evolved rapidly in the last few years as new therapies have become available and the evidence base for previously recommended treatments has matured. Clinical practice and treatment patterns in the NHS have evolved (and continue to evolve) in line with this.[6] Recent data on

treatment patterns is therefore important in order to accurately characterise the current treatment pathway and inform the decision problem. This is available from the following sources (see Appendix T for details):

- Cross-sectional UK data from a new (currently unpublished) release from the Adelphi mUC Disease Specific Programme™. This is a large, independent, multinational, cross-sectional survey of physicians and their consulting patients with mUC presenting in a real-world clinical setting. Methods have been published by Milloy et al. (2024).[33] Milloy 2024 covers data collected between November 2020 and April 2021. A later release (as yet unpublished; study report in development) contains data collected between Dec 2023 and May 2024 by 41 UK clinicians on 291 mUC patients, of whom 256 were deemed platinum-eligible.
- Proprietary market research data from the IQVIA tracker. The tracker collects prescribing in u/mUC from approximately 50 UK clinicians on an ongoing basis, including private practice. The latest wave available was June 24.[4]
- The Systemic Anti-Cancer Therapy (SACT) database. SACT dataset numbers for April 2023-March 2024 for ICD10 code C67 (bladder cancer) were provided to Astellas.

The findings of relevance to the choice of comparators and the generalisability of avelumab maintenance use in EV-302 to NHS practice are summarised in Table 3. In summary:

- MVAC is used for only 1-2% of patients who receive platinum-based chemotherapy
- Up to 10% of patients receive atezolizumab in 1L. Clinical advice indicates that its use is mainly reserved for platinum-ineligible patients, and this is supported by the Adelphi findings (see Appendix T).
- About 30% of all platinum-treated patients go on to receive avelumab maintenance

Table 3 Summary of treatment pattern data on MVAC, atezolizumab and avelumab use in 1L treatment of u/mUC

	Adelphi DSP	IQVIA	SACT (N=3960, stage and line not specified)
Use of MVAC in 1L	3 of 256 (1%) platinum-eligible patients	Data not available	37 patients (<2% of the estimated number of patients receiving 1L platinum-based therapy)
Use of atezolizumab in 1L	3% of platinum eligible patients (10% of all patients)	[redacted]% of all patients	643 patients (line not specified); Blueteq data estimates 100 in 1L and 450 in 2L
Use of avelumab maintenance	28% of those patients who received platinum-based chemotherapy in 1L	[redacted]% of 1L pts received platinum + avelumab	498 patients (line not specified); estimated ratio of 1L platinum:avelumab use of 30%

DSP, Disease Specific Programme; MVAC, methotrexate, vinblastine sulfate, doxorubicin hydrochloride (Adriamycin), and cisplatin; SACT, Systemic Anticancer Therapy Database

1.3.5.2 Current treatment pathway

The treatment pathway for u/mUC in current NHS practice is shown in Figure 2 and described below. In view of recent evolutions in the treatment landscape, this pathway is based on clinical expert opinion and on the treatment pattern data described in the previous section.

Platinum-based combination chemotherapy is the current standard of care for u/mUC in NHS practice,[34] and is received by approximately 84% of treated UK patients.[35] About 10% of patients are unsuitable for platinum-based therapy, and a substantial proportion of patients (up to 70%) do not receive any 1L treatment.[6]

- Cisplatin-based chemotherapy (usually cisplatin + gemcitabine) is the treatment of choice in line with NICE guidelines,[34] but around half of platinum-eligible patients are ineligible for cisplatin due to older age, poor performance status or comorbidities such as renal impairment.[33 35]
- For cisplatin-ineligible patients, NICE and European guidelines recommend gemcitabine and carboplatin.[8,25,29,34]

    - Atezolizumab is approved for the 1L treatment of adult patients with locally advanced or metastatic UC who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%. It was recommended by NICE in 2021 as an option for this group in TA739. However, a recent treatment pattern survey[35] and recent market research data[4] both indicate low uptake in England (see Section 1.1 and Appendix T for further details).[4]
    - An overview of systemic treatment for UC in the UK by a group of expert clinicians was published by Jones et al. in January 2024[6] and confirms that cisplatin + gemcitabine or carboplatin + gemcitabine (depending on cisplatin eligibility) remain standard of care. However, they note that "subsequent results from randomised trials have cast doubt on the relative efficacy of 1L ICI [immune checkpoint inhibitor] monotherapy treatment. As a result, 1L ICI treatment may be considered for patients who are unsuitable for or unwilling to receive platinum-based chemotherapy and who have a PDL1-positive tumour". Thus, atezolizumab is not considered by these clinical experts as an option for displacing platinum-based chemotherapy, but rather as an option for those who will not receive platinum. Further, ESMO guidelines (2022) state that carboplatin-based chemotherapy followed by avelumab maintenance is preferred over 1L ICIs in cisplatin-ineligible patients.[7]
- For patients whose disease does not progress on 1L platinum-containing chemotherapy, European guidelines recommend maintenance treatment with avelumab,[24,25,36] which was recommended by NICE in TA788.[36] However, only approximately 30% of 1L u/mUC patients receive avelumab maintenance in clinical practice (see Section 1.3.5.1 above).

Second and subsequent lines: For patients whose disease is either refractory to or relapses following treatment with platinum-based chemotherapy, paclitaxel, or atezolizumab or pembrolizumab are potential 2L treatments,[7,8,29] but of the approved immunotherapies only atezolizumab is recommended by NICE in this indication.[37]

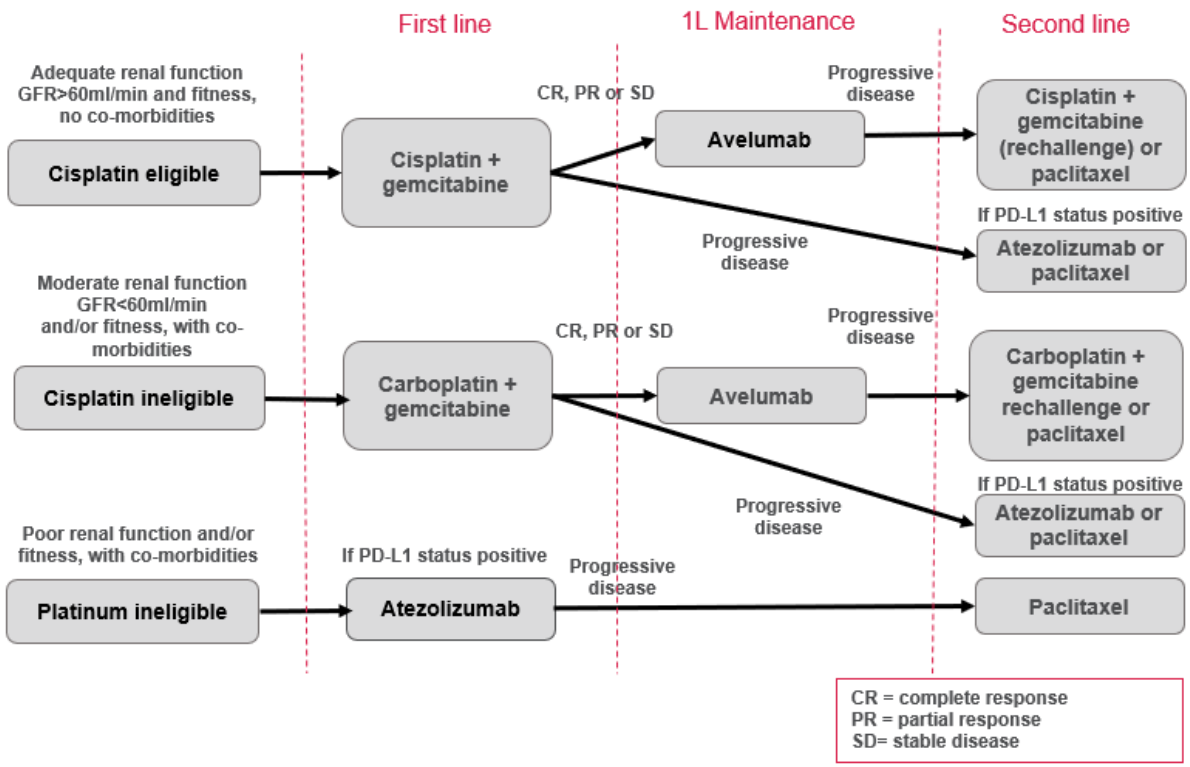


Figure 2 Current treatment of u/mUC in NHS practice in England

1.3.5.3 Treatment guidelines

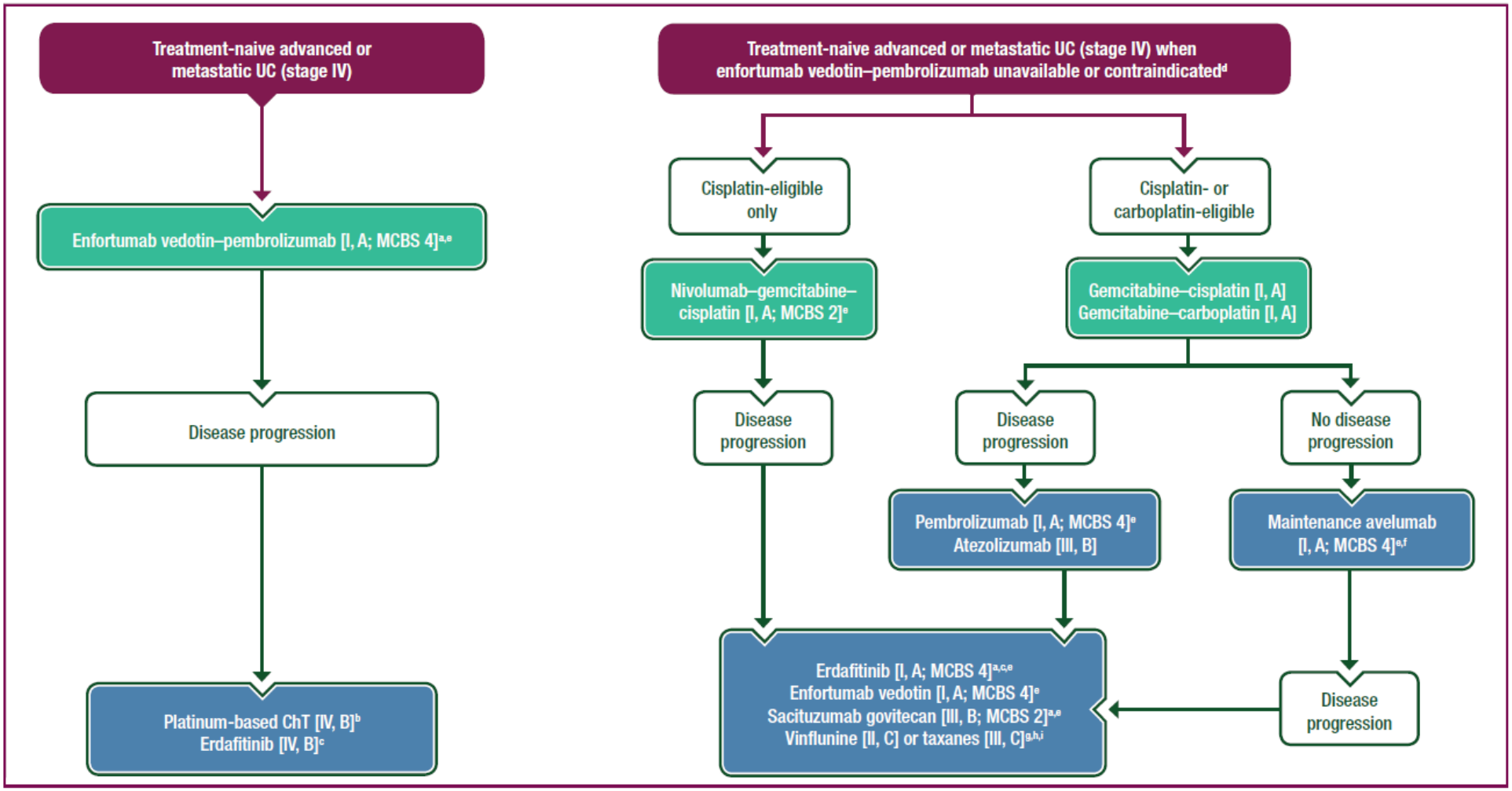
The NICE guideline on bladder cancer dates from 2015[34] and therefore does not incorporate newer therapies or recent evidence, although NICE has since made recommendations through technology assessments.[36-38] The NICE guideline recommends platinum-based chemotherapy or MVAC (now rarely used in clinical practice, see Section 1.1) as 1L treatment.

All three major European treatment guidelines now recommend EV+P as the new standard of care for 1L treatment of u/mUC:

- In March 2024 the European Society of Medical Oncology (ESMO) issued an interim update stating that EV+P "is the new standard of care in first-line advanced urothelial carcinoma". The updated ESMO management algorithm for the management of patients with mUC is shown in Figure 3.
- Similarly, an April 2024 update of the European Association of Urology (EAU) guideline on bladder cancer states that EV+P "represents the new standard of care for patients who are deemed fit for combination therapies".[29]

- The only guideline dedicated specifically to UTUC is that of the EAU 2024, which also recommends EV+P as the first choice treatment for mUTUC in patients eligible for the combination.[8] The EAU management algorithm for UTUC is shown in Figure 4.
- In all aforementioned European guidelines, platinum-based chemotherapy + gemcitabine is now recommended as 2L treatment after EV+P (unless EV+P is unavailable or contraindicated, in which case platinum-based chemotherapy + gemcitabine remains the recommended 1L treatment, followed by avelumab maintenance for patients who do not have disease progression).
    - Of note, avelumab maintenance is no longer recommended by ESMO for patients who receive platinum-based chemotherapy in 2L after EV+P, because "rechallenge with single-agent immune checkpoint inhibitor is not encouraged without further evidence".[25]

The guidelines and relevant HTAs in u/mUC are summarised in Table 4.



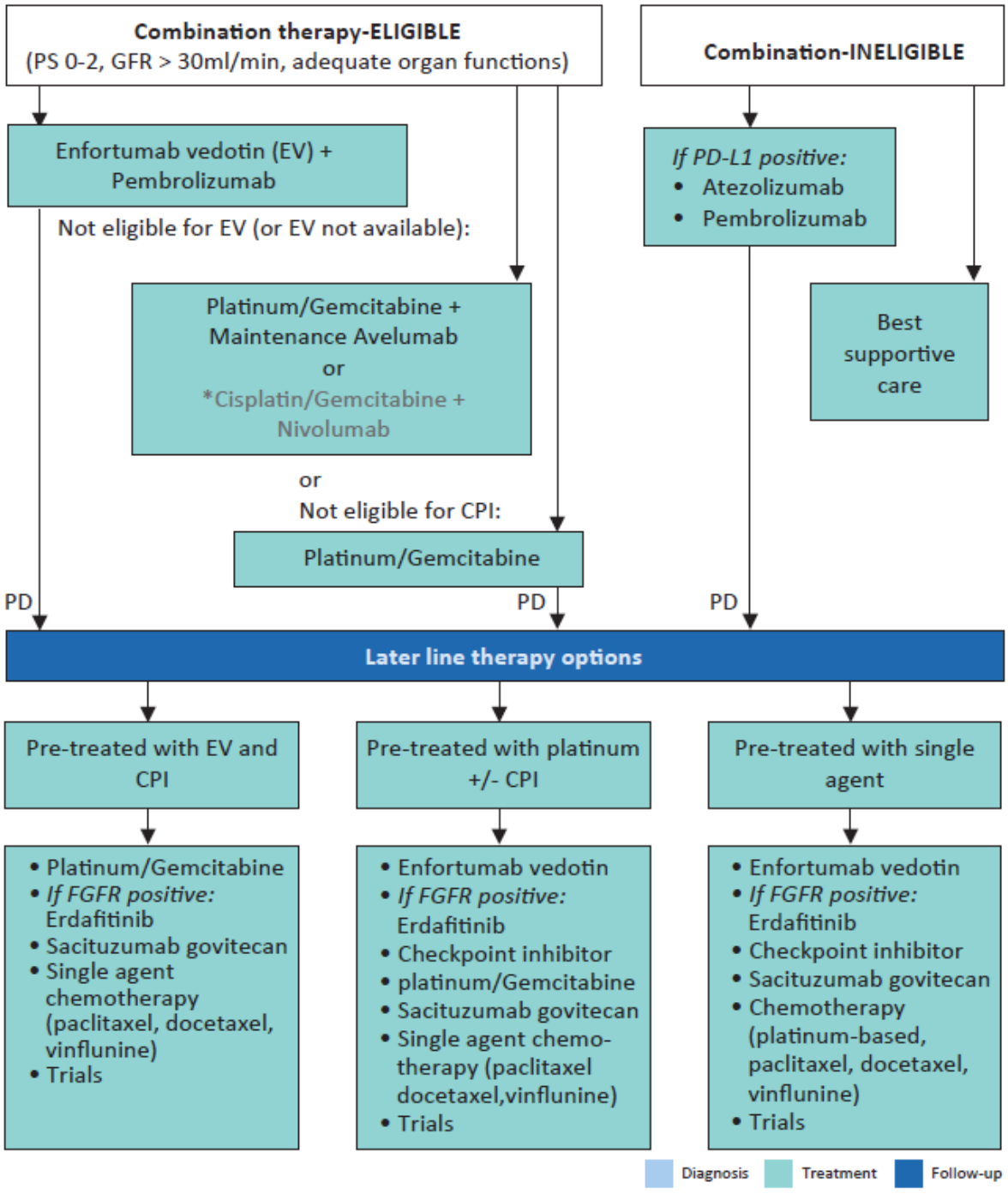
ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; UC, urothelial carcinoma.

[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 with 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: Powles et al. 2024[25]

Figure 3. Management of patients with metastatic urothelial carcinoma (ESMO 2024 guideline update)



*In view of lack of subgroup analysis data for UTUC

EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; GFR, glomerular filtration rate; PS, performance status; CPI, checkpoint inhibitor; PD-L1, programmed death-ligand 1; PD, programmed death Source: EAU 2024[8]

Figure 4. Flowchart for the management of metastatic upper tract urothelial carcinoma, European Association of Urology

Table 4. Summary of guidelines from EAU, ESMO and NICE on the treatment of locally advanced/metastatic urothelial cancer (see also pathway diagrams above).

EAU (2024) – BC[29] and UTUC[8] guidelines	
1L	• EV+P for patients fit for combination therapy • Platinum/cisplatin + gemcitabine in patients fit for combination therapy if EV is unsuitable • Platinum + gemcitabine if checkpoint inhibitor-ineligible • Pembrolizumab or atezolizumab in cisplatin- and combination therapy-ineligible, PD-L1-positive patients
2L	• Platinum + gemcitabine if pre-treated with EV and checkpoint inhibitor • EV, checkpoint inhibitor or platinum + gemcitabine if pre-treated with platinum +/- checkpoint inhibitor • Erdafitinib, sacituzumab govitecan, or single-agent chemotherapy (paclitaxel, docetaxel, vinflunine) if pre-treated with either EV and checkpoint inhibitor or platinum +/- checkpoint inhibitor • If pre-treated with single agent: EV, erdafitinib, checkpoint inhibitor, sacituzumab govitecan, or single-agent chemotherapy (paclitaxel, docetaxel, vinflunine)
3L	No recommendation
ESMO (2024 interim update)[25]	

1L	• EV+P
	• If EV+P not available or contraindicated:
	  ○ If cisplatin-eligible: cisplatin + gemcitabine or nivolumab + gemcitabine + cisplatin
	  ○ Carboplatin + gemcitabine
	  ○ Maintenance avelumab if no disease progression on platinum

2L/3L	• If received EV+P:
	  ○ Platinum-based chemotherapy
	  ○ Erdafitinib in tumours with selected *FGFR* alterations
	• If did not receive EV+P:
	  ○ Pembrolizumab or atezolizumab (if did not receive nivolumab; rechallenge with single-agent immunotherapy not encouraged)
	• 2L (if received nivolumab) or 3L (if did not receive nivolumab):
	  ○ Erdafitinib in tumours with selected *FGFR* alterations
	  ○ EV
	  ○ Sacituzumab govitecan
	  ○ Vinflunine or taxanes

NICE recommendations via technology assessments	
1L	• Avelumab maintenance if no progression on platinum chemotherapy (max 5 years of treatment)(TA788)[36] • Atezolizumab (In adults whose tumours express PD-L1 at a level of 5% or more and when cisplatin-containing chemotherapy is unsuitable TA739)[38]

2L	• Atezolizumab (In adults whose tumours express PD-L1 at a level of 5% or more who have had platinum-containing chemotherapy; max 2 years of treatment; TA525)
NICE guideline (2015)[34]	
1L	• Cisplatin-based chemotherapy (e.g. cisplatin in combination with gemcitabine, or accelerated MVAC in combination with G-CSF for people who are otherwise physically fit with adequate renal function [NB: MVAC is now rarely used in clinical practice; see Section 1.1]) • Carboplatin in combination with gemcitabine if cisplatin-based chemotherapy is unsuitable
2L	• Gemcitabine in combination with cisplatin for people who are otherwise physically fit with adequate renal function • Accelerated MVAC in combination with G-CSF for people who are otherwise physically fit with adequate renal function • Carboplatin or gemcitabine in combination with paclitaxel for whom cisplatin-based chemotherapy is not suitable
3L	No recommendation

EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; G-CSF, granulocyte colony stimulating factor; MVAC, methotrexate vinblastine doxorubicin cisplatin; P, pembrolizumab; PD-L1, programmed death-ligand 1

1.3.5.4 Position of EV+P in therapy

The proposed position of EV+P is as first-line treatment of adult patients with u/mUC who are eligible for platinum-containing chemotherapy, as per the licensed indication[1] (Figure 5). EV+P addresses an important unmet need for more effective 1L treatments for u/mUC than the current standard of care (platinum-based chemotherapy). It is therefore expected to displace platinum-based chemotherapy as 1L treatment (platinum-based chemotherapy will then become 2L treatment, in line with recently updated European clinical guidelines).[8,25,29]

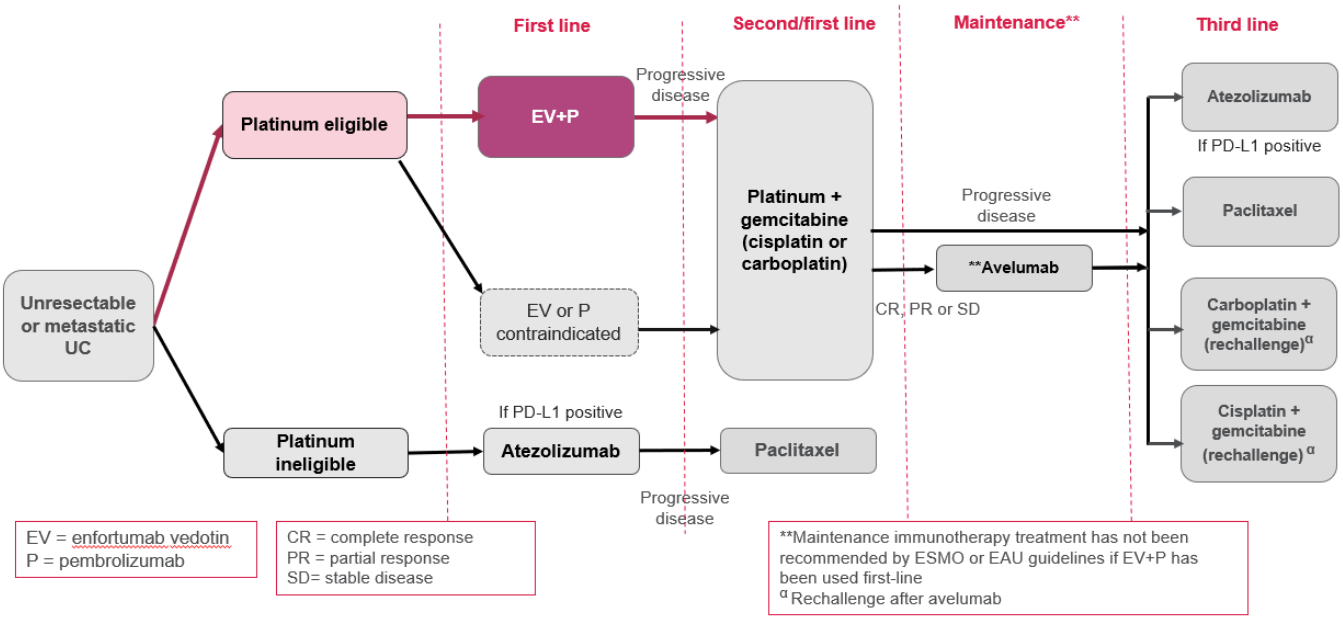


Figure 5. Proposed position of EV+P in the treatment pathway

1.4 Equality considerations

Decisions on the funding of treatments for BC disproportionately affect people living with the consequences of socioeconomic deprivation. In England, the European age-standardised incidence rate/100,000 in the most deprived Index of Multiple Deprivation (IMD) quintile was 10.5 in females and 32.3 in males, compared with 7.1 in females and 26.2 in males the least deprived quintile (2013-2017, as reported by Cancer Research UK).[9] Cancer Research UK calculated that there are an estimated 980 more cases/year than there would be if every quintile had the same age-specific crude incidence rates as the least deprived quintile. People in the most deprived IMD quintile are a key focus of Core20PLUS5, the national NHS England approach to reducing healthcare inequalities.[10]

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A systematic literature review was carried out to identify relevant studies. See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to EV+P in the 1L treatment of u/mUC. The final scope included Phase 2 and 3 studies published in the English-language from January 2000 to June 2024 in EMBASE or MEDLINE, Cochrane/CENTRAL, WHO International Clinical Trials Registry Platform (ICTRP), presentations at major scientific conferences from 2015 to 2024, health technology assessment (HTA) agency website materials, and other published SLRs. All eligible randomised controlled trials (RCTs) were included. Single-arm studies were also included for the cisplatin-ineligible patients and studies of PD-1/PD-L1 inhibitors and EV. Two studies of EV+P in the 1L treatment of u/mUC were identified (see below).

2.2 List of relevant clinical effectiveness evidence

Evidence on the clinical effectiveness of EV+P as first-line treatment of adult patients with u/mUC is available from two studies (see Appendix D – SLR report, Table 13):

- EV-302: the pivotal phase 3 randomised open-label trial, in patients eligible for platinum-containing chemotherapy.[2,39] Primary results were published by Powles et al. 2024.[2] A new data cut providing longer-term follow-up and more mature progression-free and overall survival data is expected in [redacted] and will be presented during the submission process when available.

- EV-103: a multi-cohort, non-randomised, open-label, phase 1b/2 study, in which two cohorts (A and K) studied 1L treatment with EV+P in cisplatin-ineligible patients with locally advanced or metastatic UC (la/mUC) (see Section 2.6.8). Initial results were published by Hoimes et al. 2023[11] and long-term follow-up has been presented at conferences.[40,41] The population in this study differs from the licensed indication in that patients had to be cisplatin-

ineligible (but could still be eligible for carboplatin); thus, it covers only a subgroup of the appraisal population.

EV, either as monotherapy or in combination with pembrolizumab, has also been studied in other settings in UC. An overview of the clinical trial programme is shown in Table 5 for completeness.

Table 5. Overview of the trial programme for EV and EV+P in UC

Trial name	Status	Design	Intervention	Population	Primary endpoint
Phase I					
EV-101 [42,43]	Completed	Phase I dose-expansion study investigating safety, tolerability, and anti-tumour activity of enfortumab vedotin	Single-arm enfortumab vedotin IV: • Patients with mUC treated with any dose of enfortumab vedotin (N=155) • Patients treated with enfortumab vedotin 1.25 mg/kg (N=112)	Patients with mUC who previously progressed on PD-1/L1 inhibitor therapies	Safety and tolerability, based on the rate of AEs, pharmacokinetics
EV-102[44]	Completed	Open-label, randomised, parallel assignment, two-arm Phase I study	• Arm A: Enfortumab vedotin 1.0 mg/kg IV in first cycle; dose escalation to 1.25 mg/kg IV in following cycles[†] • Arm B: Enfortumab vedotin 1.25 mg/kg IV	Japanese patients with u/mUC who have failed ≥1 prior chemotherapy regimen or were unfit for cisplatin-based chemotherapy (N=17)	Safety and tolerability, pharmacokinetics
Phase Ib/II					
EV-103[11]	Ongoing	Multi-cohort, non-randomised, open-label, Phase Ib/II study designed to determine the safety and tolerability of enfortumab vedotin alone and in combination with PEM and/or chemotherapy	Dose Escalation cohort la/mUC: • Enfortumab vedotin + PEM Dose expansion cohorts la/mUC: • Cohort A: Enfortumab vedotin + PEM • Cohort D: Enfortumab vedotin + cisplatin	Patients with la/mUC or MIBC[‡] (target enrolment: N=257)[§]	Safety and tolerability, based on the rate of AE, laboratory abnormalities

Trial name	Status	Design	Intervention	Population	Primary endpoint
		for treatment of la/mUC and MIBC‡	• Cohort E: Enfortumab vedotin + carboplatin • Cohort G: Enfortumab vedotin + chemotherapy (cisplatin or carboplatin) + PEM • Cohort K: 1) Enfortumab vedotin monotherapy arm; 2) Enfortumab vedotin + pembrolizumab arm MIBC • Cohort H: Enfortumab vedotin • Cohort L: Enfortumab vedotin		
Phase II					
EV-201[45]	Cohort 1: Ongoing Cohort 2: Ongoing	Global, Phase II, single-arm, two-cohort, multicentre study designed to evaluate the efficacy and safety of enfortumab vedotin in patients with u/mUC previously treated with a PD-1/L1 inhibitor therapy	Single-arm enfortumab vedotin IV	• Cohort 1: Patients previously treated with both platinum chemotherapy and a PD-1/L1 inhibitor therapy (N=125) • Cohort 2: Platinum-naïve, cisplatin-ineligible, and previously treated with a PD-1/L1 inhibitor therapy (N=89)	Confirmed ORR assessed by BICR
Phase III					

Trial name	Status	Design	Intervention	Population	Primary endpoint
EV-301[46]	Ongoing	Open-label, multinational study designed to assess the efficacy, safety, and tolerability of enfortumab vedotin compared with chemotherapy	• Enfortumab vedotin monotherapy (N=301) • Chemotherapy as decided by investigator: docetaxel, paclitaxel, or vinflunine (N=307)	Patients with u/mUC who have experienced disease progression or relapse either during or after treatment with a PD-1/L1 inhibitor therapy and PBT	OS
EV-302[2] Pivotal trial	Ongoing	Open-label, randomised study designed to assess the safety and efficacy of enfortumab vedotin plus PEM vs SOC gemcitabine + platinum-containing chemotherapy for the treatment of u/mUC	• Enfortumab vedotin + PEM • Gemcitabine + platinum-containing chemotherapy	Patients with u/mUC (N=886)	PFS, OS

AE, adverse event; BICR, blinded independent central review; DFS, disease-free survival; EFS, event-free survival; IV, intravenous; MIBC, muscle invasive bladder cancer; mUC, metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PBT, platinum-based chemotherapy; PD-1/L1, programmed death-1/programmed death ligand-1; pDS, pathologic downstaging; PEM, pembrolizumab; PFS, progression-free survival;; SOC, standard of care.
† At the investigator's discretion and if there were no significant toxicities during the first cycle; ‡ The study is conducted in multiple parts: u/mUC dose escalation (enfortumab vedotin + PEM) and dose expansion (cohorts A-J of enfortumab vedotin ± PEM and/or chemotherapy); and MIBC (enfortumab vedotin alone, and enfortumab vedotin + PEM); § As of the October, 2019 data cut-off, 45 patients with u/mUC treated with enfortumab vedotin 1.25 mg/kg IV + PEM 200 mg in the dose escalation cohort and dose expansion Cohort A

2.2.1 Summary of clinical studies and their use in the model

The model is based on the pivotal study, EV-302 (Table 7). In addition, long-term follow-up of patients from EV-103 (Table 7) is used to validate the survival modelling.

Table 6. Summary of EV-302

Study	**Pivotal trial: EV-302 (NCT04223856)[2]** 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
Study design	Phase 3, global, open-label, randomised trial
Population	Patients with previously untreated locally advanced or metastatic urothelial cancer
Intervention(s)	• EV: 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. • Pembrolizumab: 200 mg IV on day 1 of each 3-week cycle, as above to a maximum of 35 cycles.
Comparator(s)	Gemcitabine: gemcitabine IV 1000 mg/m2 body-surface area) on days 1 and 8 of a 3-week cycle, and either: • Cisplatin: IV 70 mg/m2 on day 1 • Carboplatin: IV AUC equivalent to 4.5-5 mg/ml/min (Calvert formula) on day 1
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	• **Overall survival** • **Progression-free survival by BICR** • Objective response rate • **Adverse effects** • **Health-related quality of life**
All other reported outcomes	• Progression-free survival by investigator assessments • Duration of response • Disease control rate • Time to pain progression

	• Mean change from baseline in worst pain at week 26

AUC, area under curve; BICR: blinded independent central review; EV, enfortumab vedotin; IV, intravenous; N/A, not applicable. Bold indicates incorporated into economic model.

Table 7. Summary of EV-103

Study	**EV-103 (NCT03288545)**[11] A Study of Enfortumab Vedotin Alone or With Other Therapies for Treatment of Urothelial Cancer (EV-103)
Study design	Phase 1b/2 multi-cohort, open-label, multicentre, global
Population	Cohorts A and K: previously untreated, cisplatin-ineligible patients with locally advanced or metastatic UC Note: Population differed between cohorts. Only cohorts A and K (EV+P arm) are relevant to the decision problem, and only cover a subset of the submission population as cisplatin-eligible patients were not included.
Intervention(s)	• EV: 1-1.25 mg/kg (up to a maximum of 125 mg) administered as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. • Pembrolizumab: 200 mg IV on day 1 of each 3-week cycle, administered 30 minutes after EV, until disease progression or unacceptable toxicity.
Comparator(s)	N/A
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No, but long-term follow-up from the study is used to validate the survival extrapolations.
Rationale if study not used in model	The study is not used in the model because the population (cisplatin-ineligible patients) only represents a subgroup of the submission (EV-302) population.
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival by BICR • Objective response rate • Adverse effects
All other reported outcomes	• Progression-free survival by investigator assessments • Duration of response • Disease control rate • Pharmacokinetic and laboratory measures

EV, enfortumab vedotin; IV, intravenous

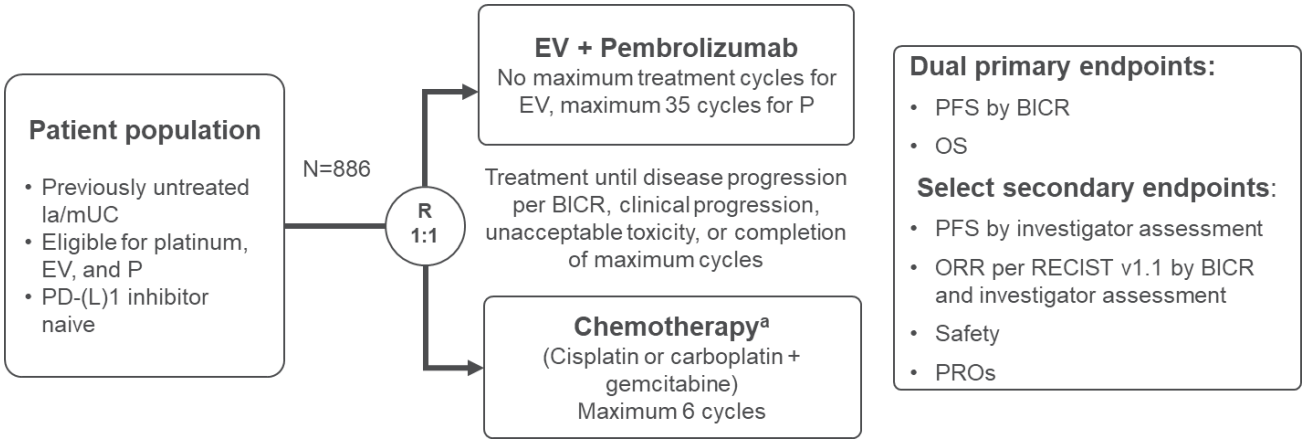
Study EV-103 was not used directly to parameterise the economic model but is included in sections 2.2 to 2.6. The results of this study provide long-term follow-up of OS in part of the submission population (cisplatin-ineligible patients with previously untreated la/m UC) and are therefore of interest. These results were used to validate the survival extrapolations in the economic model. The study was not directly used to parameterise the economic model because the population (cisplatin-ineligible patients) only represents a subgroup of the submission (EV-302) population. The submission population corresponds to the licensed indication for EV+P, which is in the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.[1]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 EV-302: Trial design and methodology

EV-302 (NCT04223856) is a global, open-label, two-arm, randomised, controlled Phase 3 trial that investigated the efficacy and safety of EV+P compared with gemcitabine plus platinum-containing chemotherapy in patients with previously untreated unresectable locally advanced or metastatic UC. There was no preselection for biomarkers, including nectin-4 and PD-L1 expression. Key exclusion criteria included previous treatment with PD-1 or PD-L1 inhibitors or other systemic therapy (except for neo-adjuvant or adjuvant chemotherapy after surgery with recurrence >12 months after completion of therapy), uncontrolled diabetes, ongoing sensory or motor neuropathy of grade 2 or higher, and previous autoimmune disease for which systemic treatment had been received in the previous two years. A total of 886 patients were randomly assigned to receive EV+P or chemotherapy at 185 sites in 25 countries.[2]

The trial design is shown in Figure 6, and its methodology is summarised in Table 8.



*Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine.

†Patients with ECOG PS of 2 were required to also meet the additional criteria: haemoglobin ≥10 g/dL and GFR ≥50 mL/min but may not have NYHA class III heart failure. ‡Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate; la/mUC, locally advanced or metastatic urothelial carcinoma; NYHA, New York Heart Association; ORR, overall response rate; OS, overall survival; P, pembrolizumab; PD-(L)1, programmed cell death-1 and programmed death ligand-1; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumours.

Source: Powles et al. 2024[2]

Figure 6. EV-302 study design.

Table 8. Summary of EV-302 study design and methodology.

Title	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
NCT number	NCT04223856
Status	Ongoing
Phase	Phase 3
Randomisation and blinding	Allocation: Randomised, using an Interactive Web Response System. Randomisation was stratified according to eligibility to receive cisplatin (eligible or ineligible), PD-L1 expression status (high or low), and liver metastases (present or absent). Blinding: None (open-label). An open-label design was chosen because the control arm contains agents not contained in the experimental arm, meaning blinding with placebo-control would be difficult and could complicate the ability to assess attribution of overlapping toxicities.[47]
Key inclusion criteria	• Aged 18 years and older

	• Histologically documented, unresectable locally advanced or metastatic urothelial carcinoma
	• Measurable disease by investigator assessment according to Response Evaluation Criteria (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
	• No 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
	• Considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, in the investigator's judgment
	• Archival tumour 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

Key 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-L1) inhibitor for any malignancy, including earlier stage urothelial cancer, 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 metastases • Ongoing clinically significant toxicity associated with prior treatment that has not resolved to ≤ Grade 1 or returned to baseline

	A complete list of exclusion criteria is available in the clinical study report.[39]
Settings and locations where the data were collected	185 sites in 25 countries United States, Canada, Netherlands, Belgium, France, Spain, Hungary, Italy, Switzerland, Czech Republic, United Kingdom, Denmark, Poland, Germany, Argentina, Australia, Singapore, Thailand, Russia, Japan, South Korea, China, Taiwan, Turkey, Israel
Trial drugs	**Intervention** EV: 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of a 21-day cycle, until disease progression or unacceptable toxicity. P: 200 mg IV on day 1 of each 3-week cycle, as above to a maximum of 35 cycles. **Comparator** Gemcitabine: 1000 mg/m^2 body surface area on days 1 and 8 of a 3-week cycle as IV infusion, in combination with either: • Cisplatin: 70 mg/m^2 on day 1 as IV infusion; given on day 2 if required by institutional standards; or • Carboplatin: AUC equivalent to 4.5 or 5 mg/ml/min (Calvert formula), according to local guidelines, on day 1 Chemotherapy was given for a maximum of 6 cycles. **Cisplatin ineligibility** Ineligibility was determined using the Galsky criteria, defined by a glomerular filtration rate of 30 to < 60 ml per minute per 1.73 m^2 of body-surface area; hearing loss of grade 2 or higher, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 2, or New York Heart Association class III heart failure at enrolment.
Maintenance therapy	The use of maintenance therapy was permitted in the chemotherapy group in geographic regions in which the maintenance therapy was available. During the trial there was an amendment to define the use of maintenance therapy after discontinuation or completion of chemotherapy, such that it was not considered to be subsequent anticancer therapy. In addition, censoring rules for subsequent therapies in relation to the PFS analysis were revised so that data from patients in the chemotherapy group who received maintenance therapy as the first subsequent therapy were not censored.
Concomitant medications	Key points are summarised below. A full description of allowed and prohibited concomitant therapies is available in the clinical study protocol. All therapies administered were to be recorded. **Allowed:** palliative radiotherapy on stable non-target bone lesions; surgical resection with curative intent in subjects with

	favourable response may be permitted after discussion; anti-emetics; granulocyte-stimulating growth factors; insulin; therapies to manage EV-associated toxicity; antimicrobial prophylaxis. **Prohibited:** medications or vaccinations prohibited by the exclusion criteria; systemic antineoplastic therapy; radiation therapy except as noted above.
Endpoint measures	**Primary endpoints** • Progression-free survival (defined as the time from randomization to the first occurrence of disease progression as assessed by blinded independent central review (BICR) according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or death from any cause (whichever occurred first) • Overall survival **Secondary endpoints** • Objective response rate per RECIST v1.1 by BICR and by investigator assessment • Time to pain progression • Mean change from baseline in worst pain at week 26 • PFS per RECIST v1.1 by investigator assessment • Duration of response per RECIST v1.1 by blinded independent central review (BICR) and by investigator assessment • Disease control rate per RECIST v1.1 by BICR and by investigator assessment • Mean scores and change from baseline of the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30), and EuroQoL 5-dimension 5-level Questionnaire (EQ-5D-5L), visual analogue scale, and utility scores. • Type, incidence, relatedness, severity and seriousness of adverse events (AEs) • Type, incidence, and severity of laboratory abnormalities • Treatment discontinuation rate due to AEs
Pre-planned subgroups	Age (<65 years, ≥65 years), race (White, other), region (North America, Europe, rest of the World), sex (male, female), ECOG PS (0, 1-2), primary disease site of origin (upper tract, lower tract), liver metastases (present, absent), PD-L1 expression (low [CPS<10], high [CPS ≥10]),* cisplatin eligibility (eligible, ineligible), metastatic disease site (visceral metastases, lymph node only), renal function (normal, mild, moderate-severe) *PD-L1 expression was assessed with the use of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and classified using the Combined Positive Score (CPS), defined

	as the total number of PD-L1-staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100. The cut-off used for 'low' was <10.

ADC, antibody drug conjugate; AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CPS: combined positive score; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EQ-5D-5L, EuroQoL 5-dimension 5-level Questionnaire; EV, enfortumab vedotin; IV, intravenous; MMAE, monomethyl auristatin E; P, pembrolizumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria

Source: Powles et al. 2024[2], Seagen Inc Clinical study protocol,[47] Clinical Study Report[39]

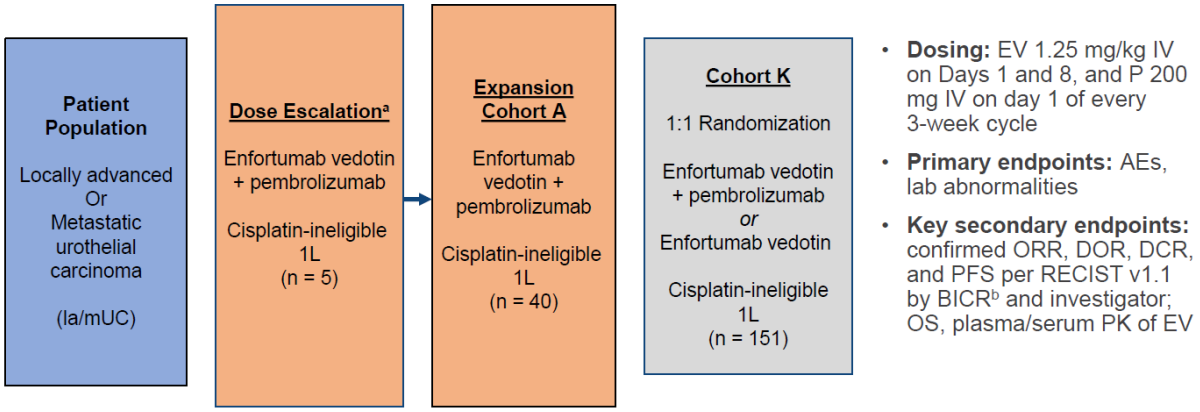
2.3.2 EV-103 trial design

EV-103 (NCT03288545) is a multi-cohort, non-randomised, open-label, Phase Ib/II trial.[11,40,41] It was designed to determine the safety and tolerability of enfortumab vedotin alone and in combination with pembrolizumab and/or chemotherapy for the treatment of locally advanced/metastatic UC and muscle-invasive BC. Patient populations and interventions varied by cohort. Two expansion cohorts are relevant to the submission because they include patients with previously untreated la/mUC treated with EV+P. Of note, only cisplatin-ineligible patients were included, whereas study EV-302 included patients eligible for either cisplatin or carboplatin-containing chemotherapy.

- Cohort A (n=40) consisted of cisplatin-ineligible la/mUC patients treated with EV+P. These were analysed together with patients from the dose escalation cohort (patients [N=5] assigned to EV 1.25 mg/kg + P on Days 1 and 8, and P 200 mg IV on Day 1 of every 3-wk cycle and for whom study treatment was administered as 1L therapy).

- Cohort K (n=151) consisted of cisplatin-ineligible la/mUC patients randomised to receive either EV monotherapy or EV+P.

Cisplatin ineligibility was determined by investigator assessment, or on the basis of any of: ECOG performance status of 2, impaired renal function (defined as creatinine clearance [calculated or measured] of ≥ 30 and <60 mL/min), hearing loss/dysfunction, age, and/ or allergy to cisplatin.[11]



Exploratory endpoints: biomarkers of activity including baseline PD-L1 status and Nectin-4 expression; **Dose Escalation/Cohort A** completed enrolment in Jan 2019; Data cutoff was 16 Sep 2022

1L, first-line; AE, adverse events; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; EV, enfortumab vedotin; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors

[a] Patients assigned to EV 1.25 mg/kg + P and for whom study treatment was administered as 1L therapy. [b] The efficacy endpoints per RECIST v1.1 by BICR are presented in the submission.

Source: Gupta 2023[41]

Figure 7 EV-103 study design

Key exclusion criteria for both cohorts included previous treatment with a PD-1, PD-L1, or PD-L2 inhibitor, treatment with stimulatory or co-inhibitory T-cell receptor agents, ongoing sensory or motor neuropathy Grade 2 or higher, active CNS metastases, ongoing clinically significant toxicity associated with prior treatment, conditions requiring high doses of steroids or other immunosuppressive medications, uncontrolled diabetes, and prior treatment with EV or other monomethyl auristatin E (MMAE)-based ADCs.

The primary endpoints investigated were AEs and lab abnormalities. Key secondary endpoints consisted of confirmed ORR, DOR, DCR, PFS per RECIST v1.1 by BICR and investigator, OS, and plasma/serum PK of EV.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical analyses in the EV-302 trial are summarised in Table 9. Further details are available in the Statistical Analysis Plan published as an appendix to Powles et al. 2024.[47] Patient disposition is shown in Section 2.6.1.

Table 9. Summary of statistical analyses in the EV-302 trial.

Determination of sample size	The trial was designed to provide at least 90% power to detect a difference between the groups in progression-free survival and overall survival at two-sided alpha levels of 0.005 and 0.045, respectively. For the OS endpoint, 489 events were required to provide 93% power to show superiority, under the assumption of an HR of 0.73 and a median duration of overall survival of 15.3 months in the chemotherapy group. For the PFS endpoint, 526 events were required to provide 90% power to show the superiority of EV+P over chemotherapy, under the assumption of an HR of 0.7 and a median duration of progression-free survival of 7 months in the chemotherapy group.
Multiplicity adjustment	The study had dual primary endpoints (PFS and OS). In order to maintain a strong control of the family-wise type I error rate at 0.05 (2-sided), the initial alpha allocation was 0.005 for PFS and 0.045 for OS. If one of the primary end points was statistically significant, the alpha initially assigned to that end point was rolled over to the other end point.
Interim analyses and stopping guidelines	The study tested PFS only once, at the PFS analysis which was performed after approximately 526 PFS events or 356 OS events, whichever was later. The threshold for statistical significance was 0.005. The study was designed to test OS twice, first at interim analysis (same time as the PFS final analysis) and second at final analysis, which was to be performed after approximately 489 events. If the OS results were statistically significant at interim analysis (threshold for statistical significance, 0.01548), no further formal testing of OS would be conducted. The efficacy boundaries at the interim and final analyses were to be determined using the Lan-DeMets spending function to approximate O'Brien-Fleming boundaries. If the results of the two primary end-point analyses were significant, select secondary end points were to be tested with the use of a gatekeeping testing strategy (see Powles et al, 2024, Suppl. Appendix).
Analysis sets	Efficacy analyses were performed in the intention-to-treat (ITT) population (defined as all patients who had been randomised to a treatment group).

	The safety population comprised all patients who had received any dose of the trial treatment.
Primary efficacy endpoints	A stratified log-rank test was used to compare progression-free survival and overall survival in the two treatment groups.
Time-to-event end points	Summarised using the Kaplan-Meier method, with hazard ratio and 95% confidence interval estimated using a stratified Cox proportional-hazards regression model.
Overall response + duration of response	The Cochran-Mantel-Haenszel test was used to compare the percentage of overall response in the treatment groups. Overall response and duration of response were evaluated in patients with measurable disease at baseline
Time to pain progression	The time to pain progression was evaluated in patients who had received any amount of the trial treatment and had answered at least one question on the Brief Pain Inventory Short-Form questionnaire at baseline.
Safety analyses	The safety analyses were performed with the use of descriptive statistics.
Handling of missing data	With the exception of scenarios detailed in the protocol and SAP, missing data were not imputed. Patients who did not have at least two (initial response and confirmation scan) post-baseline response assessments were counted as non-responders for analysis of ORR. Missing data for patient-reported outcomes (PROs) were handled according to the user manual for each individual PRO.

HR, hazard ratio; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; SAP, statistical analysis plan

Source: Powles et al. 2024[2] (including supplementary appendix)

2.5 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the EV-103 and EV-302 studies was carried out as part of the SLR, using the Cochrane Risk-of-Bias Tool for Randomized Trials (RoB2).[48] Both studies were assessed to be at low risk of bias in all 5 domains (Appendix D: SLR report Tables 53 and 54). The quality of the evidence and its relevance to the decision problem and to NHS clinical practice are discussed in Section 2.12.2 (Interpretation of evidence).

2.6 Clinical effectiveness results of the relevant studies

Key points

- EV+P resulted in a near-doubling of both median PFS and median OS compared with platinum-based chemotherapy in the pivotal EV-302 study in previously untreated patients with u/mUC:
    - Median PFS was 12.5 months in the EV arm vs 6.3 months in the chemotherapy arm, with a 55% reduction in the risk of disease progression or death (HR: 0.450; 95% CI: 0.377, 0.538; 2-sided p-value <0.00001).
    - Median OS with EV+P was 31.5 months, compared with 16.1 months in the chemotherapy arm. This equated to a 53.2% reduction in the risk of death with EV+P vs chemotherapy (HR: 0.468; 95% CI: 0.376, 0.582; 2-sided p-value <0.00001).
    - Consistent PFS and OS benefit was observed across all pre-specified subgroups, including cisplatin eligibility, PD-L1 expression status, and liver metastases.[2]
- EV+P was associated with a significantly higher response rate than chemotherapy (ORR 67.7% [95% CI: 63.1, 72.1] vs 44.4% [95% CI: 39.7, 49.2]), and a higher rate of complete response (29.1% vs 12.5%).[2]
- Responses to EV+P were substantially more durable than responses to chemotherapy: median duration was not reached (95% CI: 20.2, NE), compared with a median of 7.0 months (95% CI: 6.2, 10.2) in the chemotherapy arm.[2]
- In long-term follow-up of the EV-103 study in cisplatin-ineligible patients, the PFS rate with EV+P was 38.2% at 3 years and remained the same at 5 years. The estimated OS rate at 5 years was 41.5%, a survival rate that dramatically exceeds historical data.

Health-related quality of life

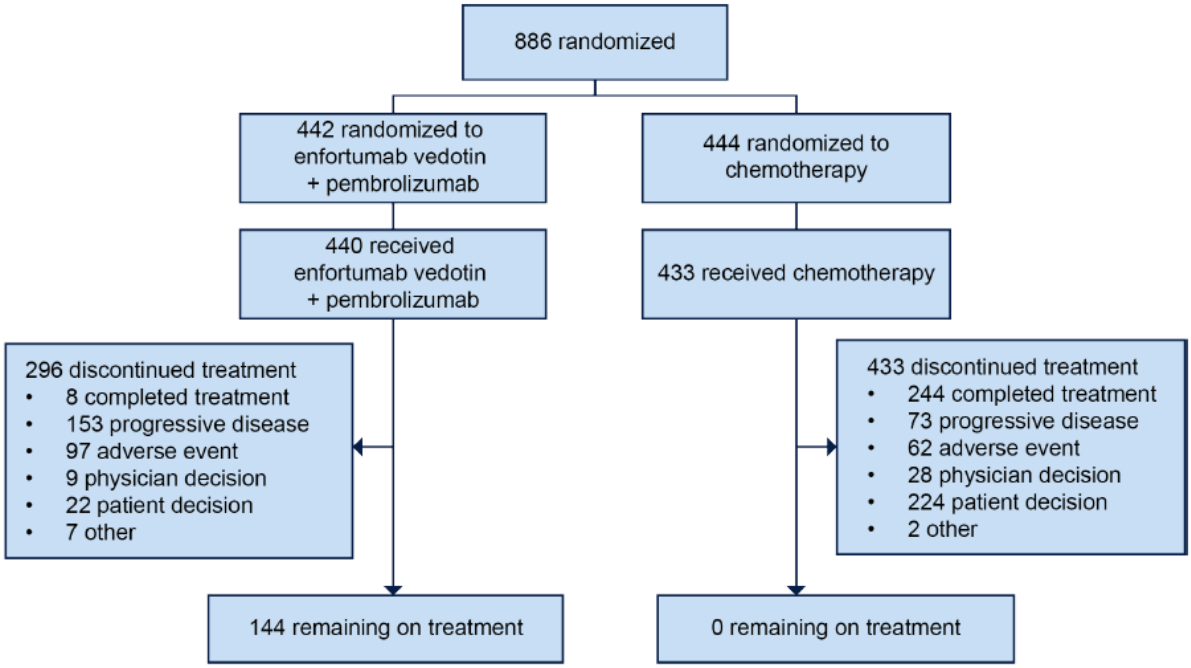
- Scores for the EORTC QLQ-C30 suggested that the PFS and OS benefits of EV+P were achieved with no meaningful changes to global health status/quality of life, pain or functioning compared with chemotherapy.[49]

- Patients in the EV+P arm had a smaller decline from baseline in functioning (least squares mean change from baseline) across all functioning domains compared to patients in the chemotherapy arm, during the first 26 weeks (exploratory analysis).[49]

Results for EV-302 are presented in Sections 2.6.1 to 2.6.7 below, and results for EV-103 in Section 2.6.8.

2.6.1 Patient disposition and baseline characteristics

Patient disposition is shown in Figure 8.



Two patients randomised to the enfortumab vedotin–pembrolizumab group did not receive treatment because the patient was either randomised by error (an error on Interactive Web Response System) or had icteric cholestasis (grade 3) and severe thrombocytopenia. Eleven patients randomised to the chemotherapy group did not receive treatment because: the patient did not meet creatinine clearance guidelines (1 patient), was randomised by error (1 patient), by physician's decision (1 patient), progressive disease (1 patient), or withdrawal of consent (7 patients). In the chemotherapy group, of the 234 cisplatin-eligible patients, 220 (94.0%) received cisplatin at first cycle, 8 received carboplatin at first cycle, and 6 were never treated. Of the 210 cisplatin-ineligible patients, 205 (97.6%) received carboplatin at first cycle; 5 were never treated. Source: Powles 2024 (Suppl.)[2]

Figure 8 Patient disposition, EV-302

A total of 886 patients were randomised. The data cut-off date was 8 August 2023 and median follow-up for survival was 17.2 months. The baseline demographic and clinical characteristics of patients in the EV+P and chemotherapy groups were generally well-balanced (Table 10). The median age was 69 years (range, 22 to 91), and the population was predominantly male (76.7%). Approximately half of patients had ECOG PS 0 and half PS 1. Almost all (95%) had metastatic disease. The primary site of origin of the disease was the upper tract in 27% of patients.[2]

Table 10. Demographic and baseline characteristics, EV-302.

Characteristic	EV + P (N=442)*	Chemotherapy (N=444)*
Median age (range), yr	69.0 (37-87)	69.0 (22-91)
Age ≥ 75 years, n (%)	102 (23.1)	108 (24.3)
Sex, n (%)		
Male	344 (77.8)	336 (75.7)
Female	98 (22.2)	108 (24.3)
Race or ethnic group, n (%)†		
Asian	99 (22.4)	92 (20.7)
Black	3 (0.7)	7 (1.6)
White	308 (69.7)	290 (65.3)
Other‡	5 (1.1)	8 (1.8)
Unknown or not reported	27 (6.1)	47 (10.6)
Geographic region, n (%)		
North America	103 (23.3)	85 (19.1)
Europe	172 (38.9)	197 (44.4)
Rest of world	167 (37.8)	162 (36.5)
ECOG performance status, n (%)§		
0	223 (50.5)	215 (48.4)
1	204 (46.2)	216 (48.6)
2	15 (3.4)	11 (2.5)
Data missing	0	2 (0.5)
Body mass index, n (%)¶		
< 25 kg/m^2	206 (46.6)	185 (41.7)
25 to < 30 kg/m^2	144 (32.6)	155 (34.9)
≥ 30 kg/m^2	89 (20.1)	101 (22.7)
Data missing	3 (0.7)	3 (0.7)
Creatinine clearance, n (%)‖		
≥ 60 mL/min	249 (56.3)	257 (57.9)

< 60 mL/min	193 (43.7)	187 (42.1)
No. of Bajorin risk factors, n (%)**		
0	179 (40.5)	183 (41.2)
1	263 (59.5)	259 (58.3)
Data missing	0	2 (0.5)
H score of nectin-4 expression††		
n	394	406
Median (range)	280 (0-300)	270 (0-300)
Disease status at randomization, n (%)		
Locally advanced	21 (4.8)	24 (5.4)
Metastatic	421 (95.2)	420 (94.6)
Primary site of origin of disease, n (%)		
Upper tract	135 (30.5)	104 (23.4)
Lower tract	305 (69.0)	339 (76.4)
Unknown	2 (0.5)	1 (0.2)
Histology type, n (%)		
Urothelial carcinoma	379 (85.7)	373 (84.0)
Urothelial carcinoma mixed types‡‡	50 (11.3)	53 (11.9)
Variant urothelial carcinoma only without typical UC	4 (0.9)	7 (1.6)
Unknown	9 (2.0)	11 (2.5)
Site of metastasis, n (%)		
Lymph node only	103 (23.3)	104 (23.4)
Visceral metastases	318 (71.9)	318 (71.6)
Bone	81 (18.3)	102 (23.0)
Liver	100 (22.6)	99 (22.3)
Lung	170 (38.5)	157 (35.4)
Cisplatin eligibility status, n (%)		
Eligible	240 (54.3)	242 (54.5)
Ineligible	202 (45.7)	202 (45.5)
PD-L1 expression, n/total n (%)§§		
High, CPS ≥10	254/438 (58.0)	254/439 (57.9)
Low, CPS <10	184/438 (42.0)	185/439 (42.1)

ALT, alanine transaminase; AST, aspartate transferase; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; Gem, gemcitabine; Max, maximum; Min, minimum; HbA1c, glycosylated haemoglobin; Pembro, pembrolizumab; Plat, platinum-based chemotherapy (cisplatin or carboplatin); PS, performance status; Q, quartile; SD, standard deviation; ITT, intent-to-treat; UC, urothelial cancer; ULN, upper limit of normal.

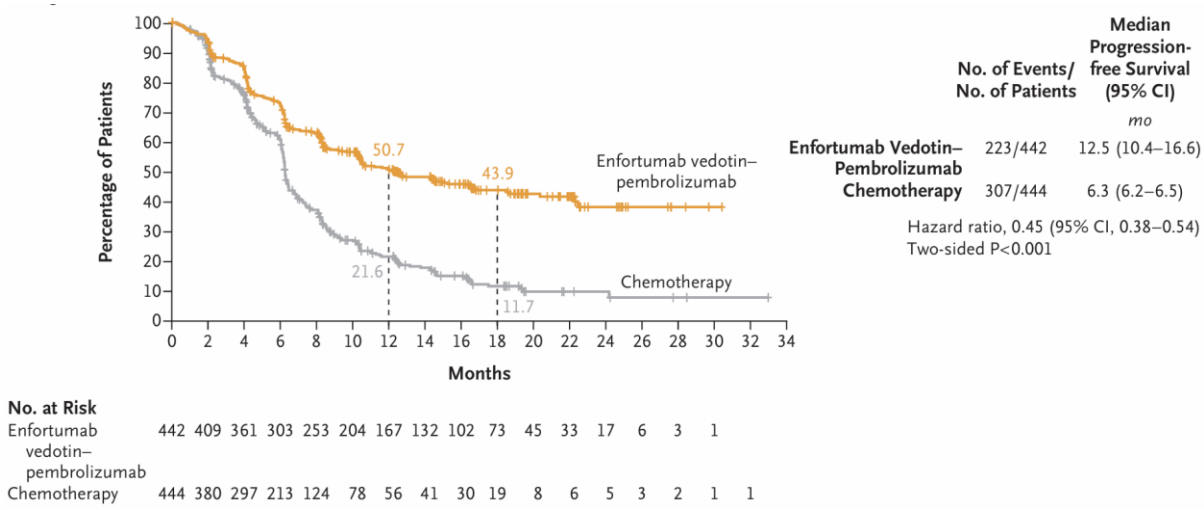
*Percentages may not total 100 because of rounding; †Race or ethnic group was reported by the patient; ‡ This category comprises other ethnic groups (including American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander) and multiple ethnic groups; § Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating

greater disability; ¶ The body-mass index is the weight in kilograms divided by the square of the height in meters; ‖ To convert the values for creatinine clearance to millilitres per second, multiply by 0.01667; ** Bajorin risk factors include visceral metastases (metastases to the bone, lung, or liver) and an ECOG performance status score of 3 or higher. Patients with an ECOG performance-status score of higher than 2 were not eligible for the trial; †† Nectin-4 H scores were determined with the use of a validated Nectin-4 immunohistochemical assay performed at Q2 Solutions. H scores range from 0 to 300, with higher values indicating higher expression; ‡‡ This category included histologic types such as squamous, glandular, and micropapillary; §§ Programmed death-ligand 1 (PD-L1) expression was assessed with the use of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). The combined positive score (CPS) is defined as the total number of programmed death-ligand 1 (PD-L1)–staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

Source: Powles et al. 2024[2]

2.6.2 Progression-free survival by BICR (primary endpoint)

Median PFS in the EV+P arm was almost double that in the chemotherapy arm, at 12.5 months (95% CI, 10.4 to 16.6) with EV+P versus 6.3 months (95% CI, 6.2 to 6.5) with chemotherapy (Figure 9). Patients in the EV+P arm had a 55% lower risk of disease progression or death compared the chemotherapy arm (HR 0.45; 95% CI, 0.38 to 0.54; P<0.001).[2]



CI, confidence interval. Dashed lines indicate PFS at 12 and 18 months. Tick marks indicate censored data.

Source: Powles et al. 2024[2]

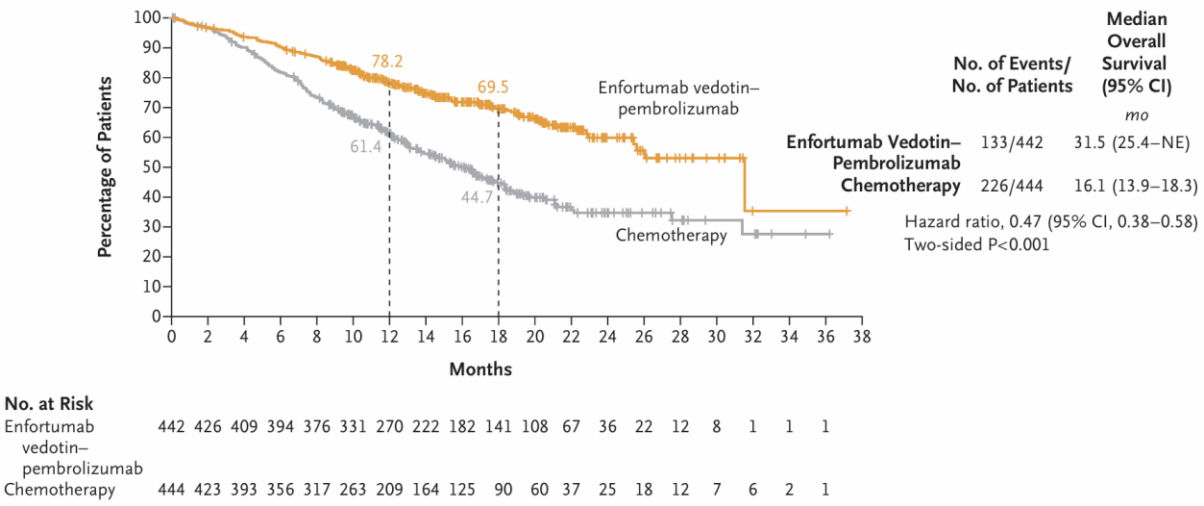
Figure 9. Kaplan-Meier estimate of PFS in the EV-302 trial (ITT population).

2.6.3 Overall survival (primary endpoint)

Median OS in the EV+P arm was almost twice as long in the EV+P arm than in the chemotherapy arm, at 31.5 months (95% CI, 25.4 to not reached) with EV+P versus 16.1 months (95% CI, 13.9 to 18.3) with chemotherapy (Figure 10). The risk of death was 53% lower in the EV+P arm than in the chemotherapy arm (HR 0.47; 95% CI, 0.38 to 0.58; P<0.001).[2]

Estimated survival at 12 months was 78.2% (95% CI, 73.9 to 81.9) in the EV+P arm and 61.4% (95% CI, 56.6 to 65.9) in the chemotherapy arm.[2]

The OS results were consistent between the ITT population and all pre-specified subgroups (see Section 2.7).



CI, confidence interval. Dashed lines indicate OS at 12 and 18 months. Tick marks indicate censored data.

Source: Powles et al. 2024[2]

Figure 10. Kaplan-Meier estimate of OS in the EV-302 trial (ITT population).

2.6.4 Overall response rate and duration of response

The confirmed overall response rate (ORR) was significantly higher with EV+P than with chemotherapy (ORR 67.7% [95% CI, 63.1 to 72.1] vs. 44.4% [95% CI, 39.7 to 49.2]; P<0.001). The rate of complete response was also higher with EV+P at 29.1% (127 of 437) vs. 12.5% (55 of 441) with chemotherapy.[2]

Median duration of response was not reached in the EV+P arm, compared with a median duration of 7.0 months in the chemotherapy arm. The percentage of patients still in remission at 12 and 19 months was 67.3% and 59.6% respectively in the EV+P arm and 35.3% and 19.3% respectively in the chemotherapy arm. Response outcomes are summarised in Table 9.[2]

Table 11. Overall response and duration of response in the EV-302 trial

Variable*	Enfortumab vedotin–pembrolizumab (N=437)	Chemotherapy (N=441)
Confirmed best overall response, n (%)		
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 (63.172.1)	44.4 (39.7–49.2)
Median time to response (range), months	2.1 (1.3–12.3)	2.1 (1.6–8.3)
Median duration of response (95% CI), months	Not reached (20.2–NE)	7.0 (6.1–10.2)

CI, confidence interval; NE, not evaluated

*Overall response and duration of response, as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were evaluated in all the patients in the intention to-treat population who had measurable disease at baseline according to RECIST, version 1.1. NE denotes could not be estimated. † Patients had a postbaseline assessment of response, but the best overall response could not be evaluated according to RECIST, version 1.1. ‡ Patients had no postbaseline assessment of response. § P<0.001.

Source: Powles et al. 2024[2]

2.6.5 Time to pain progression and worst pain

The median time to pain progression was longer in the EV+P group than the chemotherapy group (14.2 months vs. 10.0 months).[2] However, the between-group difference in the time to pain progression was not significant (HR 0.92; 95% CI, 0.72 to 1.17; P = 0.48), and therefore the additional patient-reported outcome in the

statistical hierarchy (mean change from baseline in worst pain at week 26) was not formally tested.[2] However, scores favoured the EV+P arm:

- The least squares (LS) mean reduction in worst pain at week 26 was numerically greater with EV+P vs PBC (-0.61 vs -0.03, LS mean difference [95% CI]: -0.58 [-1.05, -0.11] [nominal 2-sided p-value=0.015]).
- Patients with moderate to severe pain at baseline who were treated with EV+P (n=128, 34%) had a meaningful (> 2 point) improvement from baseline in BPI worst pain from weeks 3 through to 26.[49]

2.6.6 Health-related quality of life (HRQoL)

Overall, 731 of the 886 randomised patients completed baseline PRO questionnaires and patient compliance with PRO assessments remained >70% through week 17 in the chemotherapy arm and week 29 in the EV+P arm.[49] A post hoc analysis of individual patient-level data found that in both treatment arms, completion rates were [redacted] 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 [redacted] for EV+P than for chemotherapy. Beyond Week 86, the completion rate for all health states and treatment arms were less than [redacted]%. This analysis suggests that in the longitudinal data per visit, completion rates in the chemotherapy arm were [redacted] due to more patients having progressed.[50] In the published analysis, there was no notable change in either EORTC QLQ-C30 or EQ-5D-5L average scores over the study period.[49]

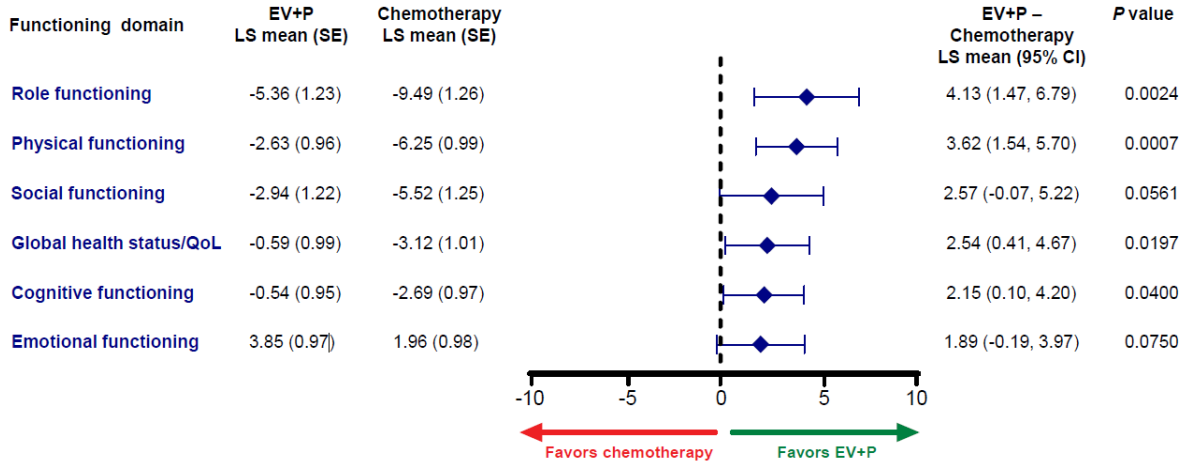
2.6.6.1 EORTC QLQ-C30

Overall, [redacted]% patients in the EV+P arm and [redacted]% in the chemotherapy arm completed at least one component of the EORTC QLQ-C30 questionnaire at baseline.[39] At baseline, the mean global health status/QoL (GHS/QoL) score was 62.4 in the EV+P arm and 60.3 in the chemotherapy arm, and the mean functional domain scores were 70 or above in both treatment arms.[49]

- GHS/QoL scores in the EV+P arm showed a transient worsening at week 3 (-6.3) that returned to baseline from weeks 4 through to 26, while patients in the

chemotherapy arm showed deterioration from weeks 1 through to 17 (range -1.2 to -7.1), when scores returned to baseline.

- Time to confirmed deterioration (TTCD) for EORTC QLQ-C30 GHS/QoL was 5.9 months with EV+P vs 3.2 months with chemotherapy (HR = 0.98 [95% CI]: 0.79 – 1.2).
- Patients in the EV+P arm had a smaller decline from baseline in functioning (least squares mean change from baseline) across all functioning domains compared to patients in the chemotherapy arm, during the first 26 weeks (Figure 11). (As the pre-specified PRO endpoint was not met, this is an exploratory analysis with nominal p-values).



CI, confidence interval; EV, enfortumab vedotin; LS, least squares; P, pembrolizumab; QoL, quality of life; SE, standard error. P values are nominal.

Source: Gupta 2024 (conference presentation, ASCO 2024)[49]

Figure 11 Change from baseline in EORTC QLQ-C30 functioning domains at 26 weeks (exploratory analysis)

2.6.6.2 EQ-5D-5L

Overall, [redacted]% of patients in the EV+P arm and [redacted]% in the chemotherapy arm completed at least one component of the EQ-5D-5L questionnaire at baseline. The mean baseline visual-analogue scale (VAS) scores were [redacted] in the EV+P arm and [redacted] in the chemotherapy arm, and the Health State Index Scores (utility scores) were [redacted] and [redacted], respectively. During the treatment period, both VAS and utility

scores remained stable, with little to no change from baseline throughout the study period.[51]

2.6.7 Subsequent anti-cancer therapies

As of the data cut-off, 32.6% (144 of 442) of the patients in the EV+P arm and none in the chemotherapy arm were still receiving treatment. A total of 31.7% (140 of 442) of patients in the EV+P arm and 70.5% (313 of 444) in the chemotherapy arm received subsequent anticancer therapies.[2]

Table 12 Summary of subsequent anti-cancer therapy

	EV+P (N=442)	Chemotherapy (N=444)
Parameters, n (%)		
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)

*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. Source: Powles 2024 (Suppl)[2]

2.6.8 Study EV-103

Study EV-103 (cohort A) provides long-term follow-up data (median follow-up 62 months) on a subset of the submission population (previously untreated cisplatin-ineligible patients). Results relevant to the submission population are also available from cohort K. Study design and inclusion criteria are described in Section 2.3.2.

2.6.8.1 Baseline patient characteristics (cohort A + dose escalation)

Baseline characteristics are shown in Table 13. Patients were predominately male (80.0%). Median age was 69 years, and 35.6% were aged ≥75 years. Visceral

metastases were present in 84.4% of patients, including 31.1% with liver metastases, and 33.3% had disease originating in the upper tract.[11] Compared with EV-302, a greater proportion of patients were aged ≥75 years (35.6% vs 23.7%), fewer had ECOG PS 0 (33.3% vs 49.4%), more had EGOG PS 2 (17.8% vs 2.9%), and more had visceral metastases (84.4% vs 71.8%). However, the sample size in EV-103 is small (N=45) so comparisons should be treated with caution. Reasons for cisplatin-ineligibility are shown in Table 14. All patients except 1 met the well-recognised Galsky[52] cisplatin ineligibility criteria.

Table 13 Key baseline characteristics, EV-103 cohort A + dose escalation[a]

Characteristic	Patients (N=45)
Median age (range), yr	69.0 (51-90)
Age ≥ 75 years, n(%)	16 (35.6)
Male sex, n (%)	36 (80.0)
White race, n(%)	42 (93.3)
ECOG performance status, n	
0	15 (33.3)
1	22 (48.9)
2	8 (17.8)
Primary site of origin of disease, n (%)	
Upper tract	30 (66.7)
Lower tract	15 (33.3)
Site of metastasis, n (%)	
Lymph nodes	34 (75.6)
Lung	19 (42.2)
Intra-thoracic/abdominal soft tissue	17 (37.8)
Liver	14 (31.1)
Visceral metastases present	38 (84.4)

[a] Patients (N=5) assigned to EV 1.25 mg/kg + P on Days 1 and 8, and P 200 mg IV on Day 1 of every 3-wk cycle and for whom study treatment was administered as 1L therapy.

Source: Hoimes 2023,[11] Rosenberg 2024[53]

Table 14. Reasons for cisplatin ineligibility in the EV-103 trial.

	Dose escalation[a] + Cohort A (N = 45)
Patients meeting at least one of the following Galsky criteria	44 (97.8%)
CrCL <60 and ≥30 mL/min[b]	25 (55.6%)
ECOG PS of 2	6 (13.3%)
≥ grade 2 hearing loss	5 (11.1%)
CrCL <60 and ≥30 mL/min and ≥ grade 2 hearing loss	5 (11.1%)
CrCL <60 and ≥30 mL/min and ECOG PS of 2	2 (4.4%)
ECOG PS of 2 and ≥ grade 2 hearing loss	1 (2.2%)
Patients considered cisplatin-ineligible by the investigator although not meeting Galsky criteria[c]	1 (2.2%)

CrCL, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; PS, performance status

[a] Patients (N=5) assigned to EV 1.25 mg/kg + P on Days 1 and 8, and P 200 mg IV on Day 1 of every 3-wk cycle and for whom study treatment was administered as 1L therapy. [b]Estimated creatinine clearance per Cockcroft-Gault formula or 24-hr urine collection or Modification of Diet in Renal Disease equation; [c]One patient in Cohort A was considered cisplatin-ineligible by the investigator due to the patient having a solitary kidney.

Source: Gupta et al. ASCO 2023[41]

2.6.8.2 Results (cohort A + dose escalation; median follow-up 62 months)

Patients received a median of 9 cycles of EV+P, 8 of EV, and 8 of P. Median duration of treatment was 7.0 months (range: 0.7-32.9) for EV+P, 6.4 months (range: 0.7-32.9) for EV, and 6.5 months (range: 0.7-28.1) for P. Durable response rate, PFS and OS results for Cohort A + dose escalation cohort are shown in Table 15 and a Kaplan-Meier plots for PFS and OS in Figure 12 and Figure 13.[53]

- Median OS was 26.1 months (95% CI, 15.51-NR), with median PFS of 12.7 months (95% CI, 6.11-NR).
- Notably, 47% of pts who responded to treatment were still in response at 2 years and remained in response at 5 years. PFS rate remained constant at 38.2% between the 3-year and 5-year time points.
- The OS rate was estimated at 41.5% at 5 years, a survival rate that dramatically exceeds historical data.[53] (For example, in the EORTC 30986 study in 1L u/mUC patients unfit for cisplatin, median OS with gemcitabine-carboplatin was 9.3 months.[54])

Outcomes in patients who experienced confirmed partial or complete response are summarised as a swimmer plot (Figure 14), showing that some patients experienced ongoing response even after stopping treatment.

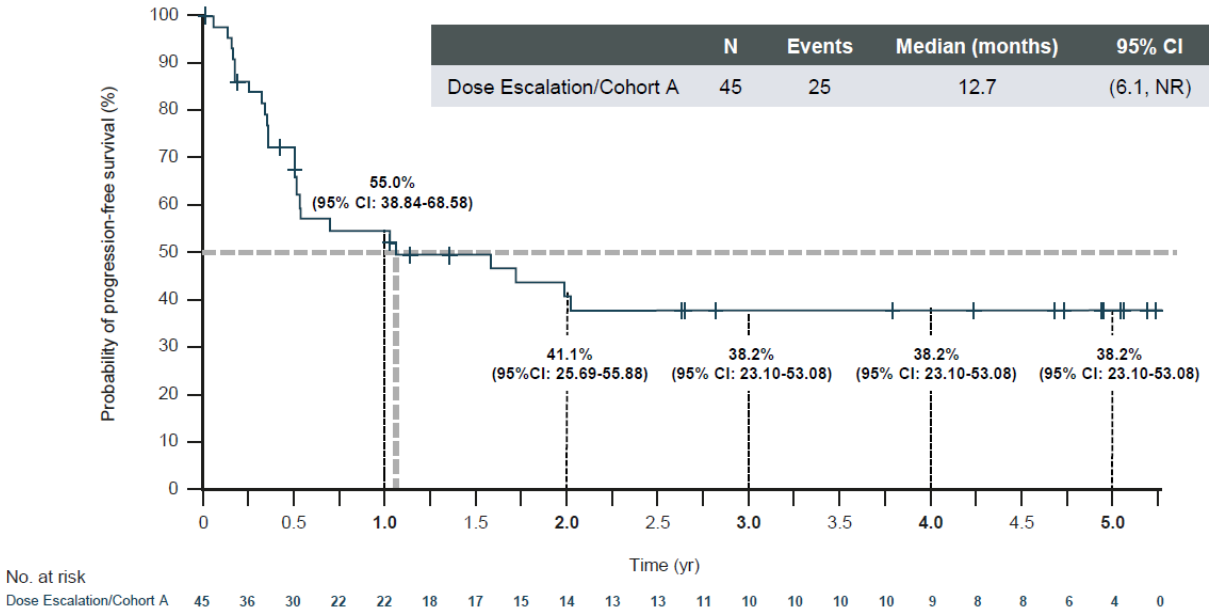
Table 15. Durable response rate, PFS (by BICR), and OS rates in EV-103 for Dose Escalation[a] + Cohort A

% (95% CI)	12 mo	24 mo	36 mo	48 mo	60 mo
Durable response rate (n=33)[b]	63.9 (44.19-78.17)	47.0 (27.57-64.31)	47.0 (27.57-64.31)	47.0 (27.57-64.31)	47.0 (27.57-64.31)
PFS rate (N=45)	55.0 (38.84-68.58)	41.1 (25.69-55.88)	38.2 (23.10-53.08)	38.2 (23.10-53.08)	38.2 (23.10-53.08)
OS rate (N=45)	83.4 (68.25-91.72)	56.4 (40.03-69.91)	49.1 (33.16-63.15)	44.1 (28.76-58.48)	41.5 (26.45-55.99)

a Patients (N=5) assigned to EV 1.25 mg/kg + P on Days 1 and 8, and P 200 mg IV on Day 1 of every 3-wk cycle and for whom study treatment was administered as 1L therapy.[41]

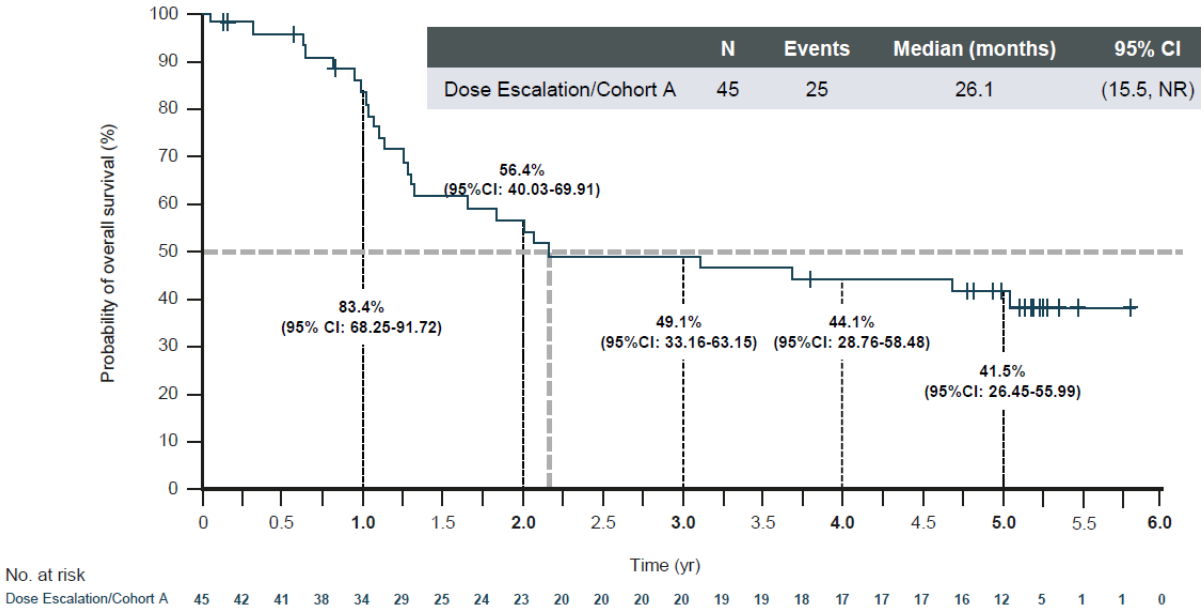
b Number of pts that responded to treatment. BICR, blinded independent central review; CI, confidence interval; mo, months; OS, overall survival; PFS, progression-free survival

Source: Rosenberg et al. 2024[53]



CI, confidence interval; Esc, escalation. Source: Rosenberg et al. 2024 (poster)[53]

Figure 12. Kaplan-Meier estimates of progression-free survival in Dose Escalation + Cohort A in the EV-103 trial.



CI, confidence interval; Esc, escalation Source: Rosenberg et al. 2024 (poster)[53]

Figure 13. Kaplan-Meier estimates of overall survival in Dose Escalation + Cohort A in the EV-103 trial.

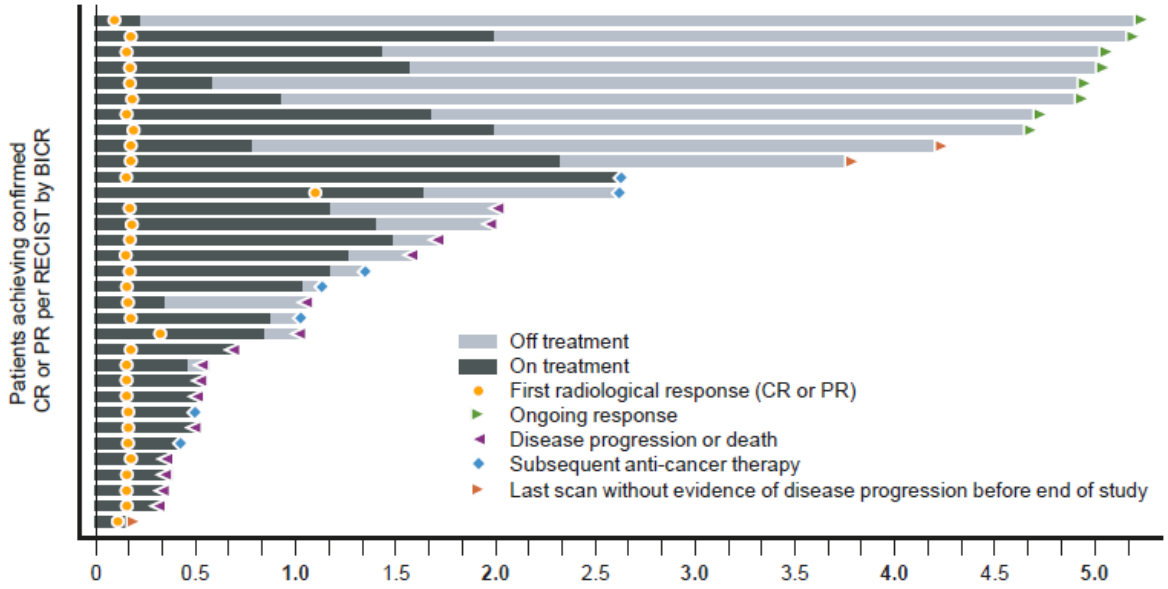
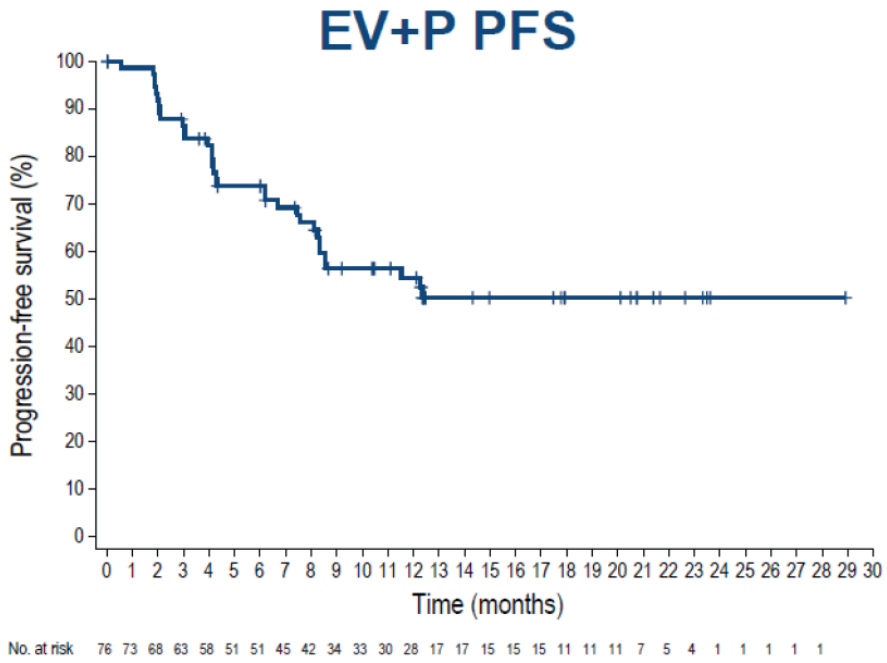


Figure 14 Time to response and DOR in patients achieving confirmed CR or PR by BICR

Source: Rosenberg et al. 2024 (poster)

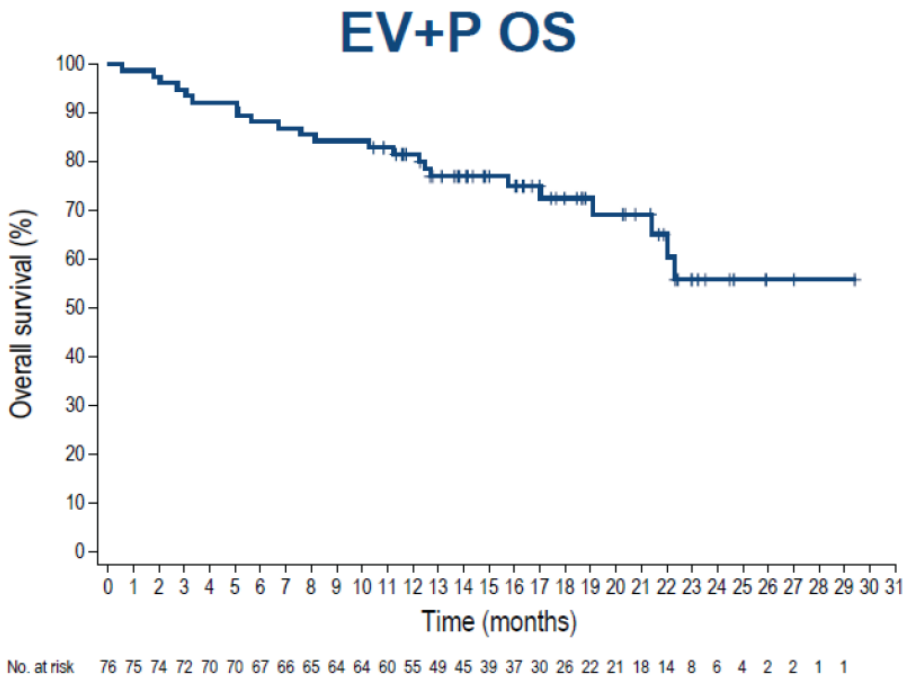
2.6.8.3 Cohort K results (median follow-up 18 months)

Cohort K consisted of cisplatin-ineligible 1L u/mUC patients randomised to either EV+P or EV monotherapy. PFS and OS results from patients randomised to EV+P are shown in Figure 15 and Figure 16, respectively. Neither median PFS nor median OS had been reached at median follow-up of 18 months.[40]



CI, confidence interval; EV, enfortumab vedotin; P, pembrolizumab Source: Friedlander et al. 2023[40]

Figure 15. Kaplan-Meier plot of progression-free survival in the EV+P arm of Cohort K in the EV-103 trial.

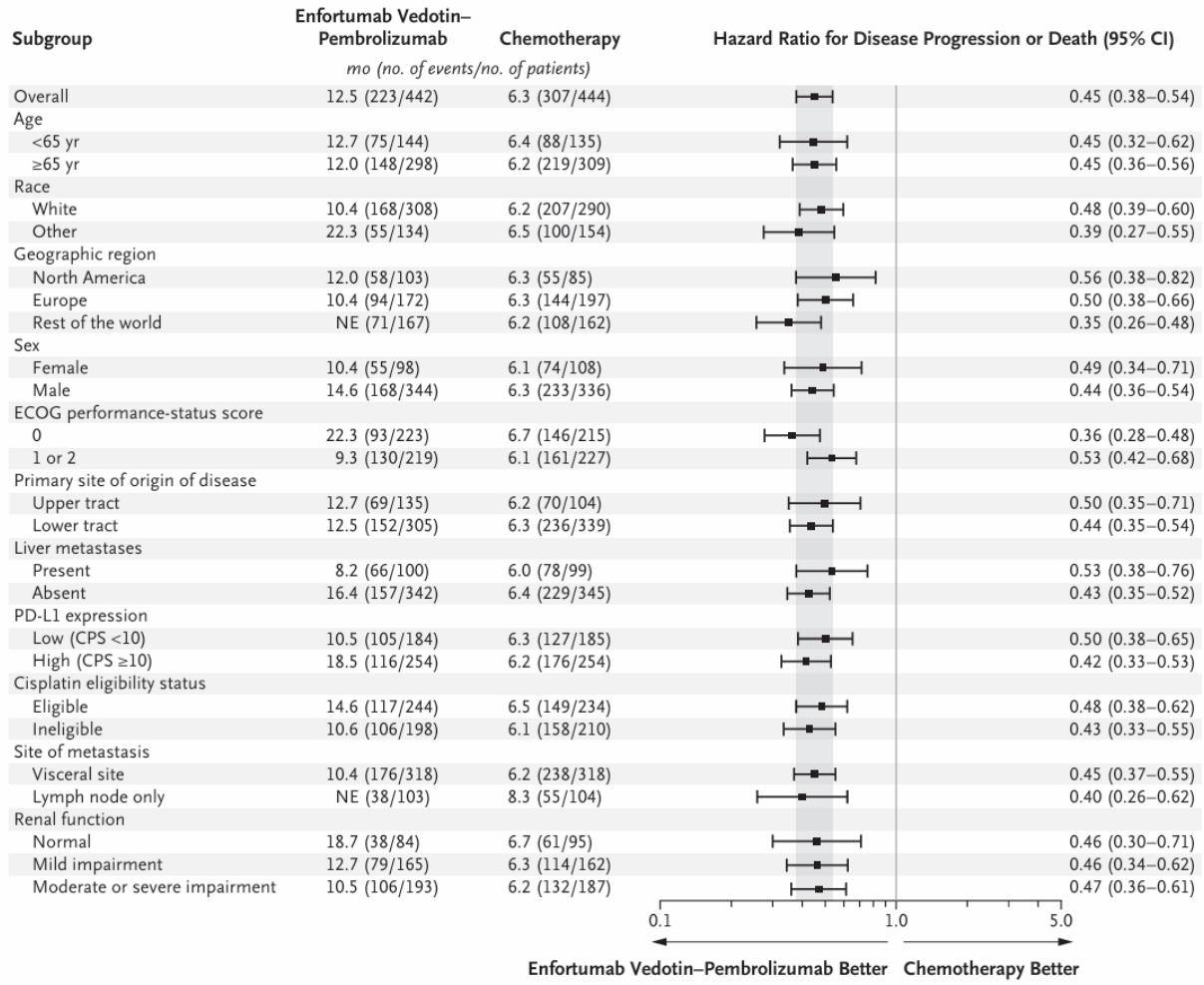


CI, confidence interval; EV, enfortumab vedotin; P, pembrolizumab Source: Friedlander et al. 2023[40]

Figure 16. Kaplan-Meier estimates of overall survival in the EV+P arm Cohort K in the EV-103 trial.

2.7 Subgroup analysis

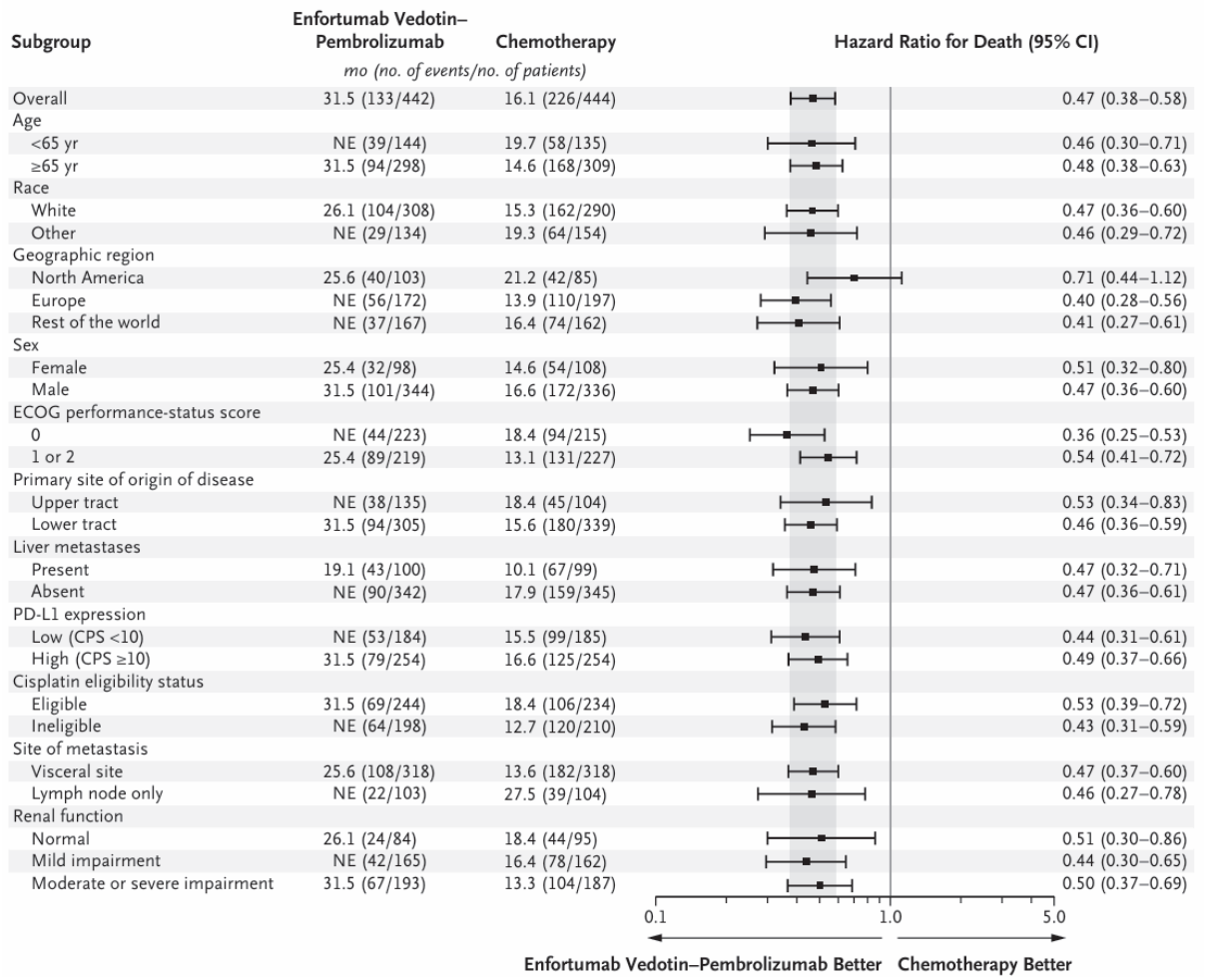
Subgroup analyses were conducted for progression-free survival (Figure 17), overall survival (Figure 18), and overall response (Figure 19). In all three analyses, the benefit of EV+P was consistent between the ITT population and all predefined subgroups, including cisplatin eligibility and PD-L1 expression status.[2] The forest plots are provided below. Kaplan-Meier plots of PFS and OS for each treatment group by PD-L1 status are provided in Appendix E.



The shaded area represents the 95% confidence intervals for the overall patient population. The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1)–staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1. Source: Powles et al. 2024[2]

Figure 17. Forest plot of the analyses of progression-free survival in all prespecified subgroups, EV-302

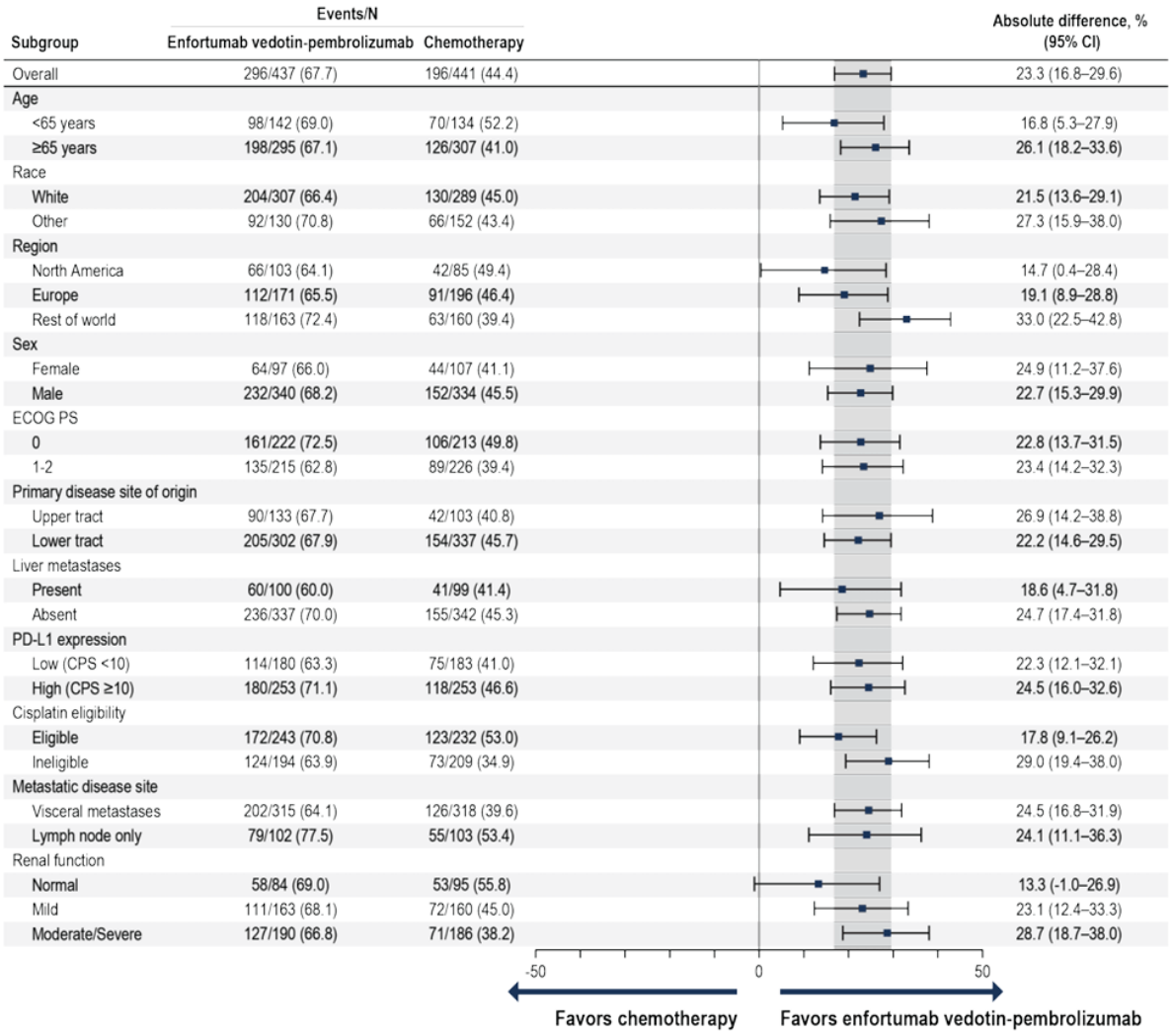


The shaded area represents the 95% confidence intervals for the overall patient population. The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1)–staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1

Source: Powles et al. 2024[2]

Figure 18. Forest plot of the analyses of overall survival in all prespecified subgroups, EV302



The shaded area represents the 95% confidence intervals for the overall patient population. The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1)–staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1

Source: Powles et al. 2024[2]

Figure 19. Forest plot of the analyses of overall response in all prespecified subgroups, EV-302

2.8 Meta-analysis

Not applicable. As discussed in Section 2.1, EV-302 is the only study comparing EV+P with platinum-based chemotherapy in first-line treatment of adult patients with

locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy (i.e. eligible for either cisplatin or carboplatin).

2.9 Indirect and mixed treatment comparisons

Atezolizumab was included in the NICE scope as a comparator for a subgroup of u/mUC patients, i.e. cisplatin-ineligible patients whose tumours have a PD-L1 expression ≥ 5%.[5] However, the Company does not consider atezolizumab to be a relevant comparator in this (or any) subgroup because of low usage in current NHS clinical practice (see Section 1.3.5.1 and Appendix T), driven by the opinion among clinicians that carboplatin + gemcitabine followed by avelumab maintenance is a more effective option for carboplatin-eligible patients.[6] See Section 1.1 for the full rationale for the decision to exclude atezolizumab as a comparator. An indirect treatment comparison (ITC) with atezolizumab is therefore not presented.

2.10 Adverse reactions

This section provides information on AEs in the EV-302 study, together with long-term follow-up in study EV-103 (cohort A + dose escalation), and the overall summary of safety with EV+P and EV monotherapy published in the SmPC. Additional safety information from the EPAR is available in Appendix F.

Key points

- The percentages of patients with treatment-emergent AEs (TEAEs; including grade 3-5 TEAEs) were similar between the EV+P and chemotherapy arms in EV-302, despite the longer duration of treatment with EV+P.[2]
- Exposure-adjusted event rates for TEAEs were lower in the EV+P arm than in the chemotherapy arm.[2]
- The most common treatment-related AEs of any grade in the EV+P group were peripheral sensory neuropathy (in 50.0% of patients), pruritus (in 39.8%), and alopecia (in 33.2%); the most common treatment-related AEs in the chemotherapy group were anaemia (in 56.6%), neutropenia (in 41.6%), and nausea (in 38.8%).[2]

- The most common treatment-related AEs of special interest of ≥ grade 3 or higher that have previously been associated with EV were skin reactions (in 15.5% of patients), peripheral neuropathy (in 6.8%), and hyperglycaemia (in 6.1%).[2] The most common AEs of special interest of ≥ grade 3 that have previously been associated with pembrolizumab were severe skin reactions (in 11.8% of patients), pneumonitis (in 3.6%), and hepatitis (in 1.8%).
    - AEs of special interest were generally manageable with dose reductions
- Dose reductions resulting from treatment-related AEs occurred in 40.7% of patients in the EV+P group and 37.9% in the chemotherapy group, and treatment-related AEs resulting in discontinuation of any treatment occurred in 35.0% and 18.5%, respectively.[2]
- No new safety concerns were seen after a median follow-up of 61 months in the EV-103 study.[53]

2.10.1 Safety in the pivotal trial (EV-302)

2.10.1.1 Safety summary

The EMA (EPAR p. 148) concludes that the safety profile for EV+P was generally consistent with the known safety profiles for EV and P monotherapy and that no new safety signals were identified.[3] The safety summary from EV-302 is shown in Table 16. The percentages of patients with any treatment-emergent adverse events (TEAE; 99.8% and 98.6% for EV+P and chemotherapy, respectively), Grade 3-5 TEAE (73.0% and 78.8%), TEAE leading to death (4.3% and 3.2%), and fatal events that were considered treatment related by the investigator (0.9% in both arms), were similar between treatment arms. This was despite a longer duration of treatment in the EV+P group. Exposure-adjusted event rates are shown on the right-hand side of the table, and were lower in the EV+P arm than in the chemotherapy arm in all categories shown.[2]

Treatment-related AEs resulting in dose reduction occurred in 40.7% of patients in the EV+P group and 37.9% in the chemotherapy group, and treatment-related AEs

resulting in discontinuation of any treatment occurred in 35.0% and 18.5%, respectively. In the EV+P group, treatment-related adverse events led to the discontinuation of EV in 29.5% of patients and to discontinuation of pembrolizumab in 21.4%.[2]

Treatment-related adverse events that resulted in death occurred in 4 patients (<1.0%) in each arm. In the EV+P group these were multiple organ dysfunction syndrome, immune-mediated lung disease, diarrhoea and asthenia (1 patient each), and in the chemotherapy group they were sepsis, febrile neutropenia, neutropenic sepsis, and myocardial infarction (1 patient each).[2]

Table 16. Safety summary of the pivotal study (EV-302)

Adverse event	Patient incidence rate		Event rate adjusted for exposure	
	EV+P (N=440) N (%)	Chemotherapy (N=433) N (%)	EV+P (PY=385.56) Events (Events/PY)	Chemotherapy (PY=147.82) Events (Events/PY)
TEAEs	439 (99.8)	427 (98.6)	7442 (19.302)	5034 (34.054)
Treatment-related	427 (97.0)	414 (95.6)	4274 (11.085)	3356 (22.703)
Grade ≥3 TEAEs	321 (73.0)	341 (78.8)	854 (2.215)	1069 (7.232)
Treatment-related	246 (55.9)	301 (69.5)	491 (1.273)	792 (5.358)
Serious TEAEs	220 (50.0)	169 (39.0)	440 (1.141)	328 (2.219)
Treatment-related	122 (27.7)	85 (19.6)	205 (0.532)	139 (0.940)
TEAEs leading to death	19 (4.3)	14 (3.2)	19 (0.049)	14 (0.095)
Treatment-related	4 (0.9)	4 (0.9)	4 (0.010)	4 (0.027)
TRAEs leading to treatment discontinuation				
Enfortumab vedotin	130 (29.5)	NA	130 (0.337)	NA
Pembrolizumab	94 (21.4)	NA	94 (0.244)	NA
Any study drug	154 (35.0)	80 (18.5)	169 (0.438)	84 (0.568)
TRAEs leading to dose interruption				
Enfortumab vedotin	266 (60.5)	NA	426 (1.105)	NA
Pembrolizumab	218 (49.5)	NA	320 (0.830)	NA
Any study drug	299 (68.0)	229 (52.9)	538 (1.395)	413 (3.795)
TRAEs leading to dose reduction of any study drugs	179 (40.7)	164 (37.9)	217 (0.563)	215 (1.454)

E, events; NA, not applicable; PY, patient-years; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

Source: Powles et al. 2024 (Suppl).[2]

2.10.1.2 Treatment-related AEs and AEs of special interest

The most common treatment-related AEs of any grade in the EV+P group were peripheral sensory neuropathy (in 50.0% of patients), pruritus (in 39.8%), and alopecia (in 33.2%); the most common treatment-related AEs in the chemotherapy

group were anaemia (in 56.6%), neutropenia (in 41.6%), and nausea (in 38.8%).[2] Treatment-related AEs occurring in ≥20% of patients in either treatment arm are shown in Table 17.

In the EV+P group, the most common treatment-related AEs of special interest of grade 3 or higher that have previously been associated with EV were skin reactions (in 15.5% of patients), peripheral neuropathy (in 6.8%), and hyperglycaemia (in 6.1%). These events did not occur in the chemotherapy group, except for skin reactions (in 0.2% of patients).[2] The most common AEs of special interest of grade 3 or higher that have previously been associated with pembrolizumab that occurred after the start of the study treatment were severe skin reactions (in 11.8% of patients), pneumonitis (in 3.6%), and hepatitis (in 1.8%); the only one of these that occurred in the chemotherapy group was pneumonitis (in 0.2% of patients).

Most of these adverse events of special interest were considered by the study authors to be manageable with dose modifications. They noted that early recognition of adverse reactions through proactive monitoring and management of symptoms remains a cornerstone of patient care with EV+P.[2]

Table 17. Treatment-related adverse events in study EV-302 occurring in ≥20% of patients in either treatment arm (any grade), or ≥5% in either arm (grade ≥3)

Adverse event	EV+P (N=440)		Chemotherapy (N=433)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	427 (97.0)	246 (55.9)	414 (95.6)	301 (69.5)
Peripheral sensory neuropathy	220 (50.0)	16 (3.6)	43 (9.9)	0
Pruritis	175 (39.8)	5 (1.1)	21 (4.8)	0
Alopecia	146 (33.2)	2 (0.5)	34 (7.9)	1 (0.2)
Maculopapular rash	144 (32.7)	34 (7.7)	14 (3.2)	0
Fatigue	129 (29.3)	13 (3.0)	156 (36.0)	18 (4.2)
Diarrhea	121 (27.5)	16 (3.6)	48 (11.1)	3 (0.7)
Decreased appetite	118 (26.8)	5 (1.1)	98 (22.6)	6 (1.4)
Nausea	89 (20.2)	5 (1.1)	168 (38.8)	12 (2.8)
Anemia	61 (13.9)	15 (3.4)	245 (56.6)	136 (31.4)
Hyperglycemia	48 (10.9)	22 (5.0)	3 (0.7)	0
Neutropenia	40 (9.1)	21 (4.8)	180 (41.6)	130 (30.0)
Neutrophil count decreased	16 (3.6)	11 (2.5)	54 (12.5)	39 (9.0)
Thrombocytopenia	15 (3.4)	2 (0.5)	148 (34.2)	84 (19.4)
Platelet count decreased	3 (0.7)	0	63 (14.5)	28 (6.5)

EV, enfortumab vedotin; P, pembrolizumab

Source: Powles et al. 2024[2]

2.10.2 Long-term follow-up (EV-103 study)

No new safety concerns were seen with EV+P after a median follow-up of 62.1 months in the EV-103 study (Dose escalation + cohort A). All patients had discontinued treatment at the time of reporting. Patients received a median of 8 cycles of EV and 8 of P. The safety profile was described by the authors as generally manageable and stable.[53] Details of the most common treatment-related AEs of special interest (AESIs) for EV at median follow-up of 62.1 months (range: 0.66-69.55) are shown in Table 18. The majority of the EV treatment-related AESIs improved or resolved:

- Median time to onset of skin reactions and hyperglycaemia was 0.7 and 0.5 months, respectively, and median time to resolution was 1.2 and 1.6 months, respectively
- Median time to onset of peripheral neuropathy was 2.4 months, while median time to resolution was 8.6 months[53]

Table 18 Treatment-related adverse events of special interest for EV, EV-103 (dose escalation + cohort A)

Adverse event	Dose escalation[a]/cohort A (N=45)	
	Any grade n (%)	Grade ≥3 n (%)
Skin reactions	30 (66.7)	10 (22.2)
Peripheral neuropathy[b]	28 (62.2)	2 (4.4)
Ocular disorders	18 (40.0)	0
Dry eye	16 (35.6)	0
Blurred vision	5 (11.1)	0
Corneal disorders	1 (2.2)	0
Hyperglycaemia	5 (11.1)	4 (8.9)
Infusion-related reactions	3 (6.7)	1 (2.2)

[a] Dose escalation patients who assigned to EV+P 1.25 mg/kg IV on Days 1 and 8, and P 200 mg IV on Day 1 of every 3-wk cycle and for whom study treatment was administered as 1L therapy; [b] Peripheral neuropathy Standardized MedDRA queries (broad scope). 8 patients had pre-existing peripheral neuropathy and 37 did not have pre-existing peripheral neuropathy. Pre-existing condition includes medical history and conditions ongoing at baseline

Source: Rosenberg et al. 2024[53]

2.10.3 Overall summary of safety with EV+P and EV monotherapy

Adverse reactions observed during clinical studies of EV as monotherapy or in combination with pembrolizumab, or reported from post-marketing use of EV, are listed in Table 19 by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.[1]

Table 19. **Adverse reactions in patients treated with enfortumab vedotin.**

	Monotherapy	**In combination with pembrolizumab**
Infections and infestations		
Common	Sepsis	Sepsis
Blood and lymphatic system disorders		
Very common	Anaemia	Anaemia
Not known[1]	Neutropenia, febrile neutropenia, neutrophil count decreased	Neutropenia, febrile neutropenia, neutrophil count decreased
Endocrine disorders		
Very common		Hypothyroidism
Metabolism and nutrition disorders		
Very common	Hyperglycaemia, decreased appetite	Hyperglycaemia, decreased appetite
Not known[1]	Diabetic ketoacidosis	Diabetic ketoacidosis
Nervous system disorders		
Very common	Peripheral sensory neuropathy, dysgeusia	Peripheral sensory neuropathy, dysgeusia
Common	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness	Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness
Uncommon	Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysaesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation	Neurotoxicity, dysaesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation
Eye disorders		
Very common	Dry eye	Dry eye
Respiratory, thoracic, and mediastinal disorders		
Very common		Pneumonitis/Interstitial lung disease[2]
Common	Pneumonitis/Interstitial lung disease[2]	
Gastrointestinal disorders		
Very common	Diarrhoea, vomiting, nausea	Diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders		

	Monotherapy	In combination with pembrolizumab
Very common	Alopecia, pruritus, rash maculo-papular, dry skin	Alopecia, pruritus, rash maculo-papular, dry skin, rash macular
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular	Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash papular, rash pruritic, rash vesicular, erythaema multiforme, dermatitis
Uncommon	Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister	Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis
Not known[1]	Toxic epidermal necrolysis, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema	Toxic epidermal necrolysis, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema
Musculoskeletal and connective tissue disorders		
Common		Myositis
General disorders and administration site conditions		
Very common	Fatigue	Fatigue
Common	Infusion site extravasation	Infusion site extravasation
Investigations		
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased
Common		Lipase increased
Injury, poisoning and procedural complications		
Common	Infusion related reaction	Infusion related reaction

[1]Based on global post-marketing experience.

[2]Includes: acute respiratory distress syndrome, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organising pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity and sarcoidosis.

Source: SmPC[1]

2.11 Ongoing studies

A further, event-driven data cut from the ongoing EV-302 study is expected in [redacted]. This will provide longer-term PFS and OS data. The Company hopes to be in a position to present this additional data to NICE, together with updated modelling results, as soon as possible.

The China portion of the EV-302 study [Protocol Amendment 07 CHN-1] was designed to evaluate the consistency of efficacy and safety in a Chinese subpopulation compared with the global population. After enrollment was completed in the global cohort, subjects in China continued to be randomised until a planned sample size of approximately 130 subjects in China was reached. Subjects in China randomised after completion of enrollment in the global population are not included in the analysis of the global population, nor are they presented in the present CSR.[39] Enrolment completed in [redacted] with [redacted] patients randomised. Interim analysis 1 is planned for [redacted] and final analysis in [redacted].

2.12 Interpretation of clinical effectiveness and safety evidence

2.12.1 Principal findings from the clinical evidence

EV+P showed statistically significant and clinically meaningful benefits over standard-of-care platinum-based chemotherapy in previously untreated patients with unresectable locally advanced or metastatic UC in the pivotal EV-302 study. Treatment with EV+P resulted in a near-doubling of both PFS and OS compared with chemotherapy (median follow-up 17.2 months).[2] Median PFS was 12.5 months in the EV arm vs 6.3 months in the chemotherapy arm, with a 55% reduction in the risk of disease progression or death (HR: 0.450; 95% CI: 0.377, 0.538; 2-sided p-value <0.00001). Median OS with EV+P was 31.5 months, compared with 16.1 months in the chemotherapy arm. This equated to a 53.2% reduction in the risk of death with EV+P vs chemotherapy (HR: 0.468; 95% CI: 0.376, 0.582; 2-sided p-value <0.00001). Consistent PFS and OS benefit was observed across all pre-specified

subgroups, including cisplatin eligibility, PD-L1 expression status, and liver metastases.[2]

EV+P was associated with a significantly higher response rate than chemotherapy (ORR 67.7% [95% CI: 63.1, 72.1] vs 44.4% [95% CI: 39.7, 49.2]), and a higher rate of complete response (29.1% vs 12.5%).[2] Responses to EV+P were substantially more durable than responses to chemotherapy: median duration was not reached (95% CI: 20.2, NE), compared with a median of 7.0 months (95% CI: 6.2, 10.2) in the chemotherapy arm.[2] A majority of the responses to EV+P were ongoing at 12 and 18 months, supporting the PFS and OS findings.[2]

In long-term follow-up of the phase 1/2 EV-103 study in cisplatin-ineligible la/mUC patients, the PFS rate with EV+P was 38.2% at 3 years and remained the same at 5 years. The estimated OS rate at 5 years was 41.5%, a survival rate that dramatically exceeds historical data in this population.[53]

EORTC QLQ-C30 and EQ-5D-5L scores over the EV-302 study period suggest that the gains in PFS and OS with EV+P were achieved without detriment to global health status/QoL, pain or functioning compared with chemotherapy.[49] Patients in the EV+P arm had a smaller decline from baseline in functioning scores (least squares mean change from baseline) across all functioning domains compared to patients in the chemotherapy arm, during the first 26 weeks.

The percentages of patients with treatment-emergent AEs (TEAEs; including grade 3-5 TEAEs) were similar between the EV+P and chemotherapy arms in EV-302, despite the longer duration of treatment with EV+P, and exposure-adjusted event rates for TEAEs were lower in the EV+P arm than in the chemotherapy arm.[2] Dose reductions due to treatment-related AEs occurred in 40.7% of patients in the EV+P group and 37.9% in the chemotherapy group, and treatment-related AEs resulting in discontinuation of any treatment occurred in 35.0% and 18.5%, respectively.[2] The study authors considered that most adverse events of special interest with EV+P were manageable with dose modifications. They noted that early recognition of

adverse reactions through proactive monitoring and management of symptoms remains a cornerstone of patient care with EV+P.[2]

The median OS seen in the chemotherapy arm in EV-302 (16.1 months) was very similar to OS in a cohort of 216 patients receiving 1L chemotherapy for locally advanced or metastatic UC at an English centre (median OS 16.2 months [IQR: 10.6–28.3 months]).[20] This supports the generalisability of the trial to NHS clinical practice and underlines the significant unmet need for a more effective 1L treatment for u/mUC than the current standard-of-care platinum-based chemotherapy, a need that is addressed by EV+P.

2.12.2 Strengths and limitations of the evidence base

The evidence base for EV+P compared with standard-of-care 1L treatment (platinum-based chemotherapy) in u/mUC is strong, being derived from a direct comparison in a high-quality randomised, controlled phase 3 trial in 886 patients (EV-302).[2] This has resulted in a grade '1, A' recommendation from ESMO that EV+P should be the new standard of care in this setting. EV+P was assessed as 4 out of a possible maximum of 5 on the ESMO Magnitude of Clinical Benefit Scale.[25] In addition, long-term follow-up data (median follow-up 62 months) are available from 45 cisplatin-ineligible patients with previously untreated u/mUC treated with EV+P in the phase 1/2 EV-103 study.[11,53]

Internal validity of the pivotal study

The EV-302 study was a multicentre, global phase 3 randomised controlled trial that randomised 886 patients. It was assessed as being at low risk of bias in all domains of the Cochrane Risk-of-Bias Tool for Randomized Trials[48] (RoB2; see Section 2.5). An open-label study design was necessary as blinding with placebo controls would have been difficult due to the four different agents administered in the trial, and could have complicated the ability to assess and attribute adverse event profiles of the different agents.[47] However, response and progression were assessed by blinded independent central review, removing the potential for bias in the PFS and ORR endpoints. For each patient, the same imaging method was used throughout the trial for consistency.

A post hoc analysis of PRO compliance rates found that in both treatment arms, completion rates were [redacted] 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 [redacted] for EV + P than for chemotherapy.[50] This analysis suggests that in the longitudinal data per visit, completion rates in the chemotherapy arm were [redacted] due to more patients having progressed. If this is the case, this could bias the PRO data in favour of chemotherapy, particularly post-progression, meaning that the HRQoL benefits of EV+P over chemotherapy may be greater than suggested by the primary PRO analysis.

Relevance to the decision problem and to patient benefits

The study is directly relevant to the decision problem as it provides direct evidence for the efficacy of EV+P versus the relevant comparator (platinum-based chemotherapy + gemcitabine) in a randomised, controlled trial (EV-302). There is a slight difference in terminology between the clinical study, which referred to locally advanced/metastatic disease, and the licensed indication, which refers to unresectable/metastatic disease.[1] However, these are the same populations, as unresectable disease was part of the inclusion criteria for the study (see Table 8).

The outcomes assessed included OS, patient-reported outcomes and adverse events, which are all highly relevant to the clinical benefits experienced by patients in practice. PFS is also relevant to patients, as being diagnosed with progression of their disease is likely to be a distressing outcome for patients even if it is not associated with an immediate change in their experience of symptoms.

Data were collected on an extensive range of patient-reported outcomes in order to capture patients' experience, including Brief Pain Inventory, a widely used cancer-specific questionnaire (EORTC-QLQ-C30), and a generic instrument from which preference-based utility scores could be derived (EQ-5D-5L). Although quality of life for caregivers was not assessed, scoping consultation responses by the British Uro-Oncology Group, ABC UK and Fight Bladder cancer all drew attention to the burden of m/uUC on patients' families and caregivers. They noted that a more effective 1L

treatment could reduce this burden, reducing some of the stress on caregivers and potentially allowing them to resume their professional lives and societal contributions.[55]

Generalisability to NHS clinical practice in England

The patient population of EV-302 is generalisable to the population of patients with u/mUC in England. The study population included patients with poor prognostic factors (e.g., liver metastases, visceral disease, and renal impairment).[2] The median age was 69 years (range 22-91) and 76.7% were male; this is similar to the largest published UK real-world cohort (Cheeseman 2020), in which the median age was 66 (range 35-83) and 72.7% were male.[20]

In EV-302, 30.5% of patients in the EV+P arm and 23.4% in the chemotherapy arm had UTUC. Although UTUC is much less common than BC at diagnosis, a recently published review by a group of UK clinical experts (Jones et al. 2024) notes that the proportion of patients with UTUC is higher in populations with advanced UC than in earlier stages, because it is more likely to be invasive at diagnosis[6] (a point also made by EAU UTUC guidelines[8]). There was a slight imbalance between treatment arms in EV-302 in the proportion of patients with UTUC (see above). However, the efficacy of EV+P was similar between tumour origin sites (see Figure 17 and Figure 18); the point estimates for HR for PFS and OS for EV+P versus chemotherapy were slightly higher for UTUC than lower tract but the confidence intervals were wider, likely due to the smaller group size. As patients in the EV+P arm were more likely to have UTUC than those in the chemotherapy arm, any effect of the imbalance on the overall trial result would be conservative in terms of EV+P efficacy. Jones et al. note the retrospective analysis of three RCTs in advanced UC by Moschini et al. 2018, which found that primary tumour location had no impact on OS or PFS in patients receiving platinum-based chemotherapy.[56] They also note that subgroup analyses from four trials in of ICI's in advanced UC have reported similar efficacy in patients with UTUC vs lower tract.[6] These observations support the argument that neither the proportion of UTUC patients in the trial, nor the slight imbalance between arms, have any bearing on the validity or generalisability of the results.

During enrolment for EV-302, avelumab was approved in various regions as maintenance therapy for patients who do not progress on platinum-based chemotherapy.[57] Avelumab maintenance was permitted as a subsequent therapy in EV-302 for eligible patients, and was reported as the first subsequent therapy for 135 patients (30.4%) in the chemotherapy arm.[2] Avelumab maintenance was recommended by NICE in 2022 and is encouraged by UK clinical experts for all patients who remain progression free after completing platinum-based chemotherapy (see Appendix P).[36] Recent UK treatment-pattern data from a variety of sources (see Section 1.3.5.1 and Appendix T) indicate that approximately 30% of patients receiving 1L therapy in England receive avelumab. Thus, the proportion who receive avelumab maintenance in clinical practice is similar to that seen in EV-302, and supports the generalisability of the trial.

Prior anti-PD-L1 immunotherapy was an exclusion criterion for EV-302. A small number of u/mUC patients in NHS practice will have received nivolumab in the adjuvant setting and would thus be outside of the EV-302 population. Clinical advisors consulted for the submission indicated that there is little data to support the use of further immunotherapy after nivolumab, and these patients may therefore not be considered eligible for EV+P. Furthermore, the NICE recommendation for adjuvant nivolumab is limited to muscle-invasive urothelial cancer that is at high risk of recurrence after radical resection in adults whose tumours express PD-L1 at a level of 1% or more and for whom adjuvant treatment with platinum-based chemotherapy is not suitable.[58] The number of such patients who would go on to be considered eligible for platinum-based chemotherapy in the u/mUC setting is likely to be small. SACT data indicate that 105 bladder cancer patients received nivolumab in the year to March 2024, but disease stage is not specified (Appendix T). In the Adelphi treatment pattern study, no 1L u/mUC patients were reported to have received prior adjuvant nivolumab.

2.12.3 Summary

EV+P addresses an important clinical need for more effective 1L treatments for u/mUC, almost doubling median PFS and OS compared with current standard of

care without detriment to patient-reported quality of life scores. This represents a ‘step-change’ in the treatment of this cancer, which has a poor prognosis under current treatment. EV+P is also innovative, offering a combination of an antibody-drug conjugate and an established immunotherapy, which have complementary mechanisms of action[1,13] that result in unprecedented efficacy in this indication.

The evidence base for EV+P versus platinum-based chemotherapy (cisplatin + gemcitabine or carboplatin + gemcitabine) is strong, being derived from a direct comparison in a high-quality RCT and with long-term follow-up data available from an earlier phase trial for a subset of patients. The outcomes assessed are directly relevant to the decision problem, and to the patient experience. The trial population and the treatments received (including the proportion of eligible patients who receive avelumab maintenance after platinum-based chemotherapy) are well generalisable to clinical practice in England and Wales.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

Details of the SLR conducted on 3 June 2024 to identify economic evidence for patients with previously untreated u/mUC are provided in Appendix G, including search terms, study eligibility criteria as well as databases searched. The review scope was broader than the scope of the current evaluation, targeting all studies conducted in the u/mUC setting which also included assessments of maintenance therapies following platinum-based chemotherapy (PBC).

The review identified 25 economic evaluations, of which 22 were cost-effectiveness / cost-utility assessments. These include seven HTA submissions; two from NICE, two from the Canadian Agency for Drugs and Technologies in Health (CADTH), two from the Scottish Medicines Consortium (SMC), and one from the Australian Pharmaceutical Benefits Advisory Committee (PBAC). A table summarising modelling approach, patient population, treatment comparison, and incremental costs and QALYs and ICER for each is given in Appendix G(b). All evaluations in this disease area applied a cohort-based approach and relied on three health states (pre-progression, progressed disease and death) to describe the disease process. Reported model structures included partitioned survival models (n=17), Markov models (n=4), and a decision tree followed by a Markov model (n=1). The interventions evaluated in the economic evaluations were all programmed death receptor-1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors. However, it is important to note that the evaluations of avelumab maintenance therapy represent a different population and at a different point in the care pathway, as patients eligible for avelumab are those who did not progress after 1L PBC. Given these differences, avelumab studies should not be directly compared with evaluations focusing on 1L treatments.

No cost-effectiveness studies were identified for EV+P, only a budget impact analysis focusing on the US is available.[59]

3.2 Economic analysis

The current economic evaluation followed the structures and main assumptions applied in the identified economic studies, taking into account the critiques received from the economic assessment group or the committees' recommendations and preferred assumptions in the two NICE technology assessments in this disease area. These are TA739 on atezolizumab for adults with untreated la/mUC whose tumours express PD-L1 at a level of 5% or more and cannot have cisplatin, and TA788 on avelumab for patients with la/mUC, following 1L PBC. The current evaluation mirrors approaches accepted in TA739 and TA788. Please note, that TA788 assessed avelumab maintenance therapy, therefore it included a selected, fitter patient population who did not progress after 1L PBC. Therefore, conclusions drawn in TA788 are not directly relevant for the entire target population of this evaluation, only for the subsection of the population receiving avelumab maintenance treatment from the timepoint that avelumab treatment started.

3.2.1 Patient population

The patient population included in the analysis matches the licensed indication for EV+P,[1] that is, it comprises first-line adult patients with unresectable or metastatic urothelial cancer (u/mUC) who are eligible for platinum-containing chemotherapy. This population also aligns with the intention-to-treat (ITT) population from the pivotal EV-302 trial. As well as matching both the licensed indication and the pivotal trial population, the ITT population is considered the most suitable for the base case for several additional reasons. The efficacy and safety of EV+P in EV-302 were not dependent on cisplatin eligibility (see Section 2.7), and the EMA (EPAR p.110) notes that "from a clinical point of view, platinum-eligibility does not seem to be an effect modifier in this setting". Given EV+P's efficacy in this mixed-cisplatin-eligibility population, ESMO and EAU treatment guidelines incorporating EV+P as the new standard of care now have platinum eligibility rather than cisplatin eligibility as the deciding factor in treatment choice (see Section 1.3.5.3). This was confirmed by UK clinicians in validation discussions (Appendix P, Section P3.1.2). Further, the costs of cisplatin and carboplatin-based chemotherapy are similar, and the duration of

treatment (6 cycles) is short, so treatment costs in the two subgroups are similar. Nonetheless, subgroup analyses are presented based on data from the cisplatin-eligible and cisplatin-ineligible subgroups in the EV-302 trial in addition to the trial ITT population to align with the NICE scope. However, increased uncertainty was noted in the subgroup-based analyses.

Patient characteristics relevant for the economic model were based on EV-302 trial data (see **Table 20**). Age and gender were used to adjust for general population background mortality and for age-adjusted utility values (if selected), while weight and body surface area (BSA) were used to inform drug dosing and costs.

Table 20 Patient characteristics relevant for the economic model

Patient characteristic	ITT	Cisplatin-eligible	Cisplatin-ineligible
Age at baseline (years, mean)	67.9	64.9	71.4
Gender (male %)	77%	79%	74%
Weight (kg)	75.89	78.34	73.01
Body surface area (m^2)	1.88	1.92	1.83

Abbreviations: kg, kilogram; m^2, meter squared

3.2.2 Model structure

The current economic model follows the same structure and assumptions as applied in previous NICE TAs in the same indication: i.e. it uses a partitioned survival model (PSM) structure. A PSM is composed of three mutually exclusive health states: alive and free from disease progression (pre-progression), alive post disease progression (post-progression), and death. A schematic of the model structure is presented in Figure 4. Patients in the pre-progression health state received either EV+P or a comparator treatment 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 treatments before moving to the death health state.

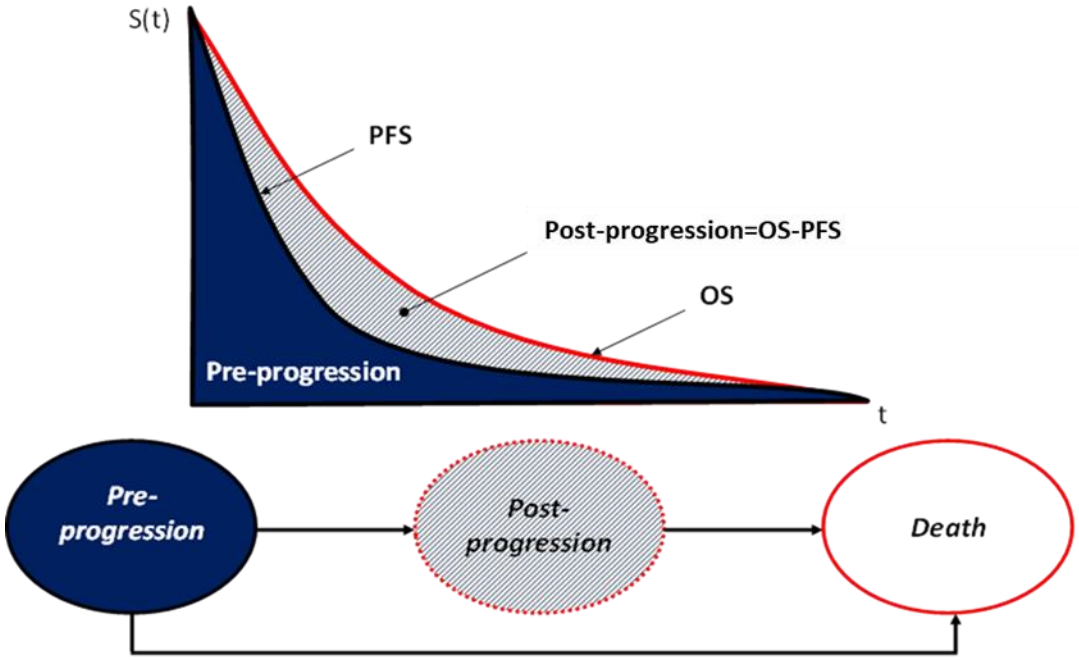


Figure 20 Partitioned survival model structure

Abbreviations: OS , overall survival; PFS, progression-free survival; S(t), survival as a function of time; t, time.

As shown in **Table 21**, the model adopted a lifetime time horizon (maximum of 30 years). Weekly cycles were used to provide the flexibility of different administration cycles for the treatments included. A discount rate of 3.5% was applied for both costs and health outcomes following the first year of the model, consistent with the latest version of the NICE health technology evaluations manual.[60]

Table 21 Features of the economic analysis

	Previous evaluations		Current evaluation	
Factor	**TA739**	**TA788**	**Chosen values**	**Justification**
Population	Adults with untreated la/mUC whose tumours express PD-L1 at a level of 5% or more and cannot have cisplatin	Patients with la/mUC, following 1L PBC	Adults with untreated u/mUC who are eligible for PBC	To match indication and pivotal trial
Time horizon	Lifetime	Lifetime	Lifetime	To include all health and cost consequences of the intervention
Treatment waning effect?	Waning applied between 5-7 years	Not considered in company submission	Not considered	There is no stopping rule for EV and a proportion of patients are expected to remain on treatment in the long-run; due to use of independent models, trends in hazards should incorporate any treatment effect waning
Source of utilities	Pivotal trial: IMvigor130	Pivotal trial: JAVELIN Bladder 100 trial	Pivotal trial: EV-302	EV-302 is only trial with data to capture treatment-specific impact on QoL; previous TA utilities tested in scenario analyses
Source of costs	BNF, eMIT 2019, NHS reference costs 2018/19, PSSRU 2019	BNF, eMIT 2019, NHS reference costs 2018/19, PSSRU 2019	BNF, eMIT 2024, NHS reference costs 2021/22, PSSRU 2023	Use of most up-to-date information

Abbreviations: 1L, first-line; BNF, British National Formulary; eMIT, pharmaceutical electronic market information tool; la/mUC, locally advanced or metastatic urothelial cancer; PBC, platinum based chemotherapy; PSSRU, Personal Social Services Research Unit

3.2.3 Intervention technology and comparators

The economic evaluation focuses on the treatments included in the EV-302 trial, because platinum-based chemotherapy (PBC) is the current mainstay of treatment in the submission population, with other options rarely used in clinical practice (see Sections 1.1 and 1.3.5.1).

The intervention is a combination treatment comprising of EV and pembrolizumab using the dosing schedule for EV as in the EV-302 trial:

- EV: 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity, and
- Pembrolizumab: 400 mg IV on day 1 of each 6-week cycle, as above to a maximum of 35 cycles.

The comparator for cisplatin-eligible patients is a combination of cisplatin and gemcitabine for a maximum of 6 cycles:

- Gemcitabine: IV 1000 mg/m2 body-surface area) on days 1 and 8 of a 3-week cycle, and
- Cisplatin: IV 70 mg/m2 on day 1.

The comparator for cisplatin-ineligible patients is a combination of carboplatin and gemcitabine for a maximum of 6 cycles:

- Gemcitabine: IV 1000 mg/m2 body-surface area) on days 1 and 8 of a 3-week cycle, and
- Carboplatin: IV target area under the concentration versus time curve (AUC) equivalent to 4.5-5 mg/ml/min (Calvert formula) on day 1

Following PBC, avelumab maintenance therapy (800mg on day 1 of a 2-week cycle) was also allowed in the EV-302 trial protocol for eligible patients based on the physicians' discretion. The protocol aligns with current treatment recommendations in the UK, therefore the cost of avelumab maintenance was also included in the comparator treatment arms for the proportion of patients as specified in **Table 22**.

Table 22 Proportion of patients receiving avelumab maintenance therapy in EV-302 trial

Population	ITT	Cisplatin-eligible	Cisplatin-ineligible
Received avelumab maintenance (%)	30.4%	[redacted]	[redacted]

In the EV-302 trial, 54.3% of patients were cisplatin-eligible (see Table 10 in section 2.6.1). This proportion was used to calculate the weighted average cost of the comparator treatment arm for the ITT analysis.

3.3 Clinical parameters and variables

The primary clinical parameters informing the evaluation included PFS, OS, time on treatment (ToT), and adverse events (AEs). As discussed in Section 2.7 and Appendix E, trial results were consistent across the sub-groups and similar to the ITT population. However, since the comparator treatments differ, clinical parameters are presented separately for the ITT, the cisplatin-eligible and the cisplatin-ineligible subgroup analyses to allow for a separate assessment of EV+P in these subpopulations also.

3.3.1 Methodology for modelling time to event data

The EV-302 data at the primary analysis (median follow-up 17.2 months) was immature for OS and PFS, particularly for the EV+P. Due to the efficacy of the combination, 223/442 (50.5%) of patients on EV+P had progressed or died and 133/442 (30.1%) had died.[2] The exception is ToT for the PBC arm, for which data is complete. Therefore, time-to-event outcomes were extrapolated over the time horizon of the cost-effectiveness analysis. The approach to extrapolations followed the guidance of NICE DSU technical support document (TSD) 14,[61] TSD 21[62] and Palmer et al.'s guide to selecting flexible survival models for the evaluation of cancer immunotherapies,[63] given that EV+P combination includes an immunotherapy (pembrolizumab).

As such, the approach to model time to event data included:

1. Review of external data.
2. Elicitation of expert beliefs about survival in the long-term.
3. Assessment of whether the proportional hazards assumption is likely to hold.
4. Consideration of turning points in the hazards.
5. Fitting of the standard parametric distributions.
6. Consideration of the impact of cisplatin eligibility on survival outcomes
7. Selection of standard parametric distributions.
8. Exploration of spline-based models.

Palmer et al. recommends considering whether a proportion of patients are cured. Given the immaturity of the survival data with this data cut, cure models will not be explored at this stage.

3.3.1.1 Review of external data

The literature and previous NICE appraisals were reviewed for relevant evidence on long-term survival with PBC.

IMvigor 30 trial

Grande et al. reports the final data cut of the IMvigor 30 trial, specifically the comparison between atezolizumab + PBC versus placebo + PBC.[64] This trial enrolled patients with untreated locally advanced or metastatic urothelial cancer and who had an ECOG performance status 0-2. In the placebo + PBC arm, 1-year survival was 55% (95% CI 50%-60%), 2-year survival was 32% (95% CI 28%-37%), and 3-year survival was 22% (95% CI 17-26%). In the atezolizumab + PBC arm, 1-year survival was 60% (95% CI 60%-65%), 2-year survival was 38% (95% CI 33%-42%), and 3-year survival was 26% (95% CI 22-30%).[64] Five year survival is not reported. Reading from the OS curve, it seems to remain relatively constant from 3 years, although numbers at risk at 5 years are 32 patients for the atezolizumab + PBC arm and 22 patients in the placebo + PBC arm.

It is difficult to make direct comparisons to EV-302. However, a comparison can be made between the 3-year (and beyond) and 2-year survival rates to infer the shape of the hazard rate. The 2-year survival with atezolizumab + PBC arm was 38%, then reduced to 26% at 3 years and remained relatively constant. Given that the 2-year survival with EV+P is over 60%, it is unlikely that 5-year survival rate for EV+P will be below 30%, and indeed it is likely to be higher.

The final OS analysis of the IMvigor130 trial for the arms atezolizumab alone (group B, N=360 patients) and placebo + PBC (group C, N=359 patients)[65] supports this inference. The overall median follow-up was 13·4 months (IQR 6·2–30·8); 14·0 months (3·6–35·9) in group B and 12·0 months (6·2–27·9) in group C. For the atezolizumab alone group, the 1-year OS rate was 57.9%, 2-year OS rate was

34.5%, and 3-year OS rate was 27.0%. Reading from the OS curve, the OS rate after 3-years remains relatively constant and between 20-25%. As noted above, given that the 2-year survival with EV+P is over 60%, it is unlikely that 5-year survival rate for EV+P will be below 30%, and indeed it is likely to be higher.

TA788 on avelumab

Avelumab is recommended as an option for maintenance treatment of locally advanced or metastatic urothelial cancer that has not progressed after PBC in adults (i.e., 4-6 cycles of PBC, or 12-24 weeks from start of PBC treatment)[36] – therefore avelumab is a subsequent therapy after PBC, in a selected patient population who has not progressed after PBC. The pivotal clinical trial was JAVELIN Bladder 100.[66,67] Two-year survival rates for avelumab were 50% versus 38% for BSC and 3-year survival for avelumab is 36% versus 30% for BSC.[66] TA788 (committee papers) reports the results of panel of 8 UK oncologists on their expected survival at 5- and 10 years, at 20-30% and 10-15% respectively.[36]

Despite the misalignment between TA788 and the EV+P patient population, this evidence is relevant to infer the extent to which survival rates are expected to reduce in the long-term, given observed survival rates in the trial. Specifically, UK oncologists expected 20-30% 5-year survival and 10-15% 10-year survival, given 2-year observed rate of 50%. Given that this is a selected patient population who did not progress following PBC, and noting that 2-year survival with EV+P is over 60%, this is further evidence that 5-year survival rate is likely to be over 30% and 10-year survival rate is likely to be over 15%.

EV-103 trial data

The EV-103 trial design is described in detail in Section 2.3.2. It included two cohorts (a dose escalation cohort which was then extended into cohort A, and cohort K) receiving 1L treatment with EV+P in cisplatin-ineligible patients with u/mUC. The population in this study differs from the licensed indication in that patients had to be cisplatin-ineligible (but could still be eligible for carboplatin). Compared with EV-302, a greater proportion of patients were aged ≥75 years (35.6% vs 23.7%), fewer had ECOG PS 0 (33.3% vs 49.4%), more had EGOG PS 2 (17.8% vs 2.9%), and more

had visceral metastases (84.4% vs 71.8%). Information from the trial was used to validate extrapolations for time to event data for the cisplatin-ineligible subgroup and should be considered a lower limit of plausible survival data for the EV-302 population. The data was also used to inform the extent to which survival rates are expected to reduce in the long-term.

After a median follow-up of 18 months, 25% of patients remained on treatment in Cohort K,[40] while after a median follow-up of 47 months (nearly 4 years) in dose escalation + Cohort A, no patients remained on treatment.[41] In fact, as shown in Figure 21, all patients discontinued treatment by 3 years. Patients received a median of 9 treatment cycles (7 months). PFS at 2-years was 44%, while OS at 2-years was 58% based on the combined results of all cohorts receiving EV+P. As shown in Figure 21 and Figure 22, long-term follow-up results indicate a decline in hazard rates for both PFS and OS with a flattening of the survival curves.

The latest update on the dose escalation cohort and cohort A includes a median follow-up of 62.1 months.[53] At 5 years the PFS rate was estimated to be 38.2% and the OS rate was estimated to be 41.5%. EV-103 results suggest that patients showing durable responses beyond 2-years are likely to maintain their health status in the longer term too.

Figure 21 Time on treatment in EV-103 (EV+P: Dose escalation cohort / Cohort A)

Abbreviations: Dose Esc, dose escalation cohort

Figure 22 Progression-free survival in EV-103 (all EV+P combined: Dose-escalation cohort / Cohort A / Cohort K) – [redacted] data cut

Abbreviations: Dose Esc, dose escalation cohort

Figure 23 Overall survival in EV-103 (all EV+P combined: Dose-escalation cohort / Cohort A / Cohort K) – [redacted] data cut

Abbreviations: Dose Esc, dose escalation cohort

3.3.1.2 Elicitation of expert estimates about survival in the long-term

Clinical experts' estimates about survival were also elicited. Details of the interviews conducted are provided in Appendix P. An international advisory board included clinical experts from Italy, Sweden, US, and Australia. A separate series of interviews was also conducted involving three clinical experts from the UK to gain local perspective and to understand whether treatment practices in the UK differ from those dictated by the protocol of EV-302. All experts were asked to provide their estimates for the proportion of patients they expect to be alive and progression free and the proportion of patients they expect to be alive at 2, 5 and 10 years from the patients enrolled in EV-302, i.e. all patients eligible for PBC. The advisory board and interviews were conducted before publication of the 5-year results for the EV-103 trial, so these did not inform the experts' predictions. Their responses are summarised in Table 23 for PFS and in Table 24 for OS. Based on the differences in response rates, experts indicated a higher probability of PFS and OS compared to PBC at all timepoints queried.

Table 23 Clinical experts' estimates of progression-free survival in the long-term

Alive and progression-free with PBC			
Time-point	**2 years**	**5 years**	**10 years**
Clinical expert 1 (UK)	10%	5%	5%
Clinical expert 2 (UK)	10%	5%	0-2%
Clinical expert 3 (UK)	6-7%	6-7%	6-7%
Clinical expert 4 (US)	7%	5%	3%
Clinical expert 5 (Italy)	10%	4-5%	0-1%
Clinical expert 6 (Sweden)	10%	3-5%	3-5%
Clinical expert 7 (Australia)	10%	5%	2.5%
Average (range) of expert estimates	9.5% (6-10%)	5% (3-7%)	3.5% (2-7%)
Alive and progression-free with EV+P			
Time-point	2 years	5 years	10 years
Clinical expert 1 (UK)	40%	30%	25%
Clinical expert 2 (UK)	40%	20%	10%
Clinical expert 3 (UK)	40%	30%	20%
Clinical expert 4 (US)	36%	20-22%	12%
Clinical expert 5 (Italy)	40%	15%	7-8%
Clinical expert 6 (Sweden)	40-50%	15-20%	5-10%
Clinical expert 7 (Australia)	35%	30%	25%
Average (range) of expert estimates	39% (36-50%)	25% (15-30%)	18% (7-25%)

Abbreviations: EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy

Table 24 Clinical experts' estimates of overall survival in the long-term

Alive after PBC			
Time-point	**2 years**	**5 years**	**10 years**
Clinical expert 1 (UK)	35%	5%	5%
Clinical expert 2 (UK)	40-45%	15-20%	5%
Clinical expert 3 (UK)	35%	5-15%	2-7%
Clinical expert 4 (US)	35%	12%	6%
Clinical expert 5 (Italy)	40%	5%	0-1%
Clinical expert 6 (Sweden)	35%	10-15%	5%
Clinical expert 7 (Australia)	30%	20%	10%
Average (range) of expert estimates	35% (30-45%)	11% (5-20%)	6% (0-10%)
Alive after EV+P			
Time-point	2 years	5 years	10 years
Clinical expert 1 (UK)	50%	25-30%	20-35%
Clinical expert 2 (UK)	60%	35%	15%
Clinical expert 3 (UK)	60%	30-40%	20-30%
Clinical expert 4 (US)	60%	28%	12%
Clinical expert 5 (Italy)	60%	20%	5-7%
Clinical expert 6 (Sweden)	60%	30%	20%
Clinical expert 7 (Australia)	55%	45%	15%
Average (range) of expert estimates	58% (50-60%)	32% (20-45%)	16% (5-35%)

Abbreviations: EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy

Clinicians anticipated the patients receiving EV+P would have better survival outcomes compared to those receiving avelumab maintenance after PBC. UK clinicians also mentioned that patients who have not progressed at five-years are expected to enter durable remission.

They also believed that longer-term follow-up data from EV-103 (which included platinum eligible, but cisplatin-ineligible patients) would be relevant for the EV-302 population too, since platinum eligibility seems to be irrelevant for EV+P outcomes. They noted however, that patients who are cisplatin eligible will generally be healthier than those who are cisplatin ineligible. Cisplatin-ineligible patients tend to

be ineligible due to comorbidities (e.g., cardiovascular mobility, age etc.), which impacts their survival outcomes.

The clinicians also recommended modelling time on treatment with EV and P separately, as time on treatment may vary for different reasons: some patients may stop EV early due to toxicity, while others may continue EV treatment beyond the two-year pembrolizumab stopping rule.

3.3.1.3 Assessment of proportional hazards

The proportional hazards (PH) assumption was evaluated in EV-302 for both the ITT and subgroup populations consistent with guidance from the NICE DSU TSD 14.[61] Appendix M contains the following plots and tests to assess the validity of proportionality assumptions and explore which extrapolation approach may be most suitable:

- Scaled Schoenfeld residuals plot (difference between the observed covariate for treatment at that time and its expected value) over time, where non-random residuals suggest violation in the PH assumption.[68,69]
- The Grambsch and Therneau test, evaluating non-zero slope in regression of the residuals as function of time, where $p<0.05$ suggests data are unlikely to support a linear PH assumption.[70]
- Log-cumulative hazard plot versus log(time) for EV+P and PBC, where non-parallel lines suggest violation in the PH assumption (based on subjective assessment), and therefore using a Cox PH model (e.g., exponential, Weibull, Gompertz, gamma) or modelling with a constant HR may not be appropriate.
- Plots of smoothed empirical hazard versus time and log(time) were generated to assess shape of hazard over time for EV+P and PBC.
- Quantile-quantile (Q-Q) plot of times of survival percentiles for EV+P and PBC where accelerated failure time (AFT) models (e.g., Weibull AFT, log-normal, log-logistic, or generalised gamma) are supported by survival percentiles that lie in a straight line that pass through (0,0). If the intercept of

the regression line on the percentiles is clearly non-null, then modelling using an AFT model may be inappropriate.

As shown in Table 25, the results of all of the above tests and assessments indicate that the PH assumption does not hold for PFS. For OS, the PH assumption may be accepted for the ITT and cisplatin-eligible subgroup, however, it is likely to be violated in the cisplatin-ineligible subgroup.

Table 25 Assessment of the proportional hazards assumption in EV-302

Progression-free survival				
Population/ subgroup	**Grambsch-Therneau test p-value**	**Schoenfeld residuals visual inspection**	**Log cumulative hazards visual inspection**	**QQ plot visual inspection**
ITT	<0.001	Treatment line falls outside confidence bounds	Overlap at early time points, then curves increasingly separate	Last survival percentile deviates from linear trajectory
Cisplatin-eligible	0.002	Treatment line falls outside confidence bounds	Curves cross and change relative locations	Last survival percentile deviates from linear trajectory
Cisplatin-ineligible	0.018	Treatment line falls within confidence bounds	Overlap at early time points, then curves increasingly separate	Last survival percentile deviates from linear trajectory
Overall survival				
Population/ subgroup	Grambsch-Therneau test p-value	Schoenfeld residuals visual inspection	Log cumulative hazards visual inspection	QQ plot visual inspection
ITT	0.963	Treatment line falls within confidence bounds	Relatively parallel, some overlap at early time points	Points generally follow linear trajectory
Cisplatin-eligible	0.358	Treatment line falls within confidence bounds	Relatively parallel	Points generally follow linear trajectory
Cisplatin-ineligible	0.193	Treatment line falls within confidence bounds	Overlap at early time points and then increasingly separate	Points generally follow linear trajectory

Abbreviations: ITT, intention to treat; QQ, quantile-quantile.

3.3.1.4 Consider turning points and data maturity

Palmer et al recommend considering turning points in the observed hazard rates and potential for future turning points. Figure 24 to Figure 27 show the observed hazard rates for PFS and OS in the EV+P and PBC arm of EV-302, while the same graphs for the cisplatin-eligible and cisplatin-ineligible subgroups are provided in Appendix M.

Figure 24 Progression-free survival hazards, EV+P ITT population
Abbreviations: AIC, Akaike's information criterion.

Figure 25 Progression-free survival hazards, PBC ITT population
Abbreviations: AIC, Akaike's information criterion.

Figure 26 Overall survival hazards, EV+P ITT population
Abbreviations: AIC, Akaike's information criterion.

Figure 27 Overall survival hazards, PBC ITT population
Abbreviations: AIC, Akaike's information criterion.

With the exception of OS in the EV+P arm of the EV-302 trial, all hazard graphs show a downturned U shape. Hazards tend to increase until 6-12 months for PFS and until 12-18 months for OS, after which hazards decrease. This trend in hazards indicates that survival functions with non-monotonous hazards capable of capturing increasing then decreasing hazards should be preferred. This means that the

lognormal, log-logistic, generalised gamma, and, depending on the parameters, the Weibull functions are most suited to represent survival in this disease area.

With the current data cut (primary analysis), OS in the EV+P arm does not display the same trend in hazards observed for all other curves. This is likely due to the insufficient length of follow-up and the overall reduced hazard, i.e. mortality, for patients in the EV+P arm. As shown in Figure 28, survival hazards for EV+P patients in Cohort A in the EV-103 trial display the same pattern as was observed for all other survival curves in EV-302, i.e. initially increasing hazards, then after 12-18 months decreasing hazards. Therefore, the expectation is that OS hazards for EV+P will also follow the expected pattern in the long term and the survival data from EV-302 should be extrapolated using the same group of functions as described above for the other survival curves.

Figure 28 Overall survival in EV-103 (EV+P: Dose-escalation cohort / Cohort A), November 2023 datacut

Abbreviations: Dose Esc, dose escalation cohort. Data from Gupta 2023.[41]

3.3.1.5 Fitting of standard parametric distributions

At a first stage, the extrapolations used the standard parametric distributions recommended by the NICE DSU technical support document (TSD) 14:[61]

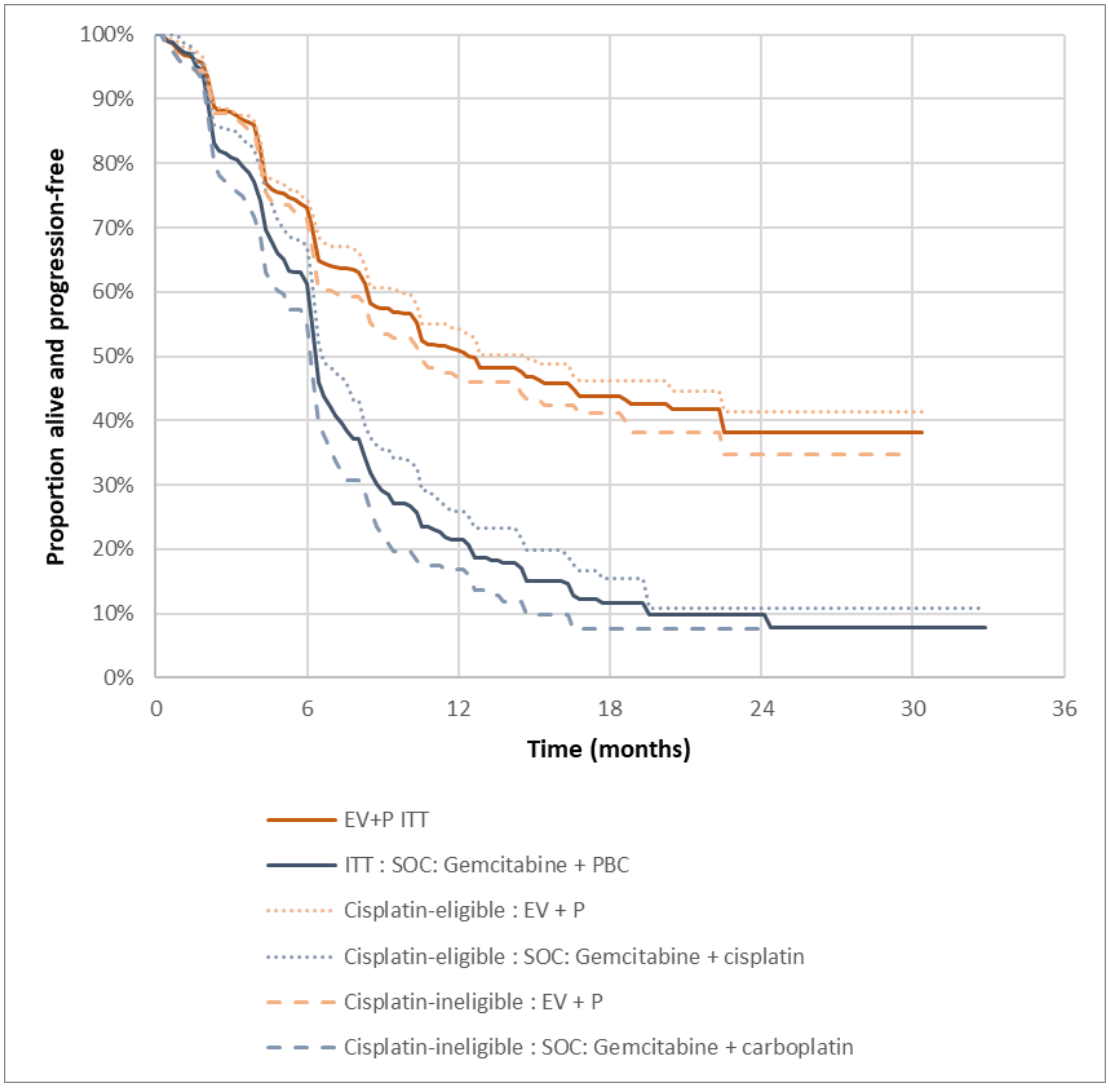
exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma. Survival models are described in more detail in Appendix M.

The analysis of EV-302 time to event data explored the suitability of different survival modelling approaches as outlined in NICE TSD 14 (see Appendix M), with the appropriateness of each approach dependent on assessment of the PH assumption (see section 3.3.1.3 above).[61,62] Since the PH assumption was clearly violated for PFS and there were signs of it being violated for OS in the cisplatin-ineligible subgroup, in the base case independent treatment effects were assumed: Kaplan-Meier (KM) curves for each treatment arm were fitted independently to derive survival parameters (i.e., shape/ancillary and scale/location parameters) for each treatment arm for each standard parametric distribution.

Alternative approaches which applied a relative treatment effect to the scale parameter, and an approach where the relative treatment effect was applied as a constant HR were tested in scenario analyses. However, these alternative methods are likely to be inappropriate given the violation of the PH assumption for many of the survival curves in the model.

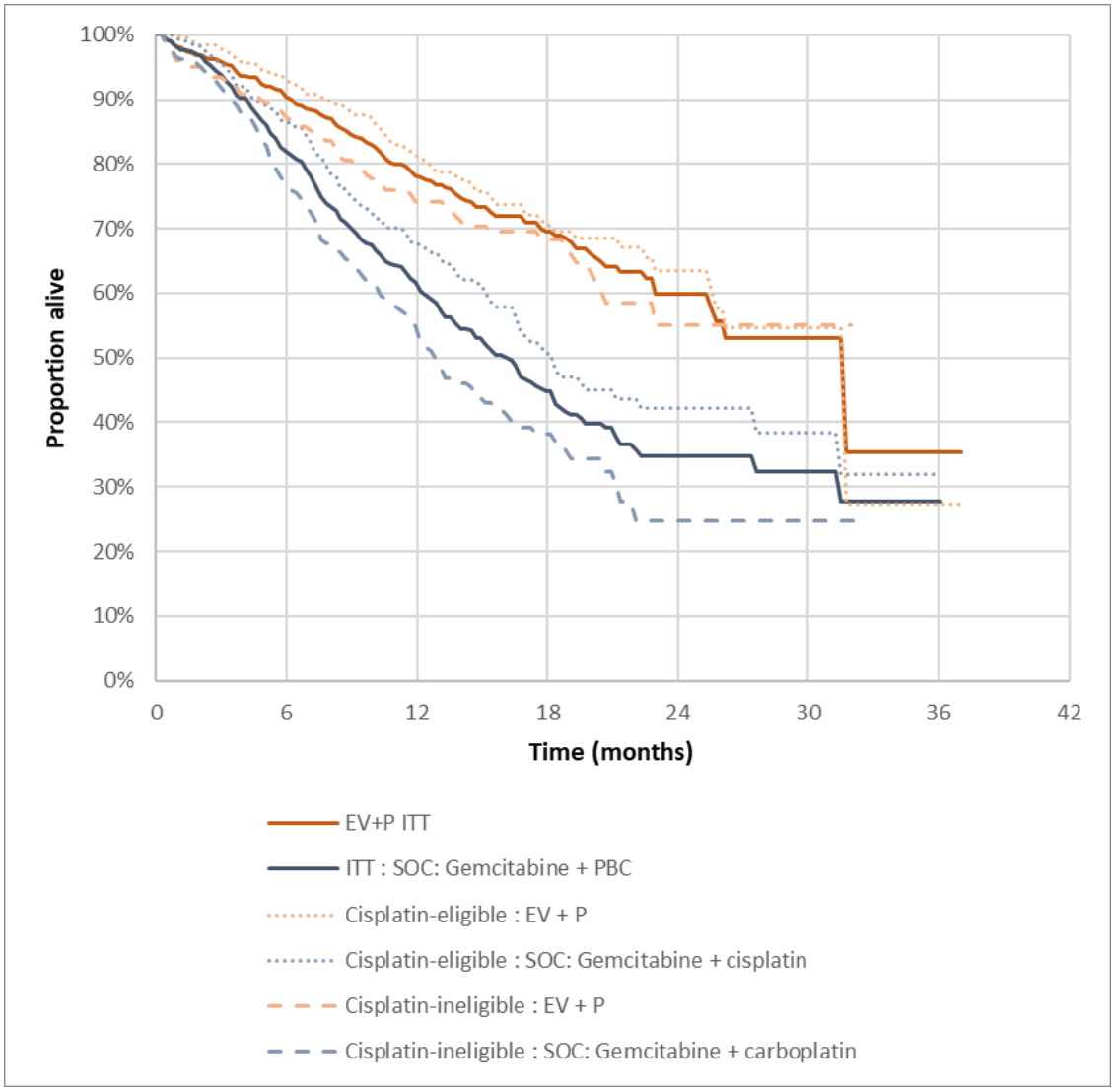
3.3.1.6 Consideration of impact of cisplatin-eligibility on survival outcomes

Figure 29 and Figure 30 show PFS and OS outcomes in the EV-302 trial for the ITT population versus the subgroups defined according to cisplatin eligibility. Results were in line with expectations of the clinicians (see section 3.3.1.2 above), such that both PFS and OS for cisplatin-ineligible patients were slightly lower than that for cisplatin-eligible patients. Although the efficacy of EV+P would not depend on cis-eligibility, patients who are cisplatin-ineligible tend to be older and suffer from more co-morbidities compared to cis-eligible patients. Therefore, in the selection of extrapolations for survival curves, this relationship between cisplatin-eligible and cisplatin-ineligible expected survival was also taken into account, i.e. cisplatin-eligible curves should predict slightly higher survival proportions at every timepoint compared to cisplatin-ineligible curves.



Abbreviations: EV, enfortumab vedotin; ITT, intention to treat; P, pembrolizumab; PBC, platinum-based chemotherapy; SOC, standard of care.

Figure 29 PFS in the ITT population and subgroups by cisplatin eligibility



Abbreviations: EV, enfortumab vedotin; ITT, intention to treat; P, pembrolizumab; PBC, platinum-based chemotherapy; SOC, standard of care.

Figure 30 OS in the ITT population and subgroups by cisplatin eligibility

3.3.1.7 Selection of standard parametric distributions

Model selection followed guidance outlined in NICE TSD 14[61] and 21.[62] Parametric models were ranked based on model fit statistics (i.e., based on lowest Akaike's information criterion [AIC] and Bayesian information criterion [BIC]) and visual inspection of the extrapolated curves to ensure they predict clinically plausible long-term estimates (e.g., no plateaus and long tails with indefinite survival, unless there is a clinical justification for tails such as an implied cure). In addition, the shape of the

observed hazards over time in the trial (see section 3.3.1.4) was used to help guide which type of survival distribution is most appropriate (i.e., those predicting initially increasing then decreasing hazards in the long-term). The population subgroups were also compared, and the base case survival curve for cisplatin-ineligible patients was required to predict slightly lower survival proportions than the curve for cisplatin-eligible patients to reflect the slight differences between patient characteristics determining cisplatin eligibility between the subgroups.

Furthermore, the plausibility of PFS extrapolations was considered using OS estimates to ensure that PFS was restricted by OS (i.e., PFS ≤OS). Similarly, the extrapolated OS estimates were checked for plausibility relative to the age and sex-adjusted mortality rates for the general population and were capped based on the UK-specific general mortality rates sourced from the Office of National Statistics (2018-2020).[71]

3.3.1.8 Exploration of spline-based models

The standard parametric distributions for OS were in line with long-term predictions by the clinical experts. However, standard parametric distributions for PFS underestimated long-term predictions by the clinical experts (see sections 3.3.1.2 and 3.3.3), therefore spline fits (i.e. piecewise polynomial fits) were also explored for PFS and OS curves.[62,72-74] Multiple methods were explored using up to three knots, which are presented in detail (including comparison of the predicted hazards from the spline models with the observed smoothed hazards in the trial and long-term predictions) in Appendix N. The knots were equidistantly distributed on the scale of the log event survival time, i.e. one internal knot would be at the median of log time, two internal knots would be at the 33% and 66% quantiles of log time, and three knots would be at the 25%, 50% and 75% quantiles of log time. The piecewise polynomials were fit to either the survival proportions, the survival hazards or the survival odds at different time periods defined by the knots.

3.3.2 Overall survival

3.3.2.1 ITT population

Extrapolations of standard parametric fits are shown in Figure 31 and Figure 32, the comparison of observed hazards to implied hazards from the fits was presented in section 3.3.1.4, while statistical indices of fits to the data and comparisons against external data sources and clinical opinion are presented in Table 26 and Table 27 for EV+P and PBC, respectively.

Abbreviations: AIC, Akaike's information criterion.

Figure 31 Overall survival extrapolations, EV+P ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 32 Overall survival extrapolations, PBC ITT population

Treatment with EV+P resulted in a significant reduction in mortality compared to PBC in the trial, therefore EV+P OS data is immature. Results of the PH testing for OS (see section 3.3.1.3 and Appendix M) suggested the proportional hazards assumption may hold. However, given the different mechanism of actions of EV+P and PBC and the 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 PBC in the base case.

All extrapolations have similar statistical fits to the observed data, however, they predict very different survival proportions at 4-years and beyond. Therefore, statistical fit alone is not sufficient for curve selection. The selection of the base case curves relied on expected trends in hazards (increasing then decreasing) and comparison of the predictions to clinicians' expectations and longer-term observations from EV-103 and previous NICE appraisals in this disease area – the model selection process is outlined above in section 3.3.1. As such:

- For the PBC arm, only the log-logistic, lognormal and generalized gamma curves matched the required trends in hazards, while these and the

exponential curve also predicted a higher than 0% survival at 10-years as predicted by the clinicians for the PBC arm.

- For the EV+P arm, the log-logistic curve provided the closest estimate to the clinicians' expectations, while the exponential and lognormal curves provide a slightly more pessimistic and optimistic estimates, respectively, while still falling within the range of predictions from the clinicians. Given the estimated OS in EV-103 at 5-years was 41.5% and the external evidence on how the OS rates are likely to change over time (see section 3.3.1.1), all extrapolations for EV+P are likely to be very conservative choices, i.e. they are likely to underestimate OS for EV+P.
- Nonetheless, the log-logistic curves were selected for both arms in the base case, with lognormal and exponential tested in scenario analyses.

Table 26 Survival model selection for OS, EV+P ITT population

Model	**AIC**	**BIC**	**Time point**		
			2 years	**5 years**	**10 years**
EV-302 EV+P KM			60%	--	--
EV-103 Cohort K, EV+P (cisplatin-ineligible)			53.5%	--	--
EV-103 Cohort Dose esc/A, EV+P (cisplatin-ineligible)			56.4%	41.5%	
TA788, avelumab maintenance, 8 UK oncologists			--	20-30%	10-15%
Astellas clinical validation, EV+P, 7 clinicians (mean, range)			58% (50-60%)	32% (20-45%)	16% (5-35%)
Exponential	***1300.89***	***1304.98***	[redacted]	[redacted]	[redacted]
Weibull	1299.77	1307.96	[redacted]	[redacted]	[redacted]
Gompertz	1300.43	1308.62	[redacted]	[redacted]	[redacted]
Gamma	1299.85	1308.03	[redacted]	[redacted]	[redacted]
Log-normal	***1307.22***	***1315.41***	[redacted]	[redacted]	[redacted]
Log-logistic	**1300.67**	**1308.85**	[redacted]	[redacted]	[redacted]
Generalised gamma	1301.76	1314.03	[redacted]	[redacted]	[redacted]

Notes: TA788 included a selected patient population at a subsequent point of the care pathway (those not-progressing after PBC), and OS at 2-years was reported to be 49.8%.[66] Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

Table 27 Survival model selection for OS, PBC ITT population

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 PBC KM			35%	--	--
TA788, BSC, 8 UK oncologist			--	5-15%	2-7%
Astellas clinical validation, PBC, 7 clinicians (mean, range)			35% (30-45%)	11% (5-20%)	6% (0-10%)
Exponential	***1892.27***	***1896.36***	[redacted]	[redacted]	[redacted]
Weibull	1879.36	1887.56	[redacted]	[redacted]	[redacted]
Gompertz	1889.96	1898.16	[redacted]	[redacted]	[redacted]
Gamma	1876.97	1885.16	[redacted]	[redacted]	[redacted]
Log-normal	***1881.00***	***1889.19***	[redacted]	[redacted]	[redacted]
Log-logistic	**1872.80**	**1880.99**	[redacted]	[redacted]	[redacted]
Generalised gamma	1876.76	1889.05	[redacted]	[redacted]	[redacted]

Notes: TA788 included a selected patient population (those not-progressing after PBC). Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BSC, best supportive care; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

3.3.2.2 Cisplatin-eligible population

The same extrapolation-selection process was followed for the cisplatin-eligible subgroup. All supporting documentation of tests carried out, as well as comparison graphs are provided in Appendix M. In this subgroup, the Weibull, Gompertz and gamma curves could be ruled out as valid options due to trends in hazards not matching observations in the EV-302 trial and, consequently, long-term extrapolations not aligning with clinical expectations. Lognormal curves had the best fit statistically. For PBC therefore the lognormal curve was selected for the base case, with loglogistic, and generalised gamma tested in scenario analyses.

However, for the EV+P arm, due to the shape of the KM curve with a steep drop at the end of the curve due to a few events happening at time points and very small patient numbers, none of the extrapolations matched the requirement that the cisplatin-eligible subgroup should have a slightly better survival outcomes compared to the average patient. This difference in survival outcomes was seen consistently in

the EV-302 data (see section 3.3.1.6), in the extrapolations for other survival curves (for the PBC arm as well as for PFS for EV+P), and aligns with expectations given that cisplatin-eligible patients are typically fitter than cisplatin-ineligible patients.

Therefore, in the base case, rather than using the subgroup-specific extrapolations for EV+P OS, the base case ITT curve was applied instead. This is a conservative assumption, as cisplatin-eligible patients are expected to have a better prognosis than the average patient. The best fitting subgroup-specific curve (lognormal) was included as part of the scenario analyses. Since subgroup analyses are always more uncertain than those including all patients due to the reductions in sample size, the scenario analysis also tested the impact of using the ITT curves for all time-to-event data in the subgroups, while still applying the costs of the comparator relevant for the specific-subgroup (i.e. gemcitabine + cisplatin for the cisplatin-eligible subgroup).

Table 28 Survival model selection for OS, EV+P cisplatin-eligible population

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 EV+P KM			63%	--	--
TA788, avelumab maintenance[a], 8 UK oncologist			--	20-30%	10-15%
Astellas clinical validation, EV+P[a], 7 clinicians (mean, range)			58% (50-60%)	32% (20-45%)	16% (5-35%)
Exponential	690.80	694.30	[redacted]	[redacted]	[redacted]
Weibull	683.71	690.71	[redacted]	[redacted]	[redacted]
Gompertz	687.52	694.51	[redacted]	[redacted]	[redacted]
Gamma	683.18	690.17	[redacted]	[redacted]	[redacted]
Log-normal	***682.95***	***689.95***	[redacted]	[redacted]	[redacted]
Log-logistic	683.12	690.11	[redacted]	[redacted]	[redacted]
Generalised gamma	684.56	695.05	[redacted]	[redacted]	[redacted]
ITT population base case: log-logistic	N/A	N/A	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the lower limit for the cisplatin-eligible population
Notes: TA788 included a selected patient population (those not-progressing after PBC), and OS at 2-years was reported to be 49.8%.[66] Base case selection is in bold, options tested in scenario analyses are in bold italics.

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

Table 29 Survival model selection for OS, PBC cisplatin-eligible

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 gemcitabine + cisplatin KM			42%	--	--
TA788, BSC[a], 8 UK oncologist			--	5-15%	2-7%
Astellas clinical validation, PBC[a], 7 clinicians (mean, range)			35% (30-45%)	11% (5-20%)	6% (0-10%)
Exponential	930.65	934.10	[redacted]	[redacted]	[redacted]
Weibull	922.11	929.02	[redacted]	[redacted]	[redacted]
Gompertz	929.54	936.45	[redacted]	[redacted]	[redacted]
Gamma	920.05	926.96	[redacted]	[redacted]	[redacted]
Log-normal	**915.91**	**922.82**	[redacted]	[redacted]	[redacted]
Log-logistic	***917.59***	***924.50***	[redacted]	[redacted]	[redacted]

Generalised gamma	***917.90***	***928.27***	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the lower limit for the cisplatin-eligible population

Notes: TA788 included a selected patient population (those not-progressing after PBC). Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BSC, best supportive care; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

3.3.2.3 Cisplatin-ineligible population

The same extrapolation-selection process was followed for the cisplatin-ineligible subgroup. All supporting documentation of tests carried out, as well as comparison graphs are provided in Appendix M. In this subgroup, the lognormal curve can be ruled out as valid option due to very optimistic predictions for EV+P. The log-logistic curve was selected for the base case for the gemcitabine + carboplatin arm, while using the exponential and gamma functions was tested in scenario analyses for PBC.

Similar to the cisplatin-eligible subgroup, the subgroup-specific OS extrapolations for the EV+P arm also did not conform to the expectation that survival outcomes of cisplatin-ineligible patients should be slightly worse than that of cisplatin-eligible patients. The subgroup-specific lognormal and log-logistic curves, the only curves whose trend is hazards aligned with the requirement of predicting declining hazards in the long-run, predicted high proportions of patients surviving at 10-year, much higher than any of the extrapolations in the ITT or cisplatin-eligible populations.

Therefore, following the same approach as for the cisplatin-eligible subgroup, in the base case, rather than using the subgroup-specific extrapolations for EV+P OS, the base case ITT curve was applied instead. This approach provides lower survival estimates for EV+P than the subgroup-specific extrapolations aligning with the expectations for trends in hazards. It is also more in line with the expectation of the relative survival difference between the cisplatin-eligible and ineligible subgroups. The best fitting subgroup-specific curve (exponential) was included as part of the scenario analyses, but note, that this scenario is likely to highly underestimate long-term OS with EV+P in the cisplatin-ineligible population: it predicts [redacted]% of patients to

be alive at 5 years, while in cohort A of the EV-103 trial, the OS rate was estimated at 41.5% of patients at 5 years.[53] To test the assumption that EV-302 will be able to replicate results of EV-103, the scenario using the subgroup-specific lognormal function (which predicts [redacted]% of patients being alive, aligning with the observation in EV-103) was also tested in scenario analysis.

Table 30 Survival model selection for OS, EV+P cisplatin ineligible population

Model	**AIC**	**BIC**	**Time point**		
			2 years	**5 years**	**10 years**
EV-302 EV+P KM			55%	--	--
EV-103 Cohort K, EV+P (cisplatin-ineligible)			53.5%	--	--
EV-103 Cohort Dose esc/A, EV+P (cisplatin-ineligible)			56.4%	41.5%	
TA788, avelumab maintenance[a], 8 UK oncologists			--	20-30%	10-15%
Astellas clinical validation, EV+P[a], 7 clinicians (mean, range)			58% (50-60%)	32% (20-45%)	16% (5-35%)
Exponential	***610.19***	***613.47***	[redacted]	[redacted]	[redacted]
Weibull	612.08	618.66	[redacted]	[redacted]	[redacted]
Gompertz	612.16	618.73	[redacted]	[redacted]	[redacted]
Gamma	612.08	618.65	[redacted]	[redacted]	[redacted]
Log-normal	***614.84***	***621.42***	[redacted]	[redacted]	[redacted]
Log-logistic	612.63	619.21	[redacted]	[redacted]	[redacted]
Generalised gamma	614.06	623.92	[redacted]	[redacted]	[redacted]
ITT population base case: log-logistic	N/A	N/A	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the upper limit for the cisplatin-ineligible population

Notes: TA788 included a selected patient population (those not-progressing after PBC), and OS at 2-years was reported to be 49.8%.[66] Base case selection is in bold, options tested in scenario analyses are in bold italics.

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

Table 31 Survival model selection for OS, PBC cisplatin-ineligible population

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 gemcitabine+carboplatin KM			25%	--	--
TA788, BSC[a], 8 UK oncologists			--	5-15%	2-7%
Astellas clinical validation, PBC[a], 7 clinicians (mean, range)			35% (30-45%)	11% (5-20%)	6% (0-10%)
Exponential	***953.97***	***957.31***	[redacted]	[redacted]	[redacted]
Weibull	948.90	955.59	[redacted]	[redacted]	[redacted]
Gompertz	953.00	959.69	[redacted]	[redacted]	[redacted]
Gamma	***948.40***	***955.10***	[redacted]	[redacted]	[redacted]
Log-normal	956.30	963.00	[redacted]	[redacted]	[redacted]
Log-logistic	**948.10**	**954.80**	[redacted]	[redacted]	[redacted]
Generalised gamma	950.33	960.37	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the upper limit for the cisplatin-ineligible population

Notes: TA788 included a selected patient population (those not-progressing after PBC). Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BSC, best supportive care; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

3.3.3 Progression-free survival

3.3.3.1 ITT population

PFS as assessed by BICR from EV-302 was used to inform progression-free survival in the model. Results of the PH testing for PFS (see section 3.3.1.3 as well as Appendix M, alongside all other results for PFS curve fittings) indicated a violation of the proportional hazards assumption, thus independent models were fitted to EV+P and PBC in the base case. The independently fitted standard parametric distributions along with the KM curves are shown for EV+P in Figure 33 and in Figure 34 for PBC.

As shown in Figure 24 and Figure 25, standard parametric fits did not appropriately capture the inflection in hazards, i.e. the change between initially increasing, but then decreasing hazard pattern, for either treatment arm. Long-term predicted hazards using standard parametric fits overestimate observed hazards. As a result, for PBC, the progression-free survival extrapolations suggest that virtually no patients remain

alive and progression-free at 10 years using standard parametric models. However, clinicians indicated that they expect around 5% of patients to still be alive and progression-free with PBC at year 5 and a few patients still alive and progression-free at 10 years (see Appendix P).

Regarding EV+P, clinicians indicated expecting around 20% of patients to be alive and progression-free at 10 years. The only function that predicts a similar proportion is the Gompertz. However, the Gompertz function predicts a plateau, i.e. that patients not progressing until 5 years, would not progress at all. This assumption lacks clinical face validity at this stage, but may be reevaluated with longer follow-up from the EV-302 trial. The next most optimistic function for EV+P (generalised gamma) predicts PFS at 5 and 10 years well below the clinicians' expectations (at [redacted]% and below [redacted]% at 5- and 10-years respectively versus 25% and 18% from clinicians). The reported PFS at 3-years for cisplatin-ineligible patients from trial EV-103 for cohort K is 46%, while the reported PFS for the dose escalation cohort / Cohort A is 38.2%. Cisplatin-ineligible patients are expected to have slightly worse survival outcomes than the ITT population, but these observations lie well above all current predictions based on EV-302. Furthermore, and as discussed earlier, all standard parametric extrapolations for the PBC comparator arm predict much shorter PFS compared to the clinicians' estimates. Therefore, spline fittings (piecewise polynomial functions) were used in the base case for PFS instead.

Abbreviations: AIC, Akaike's information criterion.

Figure 33 Progression-free survival extrapolations, standard fits, EV+P in ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 34 Progression-free survival, standard fits, PBC in ITT population

Figure 35 displays the spline fits for EV+P PFS as well as the range of estimates obtained for the three UK clinicians participating in the survey. The PFS predictions using the spline fits are better aligned to both the observed data and the clinical

expert expectations than the standard parametric fits. The hazards (as shown in Figure 36) also better mirrored the observed trend in hazards from the EV-302 trial compared to the standard fits (see section 3.3.1.4).

The fit to hazard with 2 knots had lowest AIC/BIC and falls in the middle of clinical expert predictions, therefore this was chosen as the base case fit for EV+P. The next-best spline fit to survival probabilities with 2 knots was tested in scenario analysis, as well as the standard fit with the closest predictions to clinicians' estimates and acceptable hazard trends over time, the generalised gamma. However, as noted above, the generalised gamma function predicts PFS at 5 and 10 years well below the clinicians' expectations, therefore this scenario is conservative.

Abbreviations: AIC, Akaike's information criterion.

Figure 35 Progression-free survival extrapolations, spline fits, EV+P in ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 36 Progression-free survival hazards, spline fits, EV+P in ITT population

For PBC, Figure 37 displays the spline fits alongside the range of estimates obtained for the three UK clinicians participating in the survey, while Figure 38 shows the hazards. The fit of the spline odds with 3 knots had lowest AIC/BIC and falls closest to the clinical experts' predictions. This fit was chosen as the base case for PBC, however, it may still slightly underestimate PFS for PBC, especially at 5 years. The next-best spline fit to survival probabilities with 3 knots was tested in scenario analysis, alongside the statistically best fitting standard log-logistic curve.

Abbreviations: AIC, Akaike's information criterion.

Figure 37 Progression-free survival extrapolations, spline fits, PBC in ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 38 Progression-free survival hazards, spline fits, PBC in ITT population

3.3.3.2 Cisplatin eligible population

A similar process was applied to select best fits for PFS in the subpopulations. All supporting information and graphs are provided in Appendix M. In the case of PFS, the subgroup-specific extrapolations aligned with expectations around the relative outcomes between the cisplatin-eligible and cisplatin-ineligible population, therefore the subgroup-specific data was used.

The statistically best fitting spline for EV+P PFS was the spline using hazards with 1 knot, with the next best fit was to spline using odds also with 1 knot (included as scenario). Similarly to the ITT population, the standard generalised gamma curve was the most plausible fit for EV+P here too, so this was also included as a scenario analysis. For the cisplatin + gemcitabine arm, the statistically best fitting spline for PFS was the 3 knots survival model, with the next best fit was the spline fitted to odds also with 3 knots (included as scenario). All standard fits provided similar extrapolations. The statistically best fitting lognormal function was included as a scenario analysis.

3.3.3.3 Cisplatin ineligible population

As before, all supporting information and graphs are provided in Appendix M. The statistically best fitting spline for EV+P PFS using the subgroup-specific data was the hazards spline with 2 knots, with the next best fit being survival odds also with 2 knots (included as scenario). For the carboplatin + gemcitabine arm, the statistically best fitting spline for PFS was the survival odds with 1 knot, with the next best fit was survival odds but with 3 knots (included as scenario). In both arms the log-logistic and lognormal standard fits were best fitting statistically, therefore they were tested in a scenario analysis.

3.3.4 Time on treatment

3.3.4.1 EV+P in the ITT population

As per the EV-302 trial protocol, treatment with EV could be administered for an unlimited number of cycles until a protocol-defined reason for treatment discontinuation occurs, such as progression, investigator decision, or an adverse event. In contrast, patients could receive pembrolizumab for a maximum of 35 cycles or a protocol-defined reason for treatment discontinuation occurs, whichever was first. Patients who experienced an unacceptable AE that was attributable only to pembrolizumab could continue on EV monotherapy until a protocol-defined reason for treatment discontinuation.[47]

Results of EV-302 showed a difference between PFS (median of 12.5 months) and ToT (median of 9.4 months) for the EV+P arm. Thus, ToT was included in the model separately from PFS. Furthermore, due to pembrolizumab's stopping rule (patients stop treatment after 35 cycles, which is equivalent to about 2 years of treatment), EV and pembrolizumab were modelled separately to more accurately inform treatment costs in the model.

The independently fitted parametric extrapolations along with the KM are show in Figure 39 for EV and Figure 40 for pembrolizumab (with information on hazards over time included in Appendix M). Please note that in the model calculations a 24-month

treatment stopping rule was applied for pembrolizumab, i.e. pembrolizumab use is not extrapolated further.

Based on the goodness of fit statistics (Table 32), in the base case the log-logistic curve was selected for EV and the log-normal was selected for pembrolizumab. The base-case predicts [redacted]% of patients on EV treatment in year 3, [redacted]% in year 4 and [redacted]% in year 5.

There is uncertainty in the proportion of patients who continue EV therapy in the long run. Most curves predict some patients to be still on treatment at 5 years, whereas all patients discontinued treatment by year 3 in cohort A of the EV-103 trial (see Figure 21). Furthermore, a clinical expert expected a halving of patients on treatment in every year, and that no patient would be on treatment at 5 years (as reported in Appendix P). Therefore, the approach to modelling ToT for EV can be considered conservative. Modelled ToT for EV and pembrolizumab including treatment stopping rules is available in Figure 41.

Figure 39: Time on treatment extrapolations, EV in ITT overall safety population

Abbreviations: AIC, Akaike's information criterion; EV, enfortumab vedotin.

Figure 40 Time on treatment extrapolations, pembrolizumab in ITT overall safety population

Abbreviations: AIC, Akaike's information criterion.

Table 32 Time on treatment, goodness of fit statistics for EV and pembrolizumab

Model	EV		Pembrolizumab	
	AIC	BIC	AIC	BIC
Exponential	2085.90	2089.98	2168.89	2172.97
Weibull	2082.53	2090.70	2170.85	2179.02
Gompertz	2087.89	2096.07	2170.30	2178.47
Gamma	2079.68	2087.85	2170.56	2178.73
Log-normal	2074.42	2082.59	**2165.61**	**2173.78**
Log-logistic	**2069.04**	**2077.22**	2167.81	2175.98
Generalised gamma	2073.16	2085.42	2165.23	2177.49

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin.

Figure 41: Modelled time on treatment, EV + P in ITT population

Abbreviations: EV, enfortumab vedotin; KM, Kaplan-Meier; PFS, progression-free survival; ToT, time on treatment.

3.3.4.2 PBC in the ITT population

The EV-302 trial protocol stated that patients in the PBC arm could receive a maximum of six three-week cycles of either gemcitabine + cisplatin or gemcitabine + carboplatin, with six cycles representing the full treatment course in the study.[2] Patients who did not progress following PBC could also receive avelumab maintenance as determined by the investigator.

Therefore, ToT for the PBC arm of EV-302 was modelled in three stages:

1. The ToT KM for gemcitabine + PBC was included in the model (Figure 42). Since the KM curve was complete, given that a maximum of six cycles was allowed, the KM curve was used directly to estimate proportion of patients receiving PBC each week, and fitting to standard parametric survival functions for extrapolation was not required. To align with the EV-302 protocol and UK treatment guidelines, a treatment stopping rule of 4.14 months (i.e., maximum of six three-week cycles of therapy) was also applied.
2. A washout period of [redacted] weeks, based on a post-hoc analysis of EV-302, was applied after the end of gemcitabine + PBC until the start of avelumab

maintenance. No drug acquisition, administration, or monitoring costs were applied during this treatment-free interval.

3. Avelumab maintenance ToT as reported in EV-302 was then extrapolated from the start of maintenance therapy using standard parametric distributions. Consistent with EV-302 and UK clinical practice (see Section 1.3.5.1 and Appendix T), 30% of patients received avelumab maintenance. A stopping rule at 60 months was also applied, consistent with TA788.[36]

Figure 42 ToT KM curve for gemcitabine + PBC

Abbreviations: KM, Kaplan-Meier; PBC, platinum-based chemotherapy.

The extrapolated ToT for avelumab maintenance, from the start of maintenance therapy, is shown in Figure 43 (further information can be found in Appendix M). The model selection process for avelumab ToT, including statistical fits and comparison of extrapolations to estimates from other sources is summarised in Table 33. Although the Gompertz curve provided the best statistical fit to the data, with log-normal and log-logistic also providing reasonable fits, these curves were all expected to potentially overestimate ToT for avelumab maintenance. Based on the model selection process, a Weibull curve was selected as it aligned best with TA788[36] in terms of expected long-term duration of avelumab maintenance therapy (predicting [redacted]% of patients continuing treatment up to 5 years when clinical experts in TA788 estimated this proportion to be between 4% and 7.5% with all other extrapolations

providing predictions outside this range) as well as ensuring that patients are not predicted to continue avelumab maintenance therapy beyond progression.

Figure 43 Time on treatment for avelumab maintenance after PBC in ITT safety population receiving avelumab maintenance

Notes: Time zero represents the start of maintenance therapy. Abbreviations: AIC, Akaike information criterion; PBC, platinum-based chemotherapy.

Table 33 Survival model selection for ToT avelumab maintenance for patients in PBC arm receiving avelumab

Model	AIC	BIC	Timepoint			
			6 months	1 year	2 years	5 years
EV-302 avelumab ToT KM			[redacted]	[redacted]	--	--
TA788, avelumab maintenance ToT			--	--	--	4.0-7.5%
Exponential	480.46	483.37	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	**470.00**	**475.81**	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	462.56	468.38	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	472.24	478.05	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	466.01	471.82	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	464.96	470.77	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	467.75	476.46	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Selected curve for base case is shown in bold. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; TA, technology appraisal; ToT, time on treatment; UK, United Kingdom.

3.3.4.3 Cisplatin-eligible population

Following the same process as above for ITT, but considering the subgroup-specific data only (see Appendix M for detailed information), the lognormal function was chosen for both EV and P ToT, and, similarly to ITT, the Weibull remained the function of choice for avelumab maintenance.

3.3.4.4 Cisplatin-ineligible population

Based on consideration of statistical fits to the subgroup-specific ToT information as well as the slightly worse prognosis of cisplatin-ineligible patients (i.e. patients remaining on treatment are also expected to be below those predicted for the ITT and cisplatin-eligible populations), the lognormal function was chosen for both EV and P ToT, and, similarly to ITT, the Weibull remained the function of choice for avelumab maintenance. All supporting information is presented in Appendix M.

Please note that although care was taken to account for the potential impact of cisplatin-eligibility on EV ToT, predicted proportions still on treatment in the long run

are similar between the ITT, cisplatin-eligible and cisplatin-ineligible populations. Therefore, EV ToT may be underestimated for the cisplatin-eligible subgroup, while overestimated for the cisplatin-ineligible subgroup. Especially given the observation that no one remained on treatment by year 3 in the dose escalation/cohort A of the EV-103 study, while the base case ToT curve predicts [redacted]% of cisplatin-ineligible patients to be on treatment at year 5.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

The EV-302 study collected patient reported outcomes (PROs) using the EQ-5D-5L via an electronic questionnaire. Patients completed the EQ-5D-5L questionnaire in the clinic up to 24 hours prior to their first dose of study treatment and before any study procedures or assessments were conducted (i.e., baseline assessment). The EQ-5D-5L questionnaire was then completed at home prior to clinic visits. From weeks 1 through 12, the questionnaire was completed weekly, followed by an assessment at week 14, and then every 3 weeks from Week 17 onward, including collection through disease progression and survival follow-up.[47]

The NICE guidelines recommend that utilities to be based on the UK EQ-5D-3L value set.[60] Thus, to derive utility values to inform the CEM, the EQ-5D-5L collected in EV-302 was crosswalked to EQ-5D-3L using Hernández Alava et al. 2023[75] and the Dolan et al. 1997[76] UK value set was applied. The analysis was conducted in the PRO full analysis set (FAS), which included all randomised subjects who received any amount of study treatment and completed at least one PRO assessment at baseline. Details of analyses conducted are reported in Appendix O.

The relationship between health state (i.e., progression-free or progressed disease) and patient-reported health utility was evaluated through a longitudinal analysis of utility index scores. More specifically, this analysis 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 effects model was constructed to estimate the mean EQ-5D-3L scores (based on the crosswalk with UK tariffs) for each health state and included the following covariates: treatment arm, randomisation 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.

Table 34 shows the results of the mixed effects model for utility values suggesting that within the overall PRO FAS, the treatment coefficient (i.e., treatment with EV+P vs. PBC) was significant (p <0.001). This supports the use of treatment-specific utility values in the evaluation and is in line with the approach applied in both TA739[38] and TA788.[36] The coefficient for health state (i.e., pre-progression vs. post-progression) was also significant (p <0.001), supporting differentiation of utility values for the progression-free and progressed disease health states.

Table 34 EV-302 trial mixed effects model for health state utilities

Coefficient	Overall PRO FAS
Intercept	[redacted]
Health state, pre-progression vs. post-progression	[redacted]
Time since randomisation, weeks	[redacted]
Treatment, EV+P vs. PBC	[redacted]
Cisplatin eligibility, eligible vs. ineligible	[redacted]
PD-L1 expression, high vs. low	[redacted]
Liver metastases, present vs. absent	[redacted]
Baseline utility	[redacted]

Note: If a subgroup is a stratification factor (i.e., cisplatin eligibility or PD-L1 expression), then models were adjusted for the remaining stratification factors. Abbreviations: FAS – full analysis set; PBC – platinum-based chemotherapy; PRO – patient reported outcome

3.4.2 Mapping

No mapping was required as EQ-5D-5L was collected in the EV-302 trial. However, the EQ-5D-5L scores were cross-walked to EQ-5D-3L following NICE guidelines.[60]

3.4.3 Health-related quality-of-life studies

Appendix H provides details on the SLR conducted to identify health-related quality of life studies. Fifteen studies reporting utility values or disutilities were identified. There was a wide range of pre- and post-progression utility values across studies: progression-free health state utility values ranged from 0.53 to 0.86 and post-progression HSUVs ranged from 0.51 to 0.80. Only the values identified in the previous NICE submissions for avelumab (TA788) and atezolizumab (TA739), and the SMC submission for pembrolizumab were relevant to the UK reference case. Values applied in these assessments are shown in Table 35 and were tested in scenario analyses.

Table 35 Utility values used in previous UK submissions in adults with la/mUC who have not received prior systemic therapy in the locally advanced or metastatic setting

Appraisal	Utility for pre-progression	Utility for post-progression	Source of utility data
NICE TA739[38]	Atezolizumab: 0.642 PBC: 0.527	0.567	IMvigor130
NICE TA788[36]	0.772	0.698	JAVELIN Bladder 100
SMC appraisal of pembrolizumab[77]	0.680	0.610	SMC appraisal of pembrolizumab

Abbreviations: NICE, National Institute for Health and Care Excellence; PBC, platinum-based chemotherapy; SMC, Scottish Medicines Consortium

3.4.4 Adverse reactions

Adverse events originally considered in the model included grade 3+ treatment emergent AEs, which occurred in at least 3% of patients in any treatment regimen in the EV-302 trial. Based on clinical feedback on the frequency of grade 2 peripheral neuropathies observed in patients treated with EV+P, this severity level for peripheral neuropathy was also added to the list to capture all aspects of treatment with EV+P.

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. To account for the cost and quality of life impact of adverse events in patients receiving avelumab maintenance, rates were included from the Javelin Bladder 100 study (note: this study reported any Grade 3+ AEs in the safety population). AE rates for the ITT population are reported in Table 36.

Table 36 Treatment-emergent AEs included in the model (ITT population)

Adverse Events*	**EV+P**	**PBC**	**Avelumab (maintenance)**
Source	EV-302	EV-302	JAVELIN Bladder 100
Acute kidney injury	5.0%	2.3%	0.0%
Anaemia	7.0%	34.2%	3.8%
Fatigue	3.9%	4.6%	1.7%
Hyperglycemia	7.3%	0.7%	0.0%
Hyponatremia	5.0%	3.5%	0.0%
Neutropenia	5.0%	30.0%	0.0%
Neutrophil count decreased	2.5%	9.2%	0.0%
Platelet count decreased	0.0%	6.7%	0.0%
Rash maculo-papular	8.2%	0.0%	0.3%
Thrombocytopenia	0.9%	20.1%	0.0%
Urinary tract infection	5.0%	8.1%	4.4%
Peripheral neuropathy (grade 2)	33.6%	2.5%	0.0%
Peripheral neuropathy (grade 3+)	7.7%	0.0%	0.0%

Abbreviations: AE, adverse event; ITT, intention-to-treat; PBC, platinum-based chemotherapy.

EV-302 data available in EPAR Table 79[3]

It was assumed that the impact of AEs on quality of life was not fully captured in the treatment-specific health state utility values, which were based on EQ-5D-5L data collection in EV-302. This assumption was made since the EQ-5D-5L questionnaire completion frequency tapered over time, therefore the full impact of AEs may not have been captured in the trial data. AE-specific QALY decrements were applied as a lump sum at the first cycle in the pre-progression health state, as most AEs were assumed to be associated with treatment initiation. However, a scenario analysis

was also performed excluding the impact of AEs to test outcomes in a setting where health state utilities already fully include the quality-of-life impact of AEs.

AE utility decrements were identified through NICE appraisals and the literature. The loss of QALYs per AE were calculated as the product of the utility decrement and the assumed duration of the AE, which were sourced from EV-302, if available, or from the literature, particularly from NICE submissions and the sources used therein (see Table 37). This assumes that AE utility decrements depend mostly on the specific AE rather than the specific disease area; this assumption has been applied in other NICE appraisals (e.g. TA857,[78] TA997[79]).

Table 37 AE utility decrements and duration of event

Adverse events	Decrement	Duration (days)	QALY decrement	Source
Acute kidney injury	0.075	7.0	0.0014	Decrement/duration: TA772,[80]
Anaemia	0.090	28.0	0.0069	Decrement: Beusterien et al. 2010/TA788, duration: TA581[81]/TA788[36]
Fatigue	0.073	108.0	0.0217	Decrement: Nafees et al. 2008/TA788, duration: TA581[81]/TA788[36]
Hyperglycemia	0.090	[redacted]	[redacted]	Decrement: TA858,[82] assumed as anaemia, duration: time to resolution hyperglycemia EV-302
Hyponatremia	0.090	[redacted]	[redacted]	Decrement/duration: Assume same as hyperglycaemia
Neutropenia	0.090	12.3	0.0030	Decrement: Nafees et al. 2008, duration: TA772[80]
Neutrophil count decreased	0.090	12.3	0.0030	Assumed same as neutropenia
Platelet count decreased	0.080	34.0	0.0075	Assumed same as thrombocytopenia
Rash maculo-papular	0.032	[redacted]	[redacted]	Decrement: Nafees et al. 2008/TA788, assumed rash, duration: time to resolution skin disorders EV-302
Thrombocytopenia	0.080	34.0	0.0075	Decrement/duration: TA780/581[81]
Urinary tract infection	0.009	14.0	0.0003	Decrement: Sullivan et al., 2006[83] (ICD-9 599)/TA788, duration: TA788
Peripheral neuropathy (grade 2)	0.172	[redacted]	[redacted]	Decrement: Hagiwara et al. [84], duration: time to resolution peripheral neuropathy EV-302
Peripheral neuropathy (grade 3+)	0.330	[redacted]	[redacted]	Decrement: Swinburn et al., 2015[85]/TA772,[80] duration: time to resolution peripheral neuropathy EV-302

Abbreviations: QALY, quality-adjusted life-year

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The EV-302 study collected information on patients' health-related quality of life using the EQ-5D-5L. As described in sections 3.4.1 and section 3.4.2 above, these were cross-walked to the EQ-5D-3L and using UK specific tariffs as required by NICE guidelines.[60] Similarly to other observations in the same indication (see e.g.

TA739[38]), the treatment coefficient was highly significant, therefore the base-case analysis used treatment-specific pre-progression utility values and a combined lower post-progression utility value as shown in Table 38. Utilities were estimated using patient characteristics in EV-302 to inform the mixed effects model covariates reported in Table 34 (please see Appendix O for more detail). Treatment-independent utilities for the pre-progression health state, as well as using ITT utilities in the subgroup analyses, were also tested in scenario analysis. The utility values derived from EV-302 align with observations in similar patient populations in previous TAs, with values falling in the middle of the range of utilities accepted in TA739 and TA788 (values reported in Table 35 above).

Table 38 EV-302 health state utility values

Population		**ITT**	**Cisplatin-eligible**	**Cisplatin-ineligible**
Health state	**Treatment**	**Mean (SE)**		
Pre-progression	EV+P	[redacted]	[redacted]	[redacted]
	PBC	[redacted]	[redacted]	[redacted]
	Treatment-independent	[redacted]	[redacted]	[redacted]
Post-progression	Treatment-independent	[redacted]	[redacted]	[redacted]

In accordance with guidance from NICE, utility values were also adjusted so that they reflect a decrease in health-related QoL as seen in the general population. This ensures that utility values do not exceed that of the general population at a given age as the modelled population ages.[60] The applied age-adjustment utility multipliers for each model cycle were based on the age and sex of the cohort, and were calculated following the approach suggested by Hernandez Alava et al. 2022.[86]

Table 39 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission	Justification
Pre-progression EV+P	[redacted]	[redacted]	Table 38 in this section	Significant treatment effect in EV-302
Pre-progression PBC	[redacted]	[redacted]		Significant treatment effect in EV-302
Post-progression	[redacted]	[redacted]		Significant progression effect in EV-302
Adverse reactions	See Table 37 above	10% variability assumed around the mean	Table 37 in section 3.4.4	Captures full impact of AEs, aligns with prior TAs

3.5 Cost and healthcare resource use identification, measurement and valuation

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. A one-time cost associated with terminal care was included upon transition to the death health state.

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Drug acquisition costs

Drug unit costs and dosing for each intervention are summarised in Appendix K providing details on doses per unit, pack sizes and prices. Drug acquisition costs for the comparators were based on the list prices reported in the drugs and pharmaceutical electronic market information tool (eMIT) or the British National

Formulary (BNF). Where multiple formulation sizes are available, the lowest cost per mg was selected. Dosing for the treatments was based on EV-302 trial protocol, except for pembrolizumab, as UK clinicians indicated that rather than the 200mg every 3 weeks dosing included in the EV-302 trial protocol, administering 400mg every 6 weeks instead is more common in UK clinical practice. This change does not impact the total drug dose administered, but does reduce administration costs. The original trial protocol based dosing was tested in a scenario analysis.

The weight and BSA informing dosing was also based on the EV-302 trial data (see Table 20). The distribution of patient weight or BSA in the trial was used to estimate average vial use and therefore the average dose per treatment (i.e., considers wastage). Relative dose intensity (RDI) was also taken into account for each treatment based on RDIs observed in the EV-302 trial for all treatments except carboplatin. RDI for carboplatin could not be calculated, therefore the average of RDIs reported in TA638[87] and TA819[88] were used.

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 as shown in Table 40.

Table 40 Drug dosing and total acquisition costs

Regimen		Intervention	Dosing regimen	Administrations per cycle	Cycle length (days)	RDI (%)	Cost per treatment cycle (with wastage) (£)	Modelled cost per week (with wastage) (£)
EV + P		EV	1.25 mg/kg, days 1 and 8, Q3W	2	21	80.1%	[redacted]	[redacted]
		Pembrolizumab	400 mg, day 1, Q6W	1	42	[redacted]	[redacted]	[redacted]
PBC	Gemcitabine + cisplatin	Gemcitabine	1000 mg/m^2, D1 & D8, Q3W	2	21	[redacted]	[redacted]	[redacted]
		Cisplatin	70 mg/m^2, D1 Q3W	1		[redacted]	[redacted]	
	Gemcitabine + carboplatin	Gemcitabine	1000 mg/m^2, D1 & D8, Q3W	2	21	[redacted]	[redacted]	[redacted]
		Carboplatin	AUC 4.5 (assumed dose of 450 mg), D1, Q3W	1		92.9%	44.65	

Abbreviations: AUC, area under the curve; D1, day 1; D8, day 8; EV, enfortumab vedotin; mg, milligram; P, pembrolizumab; Q2W, every 2 weeks; Q3W, every 3 weeks; PBC, platinum-based chemotherapy; RDI, relative dose intensity.

3.5.1.2 Drug administration costs

The setting and type of administration code required for each administration of each regimen was based on discussions with clinical experts as reported in Table 41. Also based on their recommendations, day case tariffs were used.

Table 41 Unit costs of drug administration

Activity	Code	Unit cost (£)[89]
Deliver simple parenteral chemotherapy at first attendance	SB12Z	313.91
Deliver more complex parenteral chemotherapy at first attendance	SB13Z	381.05
Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	SB14Z	485.23
Deliver subsequent elements of a chemotherapy cycle	SB15Z	383.54
Chemotherapy for Regimens not on the National List	SB17Z	392.04

Table 42 Total administration costs

Regimen	Intervention	Admin codes	Admin cost per treatment cycle (£)	Modelled admin cost per week (£)
EV+P	EV+P	2 * SB17Z	784	261
	EV[a]	2 * SB17Z	784	261
	Pembrolizumab[a]	1 * SB17Z	392	65
PBC	Gemcitabine + cisplatin	1* SB14Z, 1*SB15Z	869	290
	Gemcitabine + carboplatin	1* SB14Z, 1*SB15Z	869	290

Note: a) where one treatment stops (i.e., pembrolizumab at 24 months) and the other continues (i.e., EV), administration is based on administration of the monotherapy rather than combination therapy.
Abbreviations: EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy.

3.5.1.3 Monitoring costs

Drug monitoring costs were informed by the EMA and Electronic Medicines Compendium (EMC) prescribing information (Summaries of Product Characteristics) for medicines and are presented in Table 43.[5,12,47,57,90-92] 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. Please note that the costs for all of these monitoring tests were omitted from the

evaluation for TA788, but were included here to fully capture the incremental costs of active treatments, including those associated with EV+P.

Table 43 Monitoring tests, frequency and unit costs by intervention

Treatment		Blood count	Hepatic function	Adrenal function	Renal function	Thyroid function	Neurologic function	Total monitoring costs, per cycle (£)
EV + P	EV+P	1	1	1	1	1	0.0	9.15
	EV	1	1	1	1	1	0.0	9.15
	P	1	1	1	1	1	0.0	9.15
PBC	Gemcitabine + cisplatin	1	1	0	1	0	0	6.05
	Gemcitabine + carboplatin	1	1	0	1	0	1	219.55
Unit cost (£)		2.96	1.55	1.55	1.55	1.55	213.50	-

Note: Combination regimens use the maximum frequency of monitoring across all components, rather than the sum of monitoring frequencies (i.e., to prevent double counting). Abbreviations: EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy

3.5.2 Subsequent treatment costs

3.5.2.1 Avelumab maintenance treatment costs

As shown in Table 12 (Section 2.6.7), 30% of patients in EV-302 trial went on to receive avelumab maintenance treatment. This proportion corresponds to what was seen in real-world evidence in the UK and elsewhere in Europe. 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 PBC. A relative dose intensity of 95.1% was applied based on TA788.[36] The avelumab maintenance cost was applied after a maximum of six cycles of PBC and following a treatment-free washout period of approximately [redacted] weeks (based on EV-302 data). The duration of the washout period is in the range advised by clinical experts at four to ten weeks (see Appendix P). The duration of avelumab maintenance treatment was also estimated based on the observations in the EV-302 trial, section 3.3.4.2 provided a detailed description. During avelumab maintenance therapy, the same monitoring costs were applied as for EV+P.

3.5.2.2 Costs for subsequent lines of therapy

Following first-line therapy, it was anticipated that a proportion of the population would go on to receive subsequent systemic therapy after disease progression. The proportion of patients initiating a new line of therapy declines rapidly with each line.[93-95] Since most patients have progressed in the PBC arm in the EV-302 trial, the total proportion initiating a subsequent line of treatment in the PBC arm was assumed to represent the proportions starting a subsequent line of treatment for EV+P too. The types and distribution of therapies within this proportion was informed by observation from the EV-302 trial with the following exceptions:

- EV monotherapy is not reimbursed in the UK as a subsequent therapy, therefore proportions were reweighted so that the total proportion receiving subsequent therapies remained the same (as observed in the PBC arm of the trial), but those going on to EV monotherapy were reassigned to other treatments according to their originally observed proportions.
- Those who received pembrolizumab monotherapy in the trial were assumed to receive atezolizumab instead, as pembrolizumab monotherapy is not a subsequent treatment option in the UK.
- Taxane use was grouped, and costed assuming the use of paclitaxel.

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), and median treatment duration, which was informed by EV-302 trial data for duration of subsequent therapy. The subsequent treatment unit costs are reported in Appendix K. Duration of subsequent therapy, drug acquisition, and drug administration costs per course are shown in Table 44 for each subsequent therapy. 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. As for first-line therapies, the average weight and BSA informing dosing was also based on the EV-302 trial data (see Table 20) considering the distribution of patient weight or BSA in the trial. The distribution of subsequent therapies as included from EV-302

along with the estimated total cost of subsequent therapy per treatment arm are presented in Table 45.

Table 44 Subsequent therapy dosing and duration

Intervention		Dosing regimen	Duration of therapy (months)[96]	Drug acquisition cost per course (£)	Drug administration cost per course (£)
Avelumab maintenance for 30% of population (ITT)		800 mg, D1 Q2W	See section 3.3.4.2 Mean predicted: 14.85	2,919.94*	392*
Gem-citabine + cis-platin	Gem-citabine	1000 mg/m^2, D1 & D8, Q3W	[redacted]	[redacted]	[redacted]
	Cis-platin	70 mg/m^2, Q3W			
Gem-citabine + carbo-platin	Gem-citabine	1000 mg/m^2, D1 & D8, Q3W	[redacted]	[redacted]	[redacted]
	Carbo-platin	AUC 4.5 (assumed dose of 450 mg), Q3W			
Atezolizumab		1200 mg, Q3W	[redacted]	[redacted]	[redacted]
Paclitaxel		175 mg/m^2 IV, Q3W	[redacted]	[redacted]	[redacted]

* Avelumab costs are provided per cycle
Note: Only median treatment durations were reported for subsequent lines of treatments, however, since subsequent line treatment durations are generally short, medians should closely align with mean durations.
Abbreviations: AUC, area under the curve; D1, day 1; D8, day 8; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks.

Table 45 Subsequent treatment distribution and total costs

		Post-progression/subsequent treatment				Total cost per course (£)	Total admin cost per course (£)
		Gemcitabine + cisplatin	Gemcitabine + carboplatin	Atezolizumab	Paclitaxel		
1L treatment	EV+P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PBC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy

3.5.3 Health-state unit costs and resource use

The health state specific costs were assumed to be the same for all treatment arms. The healthcare activity (e.g., type of physician/nurse visit) and frequency of visits per month for each health state mirrors the assumptions used in TA788, and are presented in Table 46. The unit costs were sourced from the most recent versions of the NHS reference costs[89] and PSSRU[97] and are summarised in the same table.

Table 46 Routine care by health state per month

Activity	Progression-free, frequency per month	Progressed, frequency per month	Unit cost (£)	Reference
Consultant led oncologist follow-up visit	0.88	0.93	221.48	NHS 2021/2022; WF01A, Consultant led: Medical Oncology, Non-Admitted Face-to-Face, Follow-up
Clinical nurse specialist	0.62	1.00	68.00	PSSRU 2023; Community nurse - Band 6; Cost per working hour
Dietician	0.06	0.16	83.00	PSSRU 2023; Dietician - Average cost per group session (one-to-one)
GP home consultation	0.26	0.72	178.00	PSSRU 2023; General practitioner — unit costs per hour of GMS activity
Urologist	0.07	0.04	154.26	NHS 2021/2022; Consultant led: Urology, Non-Admitted Face-to-Face, Follow-up
District nurse	0.27	0.96	68.00	PSSRU 2023; Community nurse - Band 6; Cost per working hour
Total cost per week	73.01	111.97	-	-

Abbreviations: GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Unit; TA, technology appraisal.
Sources: PSSRU 2023,[97] NHS 2021/2022

A one-off terminal care cost was applied to cover costs of supporting patients in a palliative stage before death. The same cost was applied to both treatment arms based on the proportion of patients who died in each model cycle. The cost was sourced from Round et al. (2015),[98] a modelling study which estimated end of life

costs in people with cancer in England and Wales. This source was also included in TA788 to estimate end of life costs. The cost was inflated from 2013/14 to 2021/22 using the indices reported by the PSSRU.[97]

3.5.4 Adverse reaction unit costs and resource use

The costing codes and unit costs of hospitalisation associated with the management of AEs included within the CEM were sourced from the most recent version of the NHS reference costs and recent NICE technology appraisals.[36,37,82] Similarly to how the QoL impact of AEs were taken into account (see section 3.4.4), the cost of managing AEs were also applied as lump sum costs in the first model cycle, as treatment-related AEs were assumed to be associated with treatment initiation instead of occurring on an ongoing basis throughout the entire treatment course. Since grade 3+ AEs were included, all patients were assumed to require hospitalisation for the treatment of the AEs. The costs of treating AEs are shown in Table 47. Combining this information with the occurrence of AEs as reported in Table 36, the total AE costs were calculated to be £[redacted] and £[redacted] in total for the EV+P and PBC arms, respectively.

Table 47 Adverse event unit costs

Adverse Event	Hospitalisation cost per event (£)	NHS reference code
Acute kidney injury	2,505.44	LA07H-P (TA525)[37]
Anaemia	1,119.23	SA09G-L (TA788)[36]
Fatigue	4,071.73	WH52A (TA788)[36]
Hyperglycaemia	1,674.08	KC05G-N (Brown 2013)[99]
Hyponatraemia	1,674.08	KC05G-N (TA858)[82]
Neutropenia	753.88	WJ11Z (Brown 2013)[99]
Neutrophil count decreased	753.88	WJ11Z (Brown 2013)[99]
Platelet count decreased	753.88	WJ11Z (Brown 2013)[99]
Rash maculo-papular	1,755.59	JD07B-K (TA788)[36]
Thrombocytopenia	993.37	SA12G-K (TA788)[36]
Urinary tract infection	2,219.67	LA04H-S (TA788)[36]
Peripheral neuropathy	1,345.74	WF01A-B (TA772),[80] physiotherapy (10 sessions, gabapentin 300mg for 42 days

Abbreviations: NHS, National Health Service

3.6 Severity

Following the methods described by NICE, the absolute and proportional QALY shortfall was calculated for u/mUC. U/mUC meets the criteria for applying a 1.2 multiplier for QALYs based on proportional QALY shortfall.

Starting age and proportion of males and females was based on observations in the EV-302 trial (see Table 48). Mortality for the general population was based on the UK National life tables,[71] while general population utilities were estimated according to values provided by Hernandez Alava and colleagues, 2022.[86] Mortality and utility calculations for standard of care (PBC) arm were described in Sections 3.3.2 and 3.4.5, respectively, with the main information repeated in Table 49. Please note that the model also includes age-related utility decrements, which were included in the shortfall calculations. Previous technology assessments in the same or similar patient populations (TA739 and TA788) were conducted before the introduction of

QALY shortfall considerations and therefore did not include calculations for a severity modifier.

Table 48 Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	77% male, 23% female	Section 3.2.1, Table 20
Starting age	67.9 years	Section 3.2.1, Table 20

Table 49 Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)*	Undiscounted life years
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

* Note, the model calculations also include age-related utility decrements

Table 50 Summary of QALY shortfall analysis

Expected total discounted QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
9.80	Platinum-based chemotherapy: [redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted]

3.7 Uncertainty

According to the recommendations by NICE, this section focuses on the uncertainty associated with the disease area. For a discussion on uncertainties associated with the economic evaluation, please see section 3.14 below.

There are no known issues in generating high quality evidence due to the nature of the condition. However, as in many other fields in oncology, the treatment landscape changes rapidly. Therefore, comparability of outcomes from recent trials to results in

prior clinical trials is limited, and it is challenging to generate long-term real world evidence that would reflect current standard of care.

3.8 Summary of base-case analysis inputs and assumptions

3.8.1 Summary of base-case analysis inputs

A summary of the model base case inputs can be found in Table 51. Detailed description of values of parameters, ranges and applied distributions can be found in Appendix Q.

3.8.2 Assumptions

Table 52 summarises the key assumptions for the base-case analysis, including the rationale for the assumption and how uncertainty around the assumption can be explored in the model.

Table 51 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution) – See Appendix Q	Reference to section in submission
Time horizon	Lifetime (max 30 years) (as per NICE guidance)	Scenario with 20 years	Section 3.2.2
Discount rates	3.5% for both costs and health benefits (as per NICE guidance)	Scenarios with 0-6%	Section 3.2.2
Patient characteristics	EV-302 values	Age: normal distribution Proportion male: Beta distribution Weight and BSA: Lognormal distribution	Section 3.2.1
Treatment dosing and stopping rules	EV-302 protocol and SmPCs	Relative dose intensity: Beta distribution	Section 3.3.4
Treatment efficacy	OS, PFS, ToT extrapolated from EV-302	Multivariate correlated normal distributions	Section 3.3
Proportion cisplatin-eligible	EV-302	Beta distribution	Section 2.6.1
Proportion receiving avelumab maintenance	EV-302	Beta distribution	Section 2.6.7
Treatment safety	EV-302	Beta distributions	Section 3.4.4
Heath-state utilities	EV-302	Beta distributions	Section 3.4.5
AE disutilities	Duration: EV-302 where available Decrement: prior TAs	Decrement: Beta distributions AE duration: lognormal distribution	Section 3.4.4
Treatment costs	MIMS, BNF	Gamma distributions	Section 3.5.1.1
Administration costs	NHS Reference Costs 2021/22	Gamma distributions	Section 3.5.1.2

Relative dose-intensities	EV-302 where available; prior TAs	Beta distributions	Section 3.5.1.1
Subsequent treatment duration	EV-302	Lognormal distribution	Section 3.5.2
Proportion of patients receiving each subsequent treatment	EV-302	Beta distributions	Section 3.5.2
Monitoring test frequencies	SmPCs	Gamma distributions	Section 3.5.1.3
Monitoring test costs	NHS Reference Costs 2021/22	Gamma distributions	Section 3.5.1.3
AE treatment unit costs	Prior TAs	Gamma distributions	Section 3.5.4
Health state resource use	TA788	Gamma distributions	Section 3.5.3
Health state resource use unit costs	NHS Reference Costs 2021/22; PSSRU 2023[97]	Gamma distributions	Section 3.5.3
Terminal care cost	Round et al. (2015),[98] TA788	Gamma distributions	Section 3.5.3

Table 52 Assumptions in the economic evaluation

Assumption	Rationale	How uncertainty is handled
PFS and OS were modelled based on the ITT population from EV-302	EV-302 is the registrational study for EV+P, and is a high quality, phase III study comparing EV+P to PBC. EV-302 is the best available source of evidence for the efficacy and outcomes of EV+P.	Alternative scenarios evaluating subgroups (e.g., cisplatin-eligible, cisplatin-ineligible) have been evaluated.
Uptake of avelumab maintenance in EV-302 was assumed representative of UK clinical practice.	RWE collected by Astellas suggested similar proportions of patients who initiated PBC received avelumab maintenance. Clinical experts consulted to validate the CEM similarly agreed that around 30%, up to a maximum of 50%, of patients who initiate PBC will receive avelumab maintenance.	The costs associated with avelumab maintenance were tested in the deterministic sensitivity analysis by changing the proportion of patients receiving avelumab maintenance without impacting the corresponding efficacy.

Independent treatment effects were modelled for PFS	This approach was based on strong violation of the PH assumption, given different hazard trends observed over time for EV+P and PBC.	Alternative PFS extrapolations were explored as scenarios.
PFS was extrapolated for EV+P and SOC using spline fits.	Spline fits were selected because, for both EV+P and PBC, the standard extrapolation models provided lower estimates than the clinically plausible long-term estimates based on observations in EV-103, and lower than clinical opinion provided for this as well as prior TAs in the same indication.	Scenarios are presented with alternative standard parametric models for each treatment arm to explore alternative assumptions. Efficacy parameters are explored in the probabilistic analysis.
Independent treatment effects were modelled for OS.	Results of the PH testing for OS suggested the PH assumption may hold. However, it was considered that the OS would likely have a similar violation when it was more mature, given the different mechanisms of action for EV+P and the violation of the PH assumption for PFS. Therefore, independent models were fitted in the base case.	Scenarios are presented with dependent treatment survival models and constant HRs.
OS in the ITT population was extrapolated for EV+P and PBC using the log-logistic function for both arms.	For PBC, the log-logistic provided the best fit to the hazards, most favourable AIC/BIC, and clinically plausible long-term estimates. For EV+P, log-logistic was selected based on clinically plausible long-term estimates and given external evidence on the likely trajectory of OS rates over time.	Scenarios are presented with alternative parametric models for each treatment arm to explore alternative assumptions. Efficacy parameters are explored in the probabilistic analysis.
OS in the subgroups was extrapolated for EV+P using the base case survival curve from the ITT population.	Subgroup-specific extrapolations did not reflect the expected survival difference between cisplatin-eligible and cisplatin-ineligible patients.	Scenarios are presented using the statistically best fitting subgroup-specific curves as well as a scenario using ITT curves for all time-to-event data.
Health state utilities for the progression-free health state were assumed to be different for EV+P and PBC.	The mixed effects model for UK utilities suggested that the treatment coefficient (i.e., treatment with EV+P vs. PBC) was significant ($p < 0.001$), supporting treatment specific utilities in the progression-free health state. Although the coefficient was estimated based on the totality of the treatment population, there was uncertainty around whether	Treatment independent progression-free utilities with a UK tariff were explored as a scenario analysis.

	a treatment difference could be supported in the progressed disease health state. Clinical expert feedback suggested that although patients who received EV+P in 1L would likely enter the progressed disease health state with a higher utility than patients who received SOC, subsequent therapies for patients who received EV+P are different than subsequent therapies for patients who received PBC (i.e., higher 2L use of immunotherapies post-PBC and platinum-based therapy for EV+P). Thus, it was conservative to assume equal post progression utility in alignment with prior TAs in this disease.	
The distribution of subsequent therapies is based on EV-302, with EV removed and pembrolizumab replaced by atezolizumab in the base case.	Pembrolizumab and EV are not recommended by NICE in the UK for u/mUC.	Uncertainty not addressed directly, however, changes in use of subsequent therapies may influence survival, and alternative survival extrapolations are tested.

3.9 Base-case results

3.9.1 Base-case incremental cost-effectiveness analysis results

Results for the ITT population with and without including the calculated 1.2 QALY weights based on the severity of the disease (see section 3.6) are shown in Table 53 and Table 54.

Without the severity weighting, the EV+P arm was predicted to result in [redacted] QALYs, while the PBC arm was predicted to result in [redacted] QALYs, leading to 1.60 additional QALYs compared to PBC. The ICERs shown were calculated using the list prices for pembrolizumab, avelumab and atezolizumab. Notably, the costs of EV+P are mostly driven by the costs of pembrolizumab, given its list price (£[redacted] discounted total drug acquisition costs for EV vs £[redacted] discounted total costs for pembrolizumab over the entire treatment course means that the costs of pembrolizumab at list price account for [redacted]% of the EV+P drug acquisition costs). The ICER will reduce considerably when the confidential discounts for these treatments are taken into account.

Disaggregated results, including the breakdown between cost categories and drug acquisition costs referred to above, are presented in Appendix J.

Table 53 Base-case results for ITT population with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV,

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-	-	-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.60	[redacted]
With severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-	-	-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.92	[redacted]

Note: All other treatments were costed using list prices. Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 54 Net health benefit of EV+P versus PBC for ITT population with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Without severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.60	[redacted]	[redacted]
With severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.92	[redacted]	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

3.10 Exploring uncertainty

The main aspects of uncertainty relate to the proportion of patients expected to remain on EV treatment in the long-run, the dosing frequency and intensity following the stop of pembrolizumab treatment as well as the long-term effects of EV+P on mortality. The next data cut of the EV-302 trial will be used to update extrapolations and assumptions made for these variables, therefore is expected to reduce uncertainty in the economic assessment of EV+P.

How uncertainty was captured for each aspect of the model was detailed in Table 52. Furthermore, uncertainty was explored using probabilistic and deterministic sensitivity analyses, and different scenarios were also modelled. These explorations are described below.

3.10.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), uncertainties in the parameter values were estimated by randomly drawing a parameter value from predefined distributions and averaging model cost and QALY predictions over 1,000 iterations. Please refer to Appendix Q for estimates of cumulative incremental costs, QALYs and ICER which show the expected probabilistic ICER remains stable after approximately 200 simulations, therefore the use of 1,000 iterations was enough to capture parameter uncertainty.

Results are presented as cost effectiveness acceptability curves as well as on a cost effectiveness plane. The mean probabilistic results are presented in Table 55 and align with the deterministic results.

Table 55 Probabilistic sensitivity analysis results for the base case with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-	-	-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.58	[redacted]
With severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-	-	-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.90	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 56 Net health benefit based on probabilistic results for the base case with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Without severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.58	[redacted]	[redacted]
With severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.90	[redacted]	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

Figure 44 shows the results on cost-effectiveness plane. All of the 1,000 simulations were in the upper right-hand quadrant, indicating that EV+P is more effective although a more costly treatment option compared to PBC.

Figure 44: Base case probabilistic results on the cost effectiveness plane with no QALY weighting, but including a confidential PAS of % for EV

Note: All other treatments were costed using list prices

At the £20,000 to £30,000 threshold the probability of EV+P being cost effective compared to PBC is % with the list prices included for pembrolizumab, avelumab and atezolizumab. However, with the confidential discounts, the probability of EV+P being cost-effective will be much higher.

3.10.2 Deterministic sensitivity analysis

With the exception of survival outcomes, major model variables in the base case for which values were uncertain were tested in a one-way deterministic sensitivity analysis to identify model drivers and examine key areas of uncertainty. Where possible, confidence intervals or published ranges were used as alternative values. In the absence of confidence intervals or published ranges, upper and lower bounds

tested in the one-way sensitivity analysis were calculated assuming a standard error of 10% of the mean. Please see Appendix Q for ranges applied. Results of the deterministic sensitivity analysis without the severity modifier applied are presented as a tornado diagram (in Figure 45).

The deterministic sensitivity analysis shows that the ICER is most sensitive to the proportion of patients receiving avelumab maintenance therapy, the health state utility values, administration costs and components of monitoring and health state costs. However, none of the scenarios increased the ICER to above £[redacted]/QALY without the severity weighting applied (note without the severity weighting the base case ICER is £[redacted]/QALY).

Figure 45 Tornado diagram of impact of input parameters on base case results with no QALY weighting, but including a confidential PAS of [redacted]% for EV

Note: All other treatments were costed using list prices

Table 57: Top 20 parameters influencing the ICER with no QALY weighting, but including a confidential PAS of [redacted]% for EV

Parameter	Low value of input	High value of input	ICER at low value of input (£)	ICER at high value of input (£)	Difference (£)
Proportion of patients receiving avelumab maintenance	0.25	0.37	[redacted]	[redacted]	[redacted]
Administration cost, Chemotherapy for Regimens not on the National List	318.98	472.52	[redacted]	[redacted]	[redacted]
Health state utility values, PF - EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS HCRU monthly visits, Consultant led oncologist follow-up visit	0.72	1.06	[redacted]	[redacted]	[redacted]
Consultant led oncologist follow-up visit, HCRU unit cost	180.20	266.94	[redacted]	[redacted]	[redacted]
RDI (%), Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression treatment SOC: Gemcitabine + PBC, Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utility values, PF - SOC: Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of sub tx (months), Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients receiving: Gemcitabine + carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	74.23	77.55	[redacted]	[redacted]	[redacted]
Age (at baseline)	67.04	68.76	[redacted]	[redacted]	[redacted]
RDI (%), EV	0.79	0.82	[redacted]	[redacted]	[redacted]
Proportion of patients receiving: Gemcitabine + cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost, Complex/Prolonged Chemotherapy (First Attendance)	394.80	584.84	[redacted]	[redacted]	[redacted]
PFS HCRU monthly visits, GP home consultation	0.21	0.31	[redacted]	[redacted]	[redacted]
RDI (%), Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost, Subsequent Elements of a Chemotherapy Cycle	312.06	462.28	[redacted]	[redacted]	[redacted]

Clinical nurse specialist, HCRU unit cost	55.33	81.96	[redacted]	[redacted]	[redacted]
PFS HCRU monthly visits, Clinical nurse specialist	0.50	0.75	[redacted]	[redacted]	[redacted]

Note: All other treatments were costed using list prices

3.10.3 Scenario analysis

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties as well as alternative input sources where available. The following scenarios were tested:

- Structural assumptions:
    - Model time horizon restricted to 20 years
    - Discount rates for costs and benefits changed to 6%, 5%, 1.5% and 0%
    - Excluding the impact of adverse events
- Survival extrapolations
    - OS: different standard parametric curves
    - PFS: next best fitting spline extrapolation
    - PFS: different standard parametric extrapolations
    - ToT: different standard parametric extrapolations
- Utilities:
    - Applying non-treatment specific, health state based utilities
    - Removing age-adjustment of utilities, i.e. trial utilities are applied throughout the model time horizon
    - Testing alternative sources for the health state utilities:
        - Utilities based on NICE TA788
        - Utilities based on NICE TA739
        - Utilities based on SMC assessment of pembrolizumab
- Drug cost calculations:
    - Pembrolizumab dosing based on trial protocol (200mg every 3 weeks)

As seen with the base case results, the model is almost linear with probabilistic results being very close to deterministic results (a less than 0.2% difference in

incremental costs and 1.0% difference in incremental QALYs). Given the alignment between deterministic and probabilistic results, the deterministic results are displayed in Table 58.

The results are relatively stable, with most scenarios having an ICER between £[redacted]/QALY and £[redacted]/QALY including the severity modifier. The ICER is most affected by high discount rates and assumptions around dependence of OS curves. Specifically, relying on a common shape parameter between treatment arms results in the highest ICER, while applying a constant HR results in the lowest ICER. However, as noted above in section 3.3.1.3 on the assessment of proportional hazards, the PH assumption clearly does not hold for progression-free survival and is also unlikely to hold for the cisplatin-ineligible subgroup for OS. Additionally, there is a difference in the mechanism of action between EV+P and PBC, therefore it is unrealistic to assume proportionality for the survival outcomes between the treatment arms. Both of these scenarios are likely to be unrealistic.

The scenario where both treatment arms' OS were extrapolated using exponential functions also resulted in a relatively higher ICER. However, this scenario is overly conservative given that it predicts that only 8% of patients remain alive at 10 years after EV+P treatment, while the clinical validation described in section 3.3.1.2 resulted in an estimate of 16% on average. Furthermore, the clinical input obtained for TA788[36] also predicted 10-15% alive at 10 years with avelumab, despite lower OS rates at 2 years in JAVELIN 100 compared to EV-302.

The three most influential, while, at the same time, clinically plausible scenarios were the following:

- Using lognormal functions for the OS extrapolation: this alternative survival extrapolation predicts longer mean OS for both EV+P and PBC. It aligns better with the observed EV-103 data (where estimated 5-year survival rate was 41.5%, while the lognormal function predicts [redacted]% of patients to be alive at this point), and has a major downward impact on the ICER.

- Using the best fitting standard curves to inform PFS extrapolations: although spline fits were included in the base case to better capture changes in hazards observed over time in the trial, use of standard curves aligns with the approach taken to model all other time to event data. The scenario shows that the ICER is relatively robust to the change in survival functions.
- Using generalised gamma functions for EV+P ToT extrapolations: these functions predict shorter treatment duration for EV+P, which aligns better with observations in the EV-103 trial, where all patients discontinued treatment by year 4. This scenario reduces the predicted ICER.

Table 58 Scenario analysis results around base case, including a confidential PAS of [redacted]% for EV

Parameter	Base case	Scenario	Incremental Cost (£)	Incremental QALY (no severity modifier)	ICER (£/QALY) (no severity modifier)	ICER (£/QALY) (with severity modifier)	Difference from base case
Base Case			[redacted]	1.60	[redacted]	[redacted]	
Time horizon	Lifetime (30 years)	20 years	[redacted]	1.53	[redacted]	[redacted]	3.16%
Annual discount rate (costs and health outputs)	3.50%	6.0%	[redacted]	1.38	[redacted]	[redacted]	12.21%
		5.0%	[redacted]	1.46	[redacted]	[redacted]	7.32%
		1.50%	[redacted]	1.89	[redacted]	[redacted]	-12.08%
		0.0%	[redacted]	2.03	[redacted]	[redacted]	-16.81%
Excluding impact of AEs	AEs included	AEs not included	[redacted]	1.60	[redacted]	[redacted]	-0.23%
Pembrolizumab dosing	400mg Q6W	As per trial: 200mg Q3W	[redacted]	1.60	[redacted]	[redacted]	0.26%
OS	Independent fit Both arms log-logistic	Independent fit Both arms exponential	[redacted]	1.24	[redacted]	[redacted]	26.68%
		Independent fit Both arms log-normal	[redacted]	2.04	[redacted]	[redacted]	-18.96%
		Dependent fit: Common shape parameter, log-logistic	[redacted]	1.13	[redacted]	[redacted]	36.26%
		Constant hazard ratio, log-logistic	[redacted]	2.04	[redacted]	[redacted]	-18.67%
PFS	Spline fits	Spline fits	[redacted]	1.60	[redacted]	[redacted]	-0.37%

	EV+P: hazard 2 knots PBC: odds 3 knots	EV+P: normal, 2 knots PBC: normal, 3 knots					
		Standard fits EV+P: generalised gamma PBC: log-logistic	[redacted]	1.55	[redacted]	[redacted]	4.03%
		Standard fits Both arms log-normal	[redacted]	1.51	[redacted]	[redacted]	8.13%
		Standard fits Both arms log-logistic	[redacted]	1.51	[redacted]	[redacted]	8.42%
		Standard fits Both arms generalised gamma	[redacted]	1.56	[redacted]	[redacted]	3.64%
Time on treatment	EV: log-logistic P: log-normal Avelumab: Weibull	EV: log-logistic P: log-logistic Avelumab: Weibull	[redacted]	1.60	[redacted]	[redacted]	0.23%
		EV: generalised gamma P: generalised gamma Avelumab: Weibull	[redacted]	1.60	[redacted]	[redacted]	-8.30%
Utilities	Treatment-specific in PFS,	Health state specific, Age-adjustment,	[redacted]	1.56	[redacted]	[redacted]	2.52%

	Age-adjustment, Source: EV-302	Source: EV-302					
		Treatment-specific in PFS, No age-adjustment, Source: EV-302	[redacted]	1.66	[redacted]	[redacted]	-3.73%
		Health-state specific, Age-adjustment, Source: NICE TA788	[redacted]	1.70	[redacted]	[redacted]	-6.06%
		Health-state specific, Age-adjustment, Source: NICE TA739	[redacted]	1.54	[redacted]	[redacted]	3.72%
		Health-state specific, Age-adjustment, Source: SMC pembrolizumab	[redacted]	1.50	[redacted]	[redacted]	6.58%

Note: All other treatments apart from EV were costed using list prices
Abbreviations: AE, adverse events; EV+P, enfortumab vedotin + pembrolizumab; PBC, platinum-based chemotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks

3.11 Subgroup analysis

3.11.1 Subgroup results: Cisplatin-eligible patients

Subgroup results are presented in Table 59 and Table 60. As expected, the cisplatin-eligible patient subgroup has slightly longer survival and higher QALY gains than the ITT population (e.g., cisplatin-eligible patients were calculated to gain [redacted] life years with gemcitabine + PBC, and [redacted] life years with EV+P vs [redacted] and [redacted] in the ITT population, respectively). This is due to better PFS, higher subgroup-specific utilities, and the younger age of this subgroup (i.e. there is a lower impact of the application of age-adjustment of utilities and the general population mortality hazard caps). However, the incremental QALY gain in this subgroup is lower compared to the ITT population (at 1.44 QALYs in the cisplatin-eligible patients vs 1.60 QALYs in the ITT population, both without the severity modifier). This is likely due to the use of the ITT OS curve in the base case to represent survival in the cisplatin-eligible subgroup, given that the extrapolations based on the subgroup-specific data were likely to underestimate survival. As discussed earlier, the use of the ITT OS curve for EV+P is still likely to underestimate survival with EV+P for the subgroup, hence the QALY gain is likely underestimated and the ICER is likely overestimated.

Table 59 Base-case results for cisplatin-eligible patients, with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.44	[redacted]
With severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.72	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 60 Net health benefit of EV+P versus PBC for cisplatin-eligible patients, with and without including 1.2 QALY weights and a confidential PAS of [redacted] for EV

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Without severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.44	[redacted]	[redacted]
With severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.72	[redacted]	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

3.11.2 Subgroup results: Cisplatin-ineligible patients

As expected, total costs as well as QALY gains are slightly lower in the cisplatin-ineligible subgroup compared to the cisplatin-eligible subgroup. EV+P results in a gain of [redacted] QALYs, while gemcitabine + carboplatin is predicted to generate [redacted] QALYs (versus [redacted] QALYs and [redacted] QALYs in the ITT population, respectively). The QALY difference is larger at 1.74 incremental QALYs (versus 1.60 incremental QALYs in the ITT population). As survival with EV+P is based on the ITT OS data, the QALY gain may be an overestimate. However, and as discussed earlier in section 3.3.4.4, ToT may be overestimated as the ToT extrapolations predict a greater proportion of cisplatin-ineligible patients on treatment than the proportion observed in EV-103 and those predicted for the ITT and the cisplatin-eligible groups. These two inputs counteract each other in the ICER calculation and therefore the net impact on the direction of ICER change is difficult to predict. This highlights the higher uncertainty in the ICERs in the subgroups defined by cisplatin eligibility, supporting the use of the ITT population for decision making.

Results for the cisplatin-ineligible population are shown in Table 61 and Table 62.
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Table 61 Base-case results for cisplatin-ineligible patients, with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.74	[redacted]
With severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.09	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 62 Net health benefit of EV+P versus PBC for cisplatin-ineligible patients, with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Without severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.74	[redacted]	[redacted]
With severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	2.09	[redacted]	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

3.12 Benefits not captured in the QALY calculation

The economic model aimed to capture all benefits to patients. However, utility values for the pre-progression health state were estimated for patients based on the EV-302 trial while the majority of patients were still receiving treatment. In EV-103, very few patients continued treatment beyond 3-years, while almost 40% of patients were still progression-free at 5-years (see Section 2.6.8.2). This would indicate a long treatment-free period for a proportion of patients. Based on this observation from EV-103, there may be a proportion of the population who will discontinue EV+P treatment without progression. The full impact of this potential treatment-free period for a proportion of patients was not captured in the QALY calculations.

Scoping consultation responses by the British Uro-Oncology Group, ABC UK and Fight Bladder cancer all drew attention to the burden of u/mUC on patients' families and caregivers. They noted that a more effective 1L treatment could reduce this burden, reducing some of the stress on caregivers and potentially allowing them to resume their professional lives and societal contributions.[55] However, quality of life for caregivers was not assessed, so any such benefits are not captured in the QALY calculation.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

The cost-effectiveness analyses have undergone both conceptual and technical validation. As described in Appendix P, conceptual validation was provided by an advisory board and in depth interviews with seven global clinical experts (three of them from the UK) with experience in treating u/mUC and with the use of EV+P. Additionally, interviews covering administration settings and codes as well as validation of UK-specific resource utilisation and model assumptions were carried out. For more information please see Appendix P.

In addition to conceptual validation, a comprehensive and rigorous quality check was performed once programming was finished using the TECH-VER checklist,[100] an operational checklist for model users and/or reviewers to verify the technical

implementation of health economic decision analytical models and document their verification efforts (see Appendix R). The following steps were undertaken to ensure validity of the model:

- Technical verification and evaluation of internal consistency to ensure there are no structural, calculation, or programming errors:
    - Technical verification was done by a member of the project team not involved in the programming and included checking of formulas, calculations, links between cells (Microsoft Excel), and syntax (VBA).
    - Sensitivity analysis of all parameters and extreme value analysis were performed to determine whether model output was as expected to help identify any remaining errors.
- Internal consistency was evaluated by comparing the model outputs with source data used for the model development.
- External validation was performed by comparing the results of the developed model for the interventions of interest with results obtained from clinical trials as well as with models reported in the literature, wherever available and feasible.
- Validation meetings with clinical and health economic experts were also conducted to validate model structure and assumptions of analysis (details are provided in Appendix P).

Based on the findings, the model was corrected and updated where necessary.

3.14 Interpretation and conclusions of economic evidence

The results of the cost effectiveness analysis of EV+P compared to PBC for the treatment of u/mUC show that EV+P improves health, and specifically quality-adjusted life expectancy, compared to PBC. In the base-case analysis, EV+P was associated with increases in LYs and QALYs of [redacted] and 1.60, respectively. These health gains are large and remarkable, particularly in late stage cancer as it is the case in u/mUC.

The results for costs do not necessarily reflect the costs to the NHS, given that pembrolizumab, and subsequent treatments (atezolizumab and avelumab) are all subject to confidential discounts. Astellas do not know the extent of these discounts, but hope that applying the confidential discount for pembrolizumab (and for the other subsequent treatments) alongside the confidential discount for EV (which is [redacted]%) will result in ICERs which are considered acceptable.

Results of the probabilistic analyses were similar to the deterministic analyses, while the deterministic sensitivity analyses highlighted that the economic results were most sensitive to the proportion of patients receiving avelumab maintenance therapy, the health state utility values, and administration costs. The proportion of patients receiving avelumab maintenance therapy was based on the EV-302 trial, and multiple real-world analyses confirmed that the proportion used aligns with clinical practice in the UK. Moreover, the influence of avelumab uptake on ICER was likely overestimated due to the use of list prices and the fact that only the treatment cost was varied without impacting clinical outcomes. Results remained robust when alternative health state utility values, used in prior technology assessments by NICE (and SMC), were tested in scenario analyses. Components of monitoring and health state costs were validated by UK clinical experts and were based on those used in the economic assessment in TA788.[36]

The parameters that cannot be varied independently, such as the PFS, OS, and ToT shape and scale parameters, which are correlated through the variance/co-variance matrix, were not included in the deterministic sensitivity analyses. While most curves fit the observed data very well, they provided differing estimates of patients without events in the long run. However, the resulting uncertainty was minimized by considering elicitation of expert opinion, a review of external data and consideration of plausible long-term behaviour of hazards. Feedback from the clinical experts highlighted the high degree of tumour response achieved with EV+P. Furthermore, recent results from the EV-103 trial also seem to indicate a sharp decrease in hazards both for PFS and OS, therefore, high PFS and OS rates in the long-term. This evidence, together with other external data sources on comparators and a

careful consideration of expected trends in hazards, was considered in the selection of the extrapolation curves for the base case. The current analysis was informed by the primary analysis of EV-302 with an August 2023 data cut, which had a median follow-up of 17.2 months for both treatment arms combined. A new data cut is expected [redacted], which is likely to reduce uncertainty in the survival estimates. The updated EV-302 data will be evaluated using the same approach described in this evaluation, assessing any change in EV+P PFS and OS hazards and a potential plateauing of the tails as was seen in EV-103, and provided to NICE as soon as the results are available.

EV-302 has demonstrated that EV+P offers important health gains to patients in a population who have historically had poor outcomes. The application of the NICE guidance on the disease severity modifier resulted in an absolute QALY shortfall of 8.33 years and a proportional shortfall of 0.85 for PBC treated patients compared to patients in the general population, further highlighting the unmet need in patients with u/mUC. Therefore, this evaluation warrants a severity modifier corresponding to a QALY weight 1.2.

In the EV-302 trial, EV could be administered for an unlimited number of cycles until a protocol-defined reason for treatment discontinuation occurs, whilst patients could receive pembrolizumab for a maximum of 35 cycles or a protocol-defined reason for treatment discontinuation occurs, whichever was first. In the base case, and as per the trial protocol, a 24-month treatment stopping rule was applied for pembrolizumab while no stopping rule was applied for patients receiving EV. The ToT extrapolation predicts that [redacted]% of patients are on treatment at 3 years and [redacted]% at 5 years. However, in EV-103 dose escalation/cohort A no patients continued treatment beyond 3 years, while almost 40% of patients were still progression-free at 5 years. This would indicate a long treatment-free period for a proportion of patients. Based on this observation from EV-103, treatment costs for EV may be overestimated, as the current extrapolations for ToT predict higher proportions of patients still on treatment in the long-run. Furthermore, the potential benefits of a treatment-free

period could not be fully captured in the utility estimates based on the length of follow-up in the current data cut of the trial.

Treatment with EV+P could offer patients significant health gains compared to chemotherapy based on current results from EV-302. This was already recognised by the clinical community, with recent treatment guideline updates[25,29] recommending the use of EV+P as first-line treatment. The assessment of cost-effectiveness of EV+P is challenging due to there being confidential discounts associated with the other component in the combination treatment as well as for components for the comparator treatment pathway and for subsequent treatments. The cost-effectiveness results reported here use the list prices of pembrolizumab and of subsequent treatments in the care pathway (namely atezolizumab and avelumab). As noted in Section 3.9.1, the costs of EV+P are mostly driven by the costs of pembrolizumab, given its list price ([redacted]% of the drug acquisition costs over the entire treatment course are currently attributed to pembrolizumab). The inclusion of the discount for pembrolizumab should improve estimated cost-effectiveness of EV+P, and support its recommendation for routine care in the NHS.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy: ID6332

Addendum to company evidence submission v2

Redaction adjusted in response to NICE request; content otherwise unchanged

Feb 2025

File name	Version	Contains confidential information	Date
ID6332 New data cut clinical addendum _redacted_28Feb2025	**2**	**Yes**	**28 Feb 2025**

Contents

Tables

Figures

1 Background to addendum

The Company Submission was based on the primary results of the EV-302 study, as published by Powles et al. 2024 (data cut-off 8 August 2023, median follow-up for survival of 17.2 months). As stated in the submission, a further, event-driven data cut was expected later in 4Q 2024, and this is now available.

This data cut represents an exploratory ad hoc analysis performed as part of the FDA post-marketing commitment, and was triggered when the protocol-specified final number of OS events was reached. The data cut-off date was 8 August 2024 (median follow-up 29.1 months). This addendum presents the updated efficacy and safety results.

Kaplan-Meier curves showing comparison of model predictions based on the originally submitted data cut to the efficacy results available from the new data cut are presented in Section 3. Economic modelling results with the new data cut are not yet available.

2 Clinical effectiveness

The PFS and OS benefits of EV+P compared with platinum-based chemotherapy seen in the primary analysis were maintained after the additional 12 months of follow-up. Updated results are presented below.

2.1 Patient disposition

Patient disposition is shown in Table 1.

Table 1. Patient disposition, EV-302

	8 August 2024 data cut-off	
	EV + P (N=442) n (%)	**Chemotherapy (N=444) n (%)**
Subjects who received any amount of study drug	440 (99.5)	433 (97.5)
Subjects on treatment	54 (12.2)	0
Subjects off treatment	[redacted]	[redacted]
Primary reason for treatment discontinuation		
Completed treatment	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Subject decision	[redacted]	[redacted]
Other	[redacted]	[redacted]
Subjects on study	218 (49.3)	131 (29.5)
Subjects off study	224 (50.7)	313 (70.5)
Withdrawal of consent	[redacted]	[redacted]
Loss of follow-up	[redacted]	[redacted]
Death	[redacted]	[redacted]

EV, enfortumab vedotin; P, pembrolizumab

Two *patients randomised to the enfortumab vedotin–pembrolizumab group did not receive treatment because the patient was either randomised by error (an error on Interactive Web Response System) or had icteric cholestasis (grade 3) and severe thrombocytopenia. Eleven patients randomised to the chemotherapy group did not receive treatment because: the patient did not meet creatinine clearance guidelines (1 patient), was randomised by error (1 patient), by physician's decision (1 patient), progressive disease (1 patient), or withdrawal of consent (7 patients). In the chemotherapy group, of the 234 cisplatin-eligible patients, 220 (94.0%) received cisplatin at first cycle, 8 received carboplatin at first cycle, and 6 were never treated. Of the 210 cisplatin-ineligible patients, 205 (97.6%) received carboplatin at first cycle; 5 were never treated.*
Source: Clinical Study Report 2024[1]; Powles 2025[2]

2.2 Duration of treatment

Duration of treatment is shown in Table 2.

Table 2. Duration of treatment, EV-302.

	8 August 2024 data cut-off		
	EV + P (N=440)		
	EV	P	EV or P
Duration of treatment (months)			
Mean (STD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Number of cycles			
Mean (STD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
RDI for EV (%)			
Mean (STD)	[redacted]	-	-
Median	[redacted]	-	-
Min, Max	[redacted]	-	-

EV, enfortumab vedotin; Max, maximum; Min, minimum; P, pembrolizumab; RDI, relative dose intensity; STD, standard deviation.
Source: Clinical Study Report 2024[1]

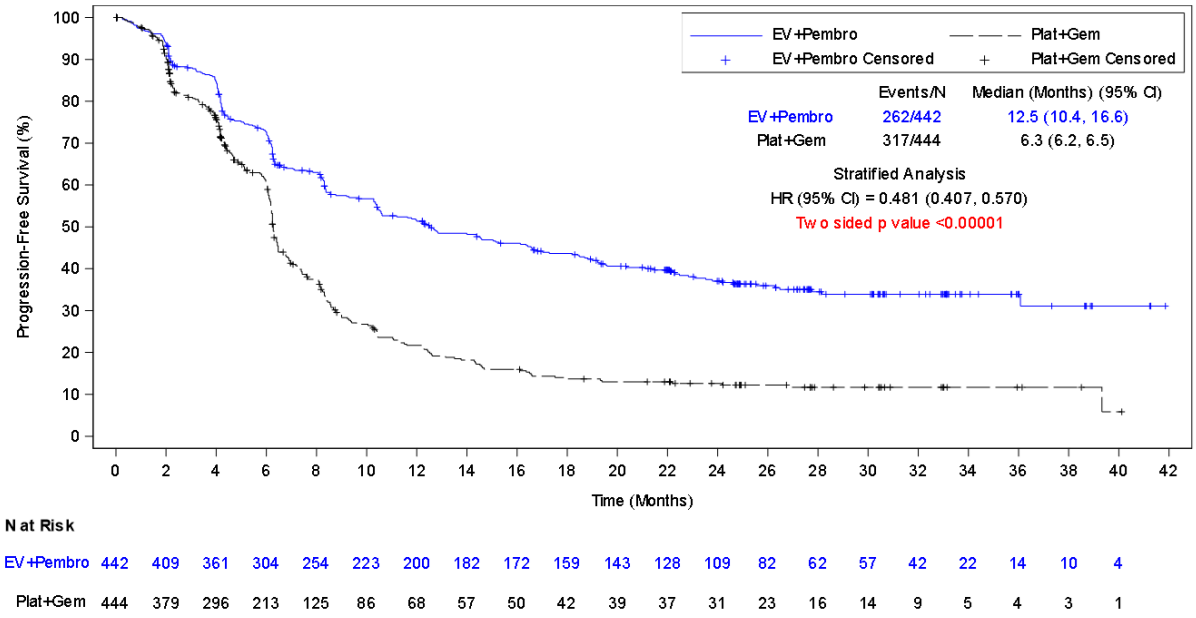
2.3 Progression-free survival by BICR (primary endpoint)

The PFS benefit of EV+P compared with platinum-based chemotherapy was maintained after an additional 12 months of follow-up. Median PFS in the EV+P arm was almost double that in the chemotherapy arm, at 12.5 months (95% CI, 10.4 to 16.6) with EV+P versus 6.3 months (95% CI, 6.2 to 6.5) with chemotherapy (Figure 1, Table 3).[1] Patients in the EV+P arm had a 52% lower risk of disease progression or death compared the chemotherapy arm (HR 0.48; 95% CI, 0.41 to 0.57; P<0.001).

Table 3. Progression-free survival, EV-302.

	8 August 2024 data cut-off	
	EV + P (N=442)	**Chemotherapy (N=444)**
# events (%)	262 (59.3)	317 (71.4)
HR (95% CI)	0.481 (0.407, 0.570)	
p-value (2-sided)	<0.00001	
Median PFS (95% CI), months	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
PFS at		
6 months	72.7%	60.6%
12 months	51.4%	21.7%
18 months	43.7%	13.7%
24 months	37.1%	12.6%

CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival
Source: Clinical Study Report 2024[1]; Powles 2025[2]



CI, confidence interval; EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; Pembro, pembrolizumab; Plat, platinum chemotherapy
Dashed lines indicate PFS at 12 and 18 months. Tick marks indicate censored data.
Source: Clinical Study Report 2024[1]; Powles 2025[2]

Figure 1. Kaplan-Meier estimate of PFS in the EV-302 trial (ITT population) (data cut-off: 8 August 2024).

2.4 Overall survival (primary endpoint)

The benefit of EV+P compared with platinum-based chemotherapy was maintained after an additional 12 months of follow-up. Median OS in the EV+P arm was almost twice as long in the EV+P arm as in the chemotherapy arm, at 33.8 months (95% CI, 26.1 to 39.3) versus 15.9 months (95% CI, 13.6 to 18.3) (Figure 2, Table 4).[1] The risk of death was 49% lower in the EV+P arm than in the chemotherapy arm (HR 0.51; 95% CI, 0.43 to 0.61; P<0.001).

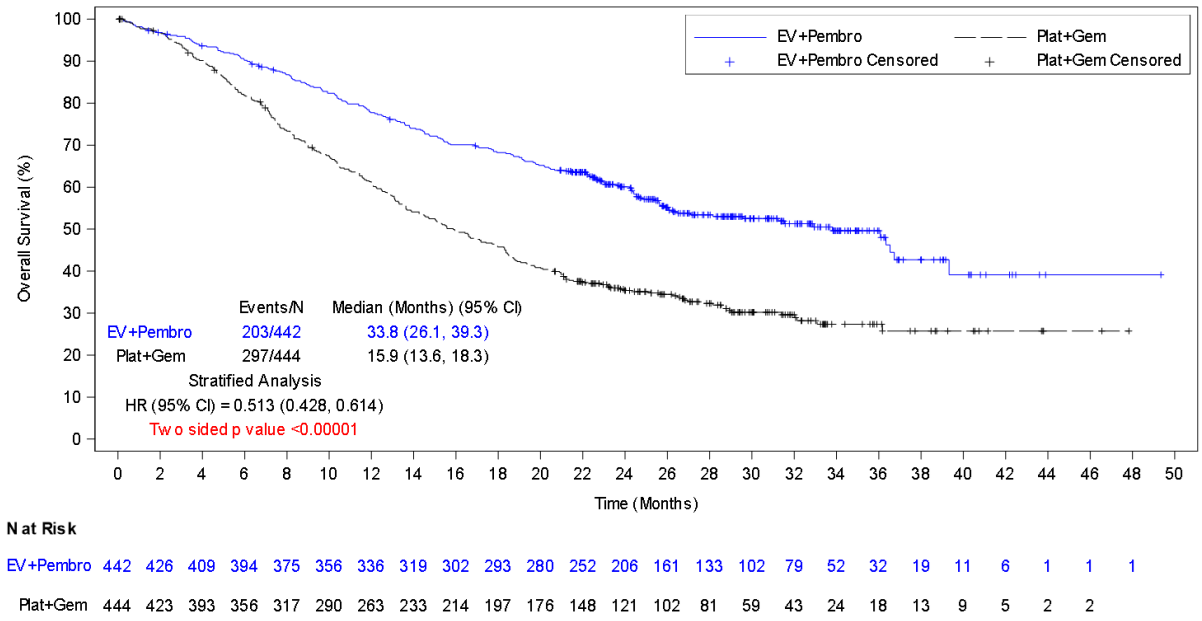
Estimated survival at 24 months was 60.1% [redacted]) in the EV+P arm and 35.4% [redacted]) in the chemotherapy arm.

The OS results were consistent between the ITT population and all pre-specified subgroups (see Section 2.9).

Table 4. Overall survival, EV-302.

	8 August 2024 data cut-off	
	EV + P (N=442)	**Chemotherapy (N=444)**
# events (%)	203 (45.9)	297 (66.9)
HR (95% CI)	0.513 (0.428, 0.614)	
p-value (2-sided)	<0.00001	
Median OS (95% CI), months	33.8 (26.1, 39.3)	15.9 (13.6, 18.3)
OS at		
6 months	90.2%	81.9%
12 months	77.7%	61.1%
18 months	68.2%	45.7%
24 months	60.1%	35.4%
Median f/u (range), months		29.1 (0.07, 49.35)

CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; OS, overall survival; Pembro, pembrolizumab
Source: Clinical Study Report 2024[1]; Powles 2025[2]



CI, confidence interval; EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; Pembro, pembrolizumab; Plat, platinum chemotherapy.
Dashed lines indicate OS at 12 and 18 months. Tick marks indicate censored data.
Source: Clinical Study Report 2024[1]; Powles 2025[2]

Figure 2. Kaplan-Meier estimate of OS in the EV-302 trial (ITT population) (data cut-off: 8 August 2024).

2.5 Overall response rate and duration of response

The confirmed overall response rate (ORR) was consistent with results at the primary analysis. ORR was significantly higher with EV+P than with chemotherapy (ORR 67.5% [95% CI, 62.9 to 71.9] vs. 44.2% [95% CI, 39.5 to 49.9]; P<0.001).[1] The rate of complete response was also higher with EV+P at 30.4% (133 of 437) vs. 14.5% (64 of 441) with chemotherapy.

Median duration of response was 23.3 months in the EV+P arm, compared with 7.0 months in the chemotherapy arm.[1] The percentage of patients still in response at 24 months was 49.4% in the EV+P arm and 24.0% in the chemotherapy arm. Response outcomes are summarised in Table 5.

Table 5. Overall response and duration of response in the EV-302 trial

	8 August 2024 data cut-off	
	EV+P (N=437)	**Chemotherapy (N=441)**
Confirmed best overall response, n (%)		
Complete response	133 (30.4)	64 (14.5)
Partial response	162 (37.1)	131 (29.7)
Stable disease	83 (19.0)	149 (33.8)
Progressive disease	[redacted]	[redacted]
Could not be evaluated†	[redacted]	[redacted]
No assessment‡	[redacted]	[redacted]
Confirmed overall response (95% CI), %§	67.5 (62.9–71.9)	44.2 (39.5–49.0)
Median time to response (range), months	[redacted]	[redacted]
Median duration of response (95% CI), months	[redacted]	[redacted]

CI, confidence interval; NE, not evaluated
**Overall response and duration of response, as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were evaluated in all the patients in the intention to-treat population who had measurable disease at baseline according to RECIST, version 1.1. NE denotes could not be estimated. † Patients had a postbaseline assessment of response, but the best overall response could not be evaluated according to RECIST, version 1.1. ‡ Patients had no postbaseline assessment of response. § P<0.001.*
Source: Clinical Study Report 2024[1]; Powles 2025[2]

2.6 Time to pain progression and worst pain

The median time to pain progression was longer in the EV+P group than the chemotherapy group ([redacted] months [redacted] vs. [redacted] months [redacted]).[1] However, the between-group difference in the time to pain progression was not significant (HR [redacted]).

2.7 Health-related quality of life (HRQoL)

EORTC QLQ-C30

Both completion rates (defined as the proportion of subjects who completed at least one question of the instrument among the ITT analysis set) and compliance rates (the proportion of subjects who completed at least one question of the instrument

among those expected to complete at each visit) were consistently higher in the EV+P arm from approximately Week 8 onwards (see 2024 CSR Figures 12.3.8.2 and 12.3.8.3).[1] The mean change from baseline in EORTC QLQ-30 over the extended follow-up period followed as similar pattern as in the original data cut (see 2024 CSR Figure 12.3.8.3).

Results should be interpreted with caution because the compliance rate is lower in the chemotherapy arm compared to the EV+P arm from week 6. This means that the proportion of patients who filled in at least one question of the instrument among those expected to complete it at each visit and the scheduled visit occurred is lower in the chemotherapy arm than in the EV+P arm. If patients who did not complete the questionnaire experience worse HRQoL (e.g., due to progression), the observed HRQoL by trial arm may not be representative of the HRQoL experienced by all patients in the trial arm. If this is the case, the lower the compliance rate, the larger the difference between the observed HRQoL and the experienced ('true') HRQoL. As compliance rate is lower in the chemotherapy arm than in the EV+P arm, the trial arms are disproportionally affected, and the observed HRQoL in the chemotherapy arm may be more overestimated compared to the experienced HRQoL than in the EV+P arm.

EQ-5D-5L

As for EORTC-QLQ C30, completion and compliance rates were consistently higher in the EV+P arm from approximately week 8. As with EORTC QLQ-C30 results, the observed EQ-5D-5L VAS score should be interpreted with caution as the HRQoL reported by patients who completed the questionnaires may not be representative of patients who did not, and this is likely to affect the chemotherapy arm to greater extent than the EV+P arm. There were numerical differences in EQ-5D VAS over time between the trial arms, however the 95% confidence intervals overlapped (see 2024 CSR Figure 12.3.9.3).

2.8 Subsequent treatments

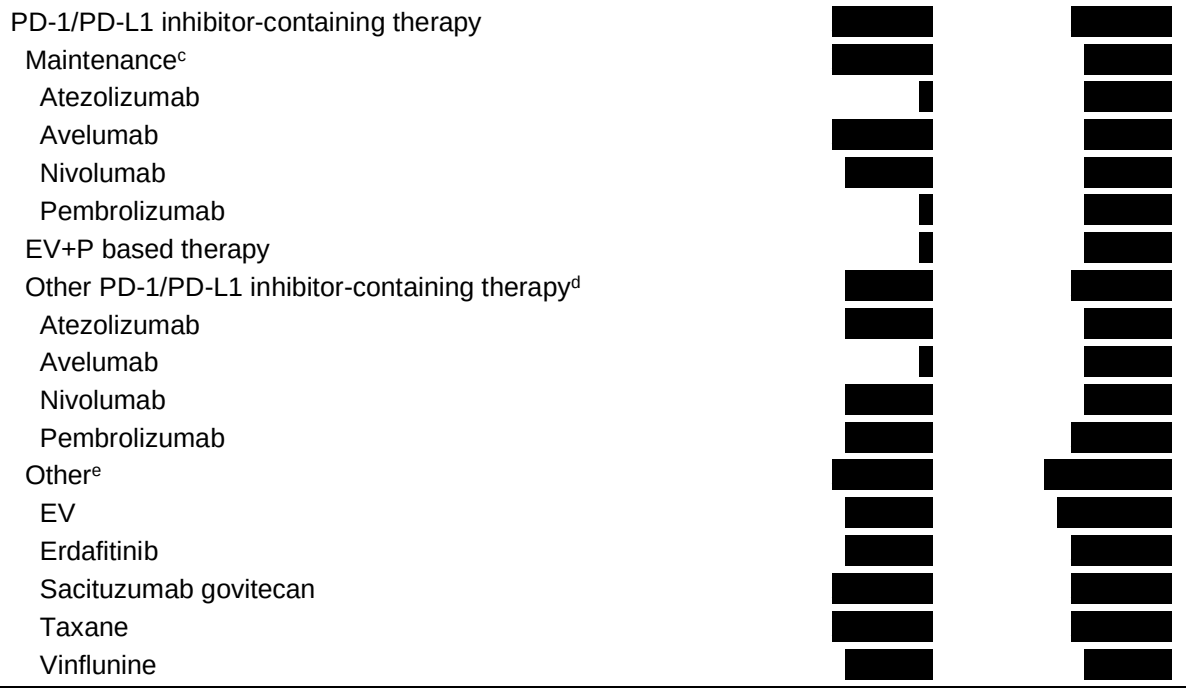
As of the data cut-off, 12.2% (54 of 442) of the patients in the EV+P arm and none in the chemotherapy arm were still receiving treatment. A total of [redacted]% [redacted] of patients in the EV+P arm and [redacted]% [redacted] in the chemotherapy arm received subsequent anticancer therapies. A summary of subsequent anti-cancer therapy is displayed in Table 6.

Some patients had subsequent anti-cancer therapies which are not recommended by NICE, and this was more frequent in the chemotherapy arm. The most frequently used anti-cancer therapies not recommended by NICE were:

- EV monotherapy, by [redacted]([redacted]%) patients in the chemotherapy arm as second and beyond subsequent therapy (the use of EV monotherapy in the EV+P arm and in first subsequent therapy was negligible).
- Pembrolizumab monotherapy, by [redacted]([redacted]%) patients in the chemotherapy arm as first subsequent therapy (its use in the EV+P arm and as second subsequent therapy was minor).

Table 6. Summary of subsequent cancer-related therapy

	8 August 2024 data cut-off	
	EV+P (N=442) n(%)	Chemotherapy (N=444) n(%)
Patients who received subsequent anticancer therapies	[redacted]	[redacted]
Palliative radiotherapy	[redacted]	[redacted]
Non-palliative radiotherapy	[redacted]	[redacted]
Systemic therapy	[redacted]	[redacted]
For progressive disease	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Other	[redacted]	[redacted]
For secondary malignancy	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]
Surgical procedure	[redacted]	[redacted]
Number of lines of subsequent systemic anticancer therapy		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
First subsequent systemic therapy		
Platinum-based therapy[b]	[redacted]	[redacted]
Cisplatin-based regimen	[redacted]	[redacted]
Carboplatin-based regimen	[redacted]	[redacted]
Other	[redacted]	[redacted]
PD-1/PD-L1 inhibitor-containing therapy	[redacted]	[redacted]
Maintenance[c]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
EV+P based therapy	[redacted]	[redacted]
Other PD-1/PD-L1 inhibitor-containing therapy[d]		
Avelumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Other[e]	[redacted]	[redacted]
Second and beyond subsequent systemic therapy	[redacted]	[redacted]
Platinum-based therapy[b]		
Cisplatin-based regimen	[redacted]	[redacted]
Carboplatin-based regimen	[redacted]	[redacted]

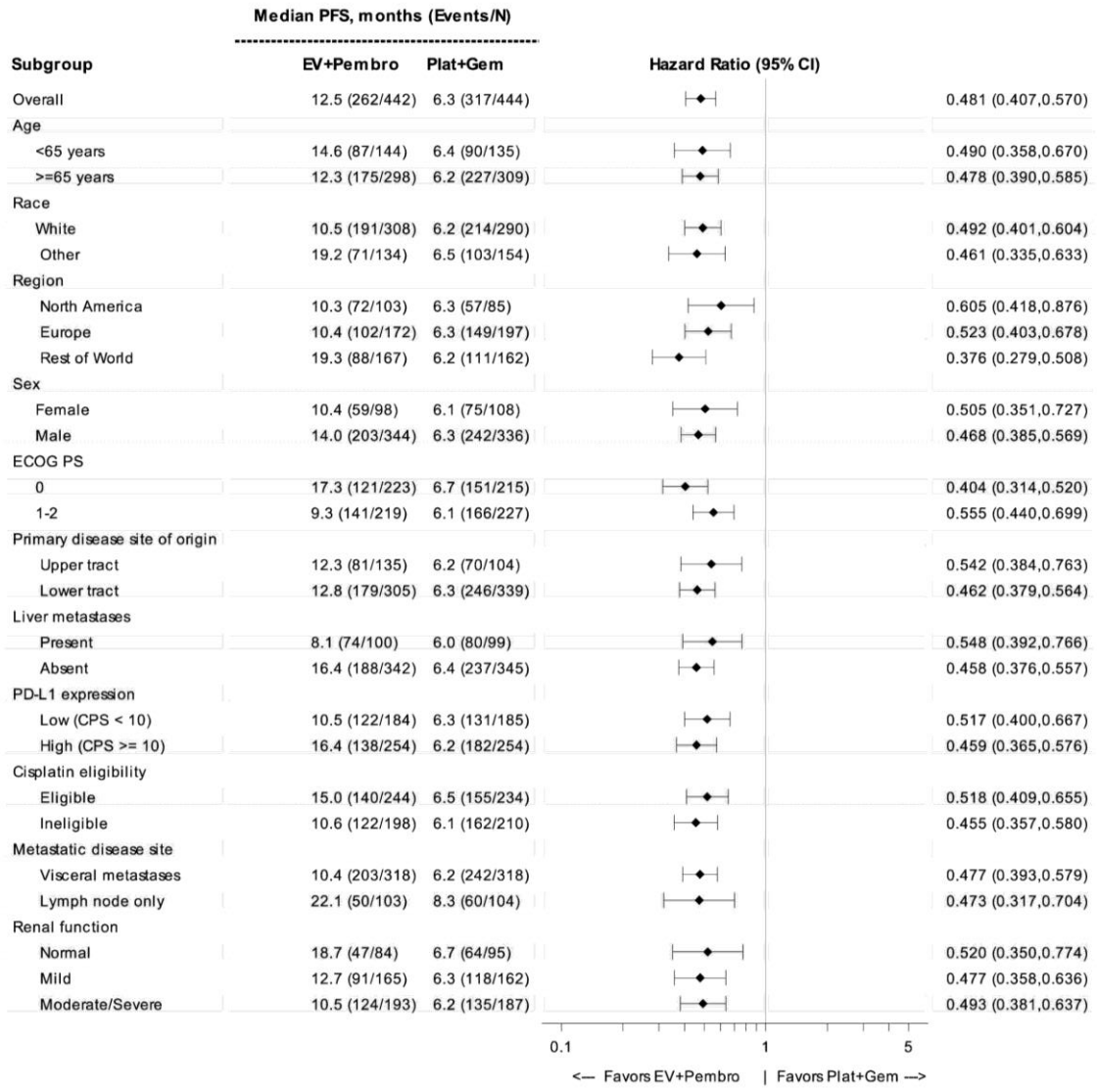


PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
a. Includes systemic therapies other than for progressive disease, maintenance, or secondary malignancy, that were received after discontinuation of study treatment.
b. When platinum-based therapy and a PD-1/L1 agent were given in the same line of therapy, the therapy was categorized under platinum-based therapy.
c. Subjects can receive more than one PD-1/L1 agent in the same line of therapy.
d. Additional experimental PD-1/L1 agents were not listed.
e. Select agents of interests were listed. Includes EV, erdafitinib, sacituzumab vedotin, taxane and vinflunine; each were received by <1% of patients in each group as 1st subsequent therapy

Source: Clinical Study Report 2024[1]

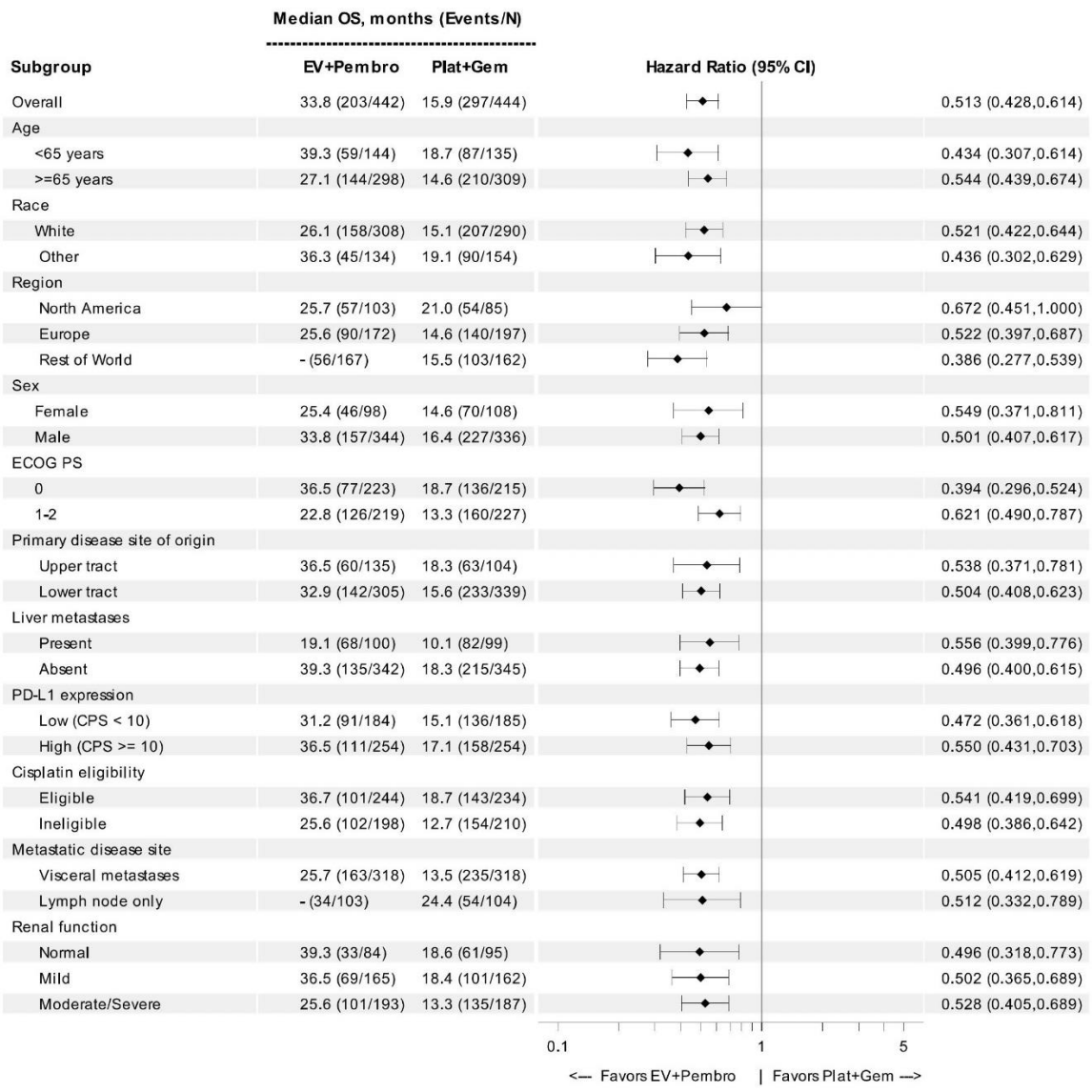
2.9 Subgroup analysis

Subgroup analyses were conducted for progression-free survival (Figure 3), overall survival (Figure 4), and overall response (Figure 5). In all three analyses, the benefit of EV+P was consistent between the ITT population and all predefined subgroups, including cisplatin eligibility and PD-L1 expression status.



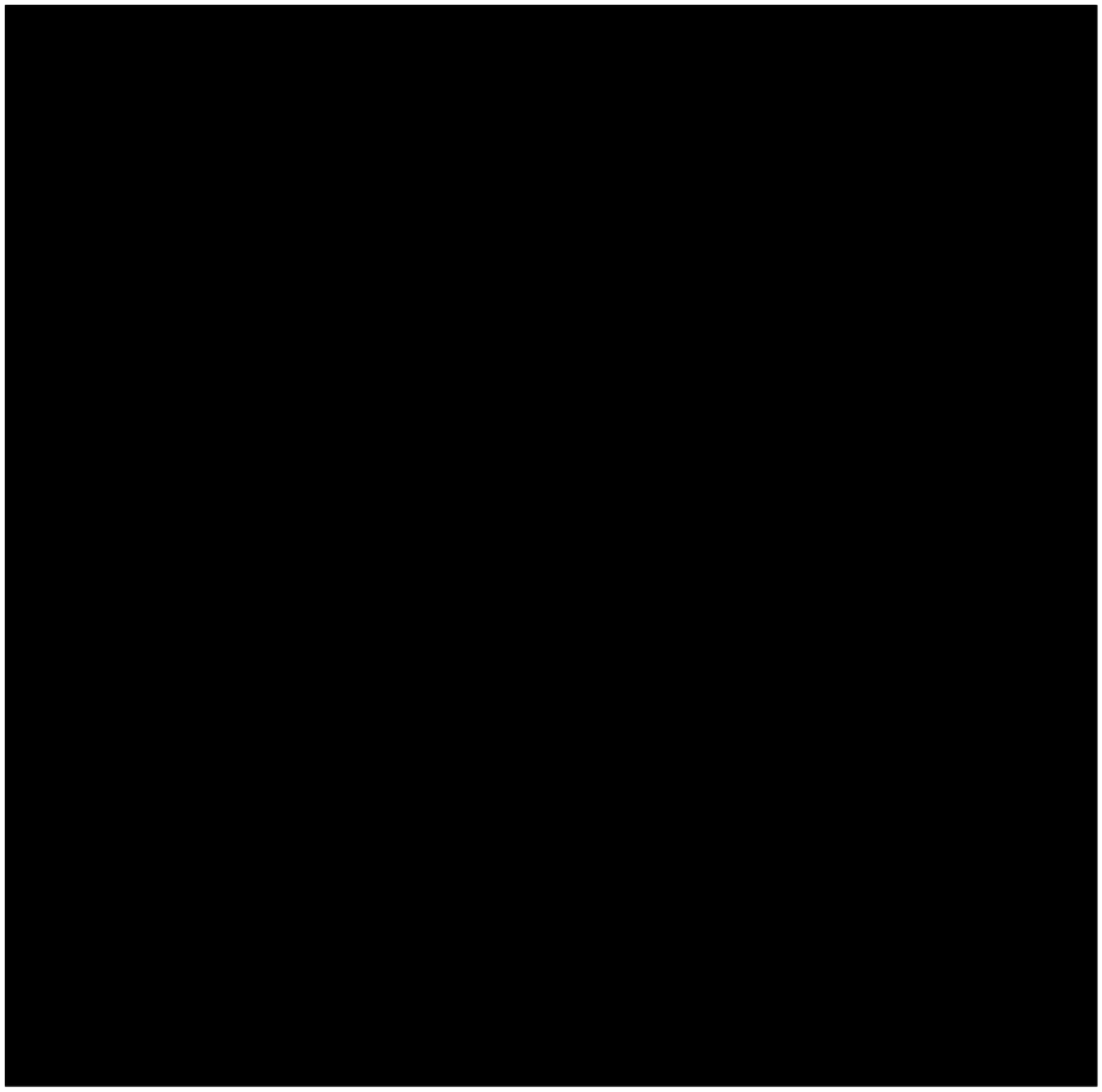
CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.
The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1) staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.
Source: Clinical Study Report 2024[1]; Powles 2025[2]

Figure 3. Forest plot of the analyses of progression-free survival in all prespecified subgroups, EV-302 (data cut-off: 8 August 2024).



CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1
The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1) -staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.
Source: Clinical Study Report 2024[1]; Powles 2025[2]

Figure 4. Forest plot of the analyses of overall survival in all prespecified subgroups, EV302 (data cut-off: 8 August 2024).



The combined positive score (CPS) is defined as the total number of programmed death ligand 1 (PD-L1)–staining cells (tumour and immune cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.
CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1
Source: Clinical Study Report 2024[1]

Figure 5. Forest plot of the analyses of overall response in all prespecified subgroups, EV-302 (data cut-off 8 August 2024).

2.10 Adverse reactions

2.10.1 Safety summary

The safety summary from EV-302 is shown in Table 7. The percentages of patients with any treatment-emergent adverse events (TEAE; [redacted]% for EV+P and chemotherapy, respectively), Grade 3-5 TEAE ([redacted]), TEAE leading to death ([redacted]), and fatal events that were considered treatment related by the investigator ([redacted]), were similar between treatment arms. This was despite a longer duration of treatment in the EV+P group. Exposure-adjusted event rates were lower in the EV+P arm than in the chemotherapy arm in all categories shown.

Treatment-related AEs resulting in dose reduction of any study drugs occurred in [redacted]% of patients in the EV+P group and [redacted]% in the chemotherapy group, and treatment-related AEs resulting in discontinuation of any treatment occurred in [redacted]% and [redacted]%, respectively. In the EV+P group, treatment-related adverse events led to the discontinuation of EV in [redacted]% of patients and to discontinuation of pembrolizumab in [redacted]%.[1]

Treatment-related adverse events that resulted in death occurred in [redacted] patients ([redacted]%) in the EV+P arm and in [redacted] patients [redacted]%) in the chemotherapy arm. In the EV+P group these were multiple organ dysfunction syndrome, immune-mediated lung disease, diarrhoea, pneumonitis, and asthenia ([redacted] each), and in the chemotherapy group they were sepsis, febrile neutropenia, neutropenic sepsis, and myocardial infarction ([redacted] each).[1]

Table 7. Safety summary of the pivotal study (EV-302).

	8 August 2024 data cut-off			
Adverse event	**Patient incidence rate**		**Event rate adjusted for exposure**	
	EV+P (N=440) N (%)	**Chemotherapy (N=433) N (%)**	**EV+P (PY=[redacted]) Events (Events/PY)**	**Chemotherapy (PY=[redacted]) Events (Events/PY)**
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs leading to treatment discontinuation				
Enfortumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Any study drug	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs leading to dose interruption				
Enfortumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Any study drug	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs leading to dose reduction of any study drugs	[redacted]	[redacted]	[redacted]	[redacted]

E, events; NA, not applicable; PY, patient-years; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.
Source: Clinical Study Report 2024[1]

2.10.2 Treatment-related AEs and AEs of special interest

The most common treatment-related AEs of any grade in the EV+P group were peripheral sensory neuropathy (in 51.8% of patients), pruritus (in 40.7%), and alopecia (in 33.2%); the most common treatment-related AEs in the chemotherapy group were anaemia (in 56.6%), neutropenia (in 41.6%), and nausea (in 38.8%).[1] Treatment-related AEs occurring in ≥20% of patients in either treatment arm are shown in

Table 8. Adverse events of special interest with EV treatment are shown in Table 9

Table 8. Treatment-related adverse events in study EV-302 occurring in ≥20% of patients in either treatment arm (any grade), or ≥5% in either arm (grade ≥3).

	8 August 2024 data cut-off			
Adverse event	**EV+P (N=440)**		**Chemotherapy (N=433)**	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any adverse event	428 (97.3)	252 (57.3)	[redacted]	[redacted]
Peripheral sensory neuropathy	228 (51.8)	18 (4.1)	[redacted]	[redacted]
Pruritis	179 (40.7)	6 (1.4)	[redacted]	[redacted]
Alopecia	146 (33.2)	2 (0.5)	[redacted]	[redacted]
Maculopapular rash	144 (32.7)	34 (7.7)	[redacted]	[redacted]
Fatigue	131 (29.8)	14 (3.2)	[redacted]	[redacted]
Diarrhea	123 (28.0)	17 (3.9)	[redacted]	[redacted]
Decreased appetite	119 (27.0)	5 (1.1)	[redacted]	[redacted]
Nausea	93 (21.1)	5 (1.1)	[redacted]	[redacted]
Anemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]

EV, enfortumab vedotin; P, pembrolizumab
Source: Clinical Study Report 2024[1]; Powles 2025[2]

Table 9. Enfortumab vedotin adverse events of special interest, EV-302.

Adverse event	8 August 2024 data cut-off			
	EV + P (N=440)		Chemotherapy (N=433)	
	All Grade n (%)	≥ Gr 3 n (%)	All Grade n (%)	≥ Gr 3 n (%)
Peripheral Neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Skin reactions	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
SCAR	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycemia	[redacted]	[redacted]	[redacted]	[redacted]
Ocular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]
Corneal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reactions	[redacted]	[redacted]	[redacted]	[redacted]

EV, enfortumab vedotin; P, pembrolizumab; SCAR, severe cutaneous adverse reaction.
Source: Clinical Study Report 2024[1]

3 Comparison of model predictions based on the originally submitted data cut to the efficacy results available from the new exploratory data cut (DCO2).

The extrapolations included in the economic model aligned well with the observations from the new exploratory data cut. The only two instances where there may be a slight difference are the OS predictions for the chemotherapy arm and the time on treatment (ToT) predictions for EV. To understand the impact on the ICER, the model inputs based on the EV-302 trial data will be re-estimated using DCO2, and an updated cost-effectiveness model and addendum with updated model inputs and results are planned to be submitted to NICE on 29 November.

Dotted line refers to 8 Aug 2023 data cut (DC01), and the curves of the extrapolations refer to the base-case extrapolations using the same data cut. DCO2, data cut-off 2; EV, enfortumab vedotin; KM, Kaplan Meier; P, pembrolizumab; PBC, platinum-based chemotherapy; SOC, standard of care.

Figure 6. Comparison of PFS Kaplan Meier curves from the original and new data cut to model predictions.

Dotted line refers to 8 Aug 2023 data cut (DC01), and the curves of the extrapolations refer to the base-case extrapolations using the same data cut. DCO2, data cut-off 2; EV, enfortumab vedotin; KM, Kaplan Meier; P, pembrolizumab; PBC, platinum-based chemotherapy; SOC, standard of care.

Figure 7. Comparison of OS Kaplan Meier curves from the original and new data cut to model predictions.

Dotted line refers to 8 Aug 2023 data cut (DC01), and the curves of the extrapolations refer to the base-case extrapolations using the same data cut. DCO2, data cut-off 2; EV, enfortumab vedotin; KM, Kaplan Meier; PBC, platinum-based chemotherapy.

Figure 8. Comparison of ToT Kaplan Meier curves from the original and new data cut to model predictions.

4 References

1. Astellas Pharma Global Development Inc. 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: Clinical Study Report (data cut-off 8 August 2024), (2024).

2. Powles T., et al. EV-302: Updated analysis from the phase 3 global study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC). ASCO Genitourinary Cancers Symposium, February 26-28, San Francisco, CA

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy: ID6332

Economic addendum to company evidence submission v3

Redaction adjusted in response to NICE request; content otherwise unchanged

Mar 2025

File name	Version	Contains confidential information	Date
ID6332 New data cut economic addendum redacted_5Mar2025	**3**	**Yes**	**5 Mar 2025**

Contents

Tables

Figures

1 Background to addendum

The Company Submission was based on the primary results of the EV-302 study, as published by Powles et al. 2024 (data cut-off 8 August 2023, median follow-up for survival of 17.2 months).[1] As stated in the submission, a further, event-driven data cut was expected later in 4Q 2024, and this is now available.

This data cut represents an exploratory ad hoc analysis performed as part of the FDA post-marketing commitment, and was triggered when the protocol-specified final number of OS events was reached. The data cut-off date was 8 August 2024 (median follow-up 29.1 months).[2] This addendum presents the updated inputs and results of the cost effectiveness analysis with the new data cut. As part of the update with this data cut, addendums to the following appendices to the original submission are also presented: updated Appendix J with the disaggregated cost-effectiveness results, updated Appendix M with the results of the parametric survival modelling, updated Appendix N with the results of the spline-based survival modelling, and updated Appendix O with the results of the utility analysis.

2 Clinical parameters and variables

As discussed in section 2.7 of the company submission, trial results were consistent across the subgroups and similar to the ITT population, and this consistency was maintained in the new data cut. Consistent with the original submission, clinical parameters are presented separately for the entire eligible population (i.e., ITT of EV-302 trial), as well as the cisplatin-eligible and the cisplatin-ineligible subgroups.

2.1 Turning points and data maturity

As outlined in section 3.3.1.4 of the company submission, turning points in the observed hazard rates and potential for future turning points were considered. Figure 1 to Figure 4 show the observed hazard rates for PFS and OS in the EV+P and PBC arm of EV-302 (new data cut) overlaid with the estimated hazard rates from the standard parametric models, while the same graphs for the cisplatin-eligible and cisplatin-ineligible subgroups are provided in updated Appendix M.

Figure 1 Progression-free survival hazards, EV+P ITT population
Abbreviations: AIC, Akaike's information criterion.

Figure 2 Progression-free survival hazards, PBC ITT population
Abbreviations: AIC, Akaike's information criterion.

Figure 3 Overall survival hazards, EV+P ITT population
Abbreviations: AIC, Akaike's information criterion.

Figure 4 Overall survival hazards, PBC ITT population
Abbreviations: AIC, Akaike's information criterion.

All hazard graphs continue to show a downturned U shape. Hazards tend to increase until 6-12 months for PFS and until 12-18 months for OS, after which hazards decrease. This trend in hazards indicates that similarly to the first data cut, survival functions with non-monotonous hazards capable of capturing increasing then decreasing hazards should be preferred.

2.2 Overall survival

2.2.1 ITT population

Extrapolations of standard parametric fits for the new data cut are shown in Figure 5 and Figure 6.

Abbreviations: AIC, Akaike's information criterion.

Figure 5 Overall survival extrapolations, EV+P ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 6 Overall survival extrapolations, PBC ITT population

All extrapolations have similar statistical fits to the observed data, however, they predict very different survival proportions at 4 years and beyond. As such:

1. For the PBC arm, only the log-logistic, lognormal and generalized gamma curves matched the required trends in hazards, while these and the exponential and Gompertz curve also predicted a higher than 0% survival at 10-years, as predicted by the clinicians for the PBC arm (see CS Appendix P for clinical validation).
2. For the EV+P arm, the log-logistic curve provided the closest estimate to the clinicians' expectations. The exponential and lognormal curves provided slightly more pessimistic and optimistic estimates, respectively, while still falling within the range of predictions from the clinicians. Given the observed OS rate in EV-103 at 5-years was 41.5% and the external evidence on how the OS rates are likely to change over time (see section 3.3.1.1 of the company submission), all extrapolations for EV+P are likely to be very conservative choices, i.e. they are likely to underestimate OS for EV+P in the long-term.
3. As such, to extrapolate the OS based on the data from cut-off date of 8 August 2024, the log-logistic curves were selected for both arms in the base case, with lognormal and exponential tested in scenario analyses – this is consistent with the parametric survival models selected for the base-case and scenarios in the original submission (which used the data cut from 8 August 2023).

Table 1 Survival model selection for OS, EV+P ITT population

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 EV+P KM			60%	--	--
EV-103 Cohort K, EV+P (cisplatin-ineligible)			53.5%	--	--
EV-103 Cohort Dose esc/A, EV+P (cisplatin-ineligible)			56.4%	41.5%	
TA788, avelumab maintenance, 8 UK oncologists			--	20-30%	10-15%
Astellas clinical validation, EV+P, 7 clinicians (mean, range)			58% (50-60%)	32% (20-45%)	16% (5-35%)
Exponential	***1971.25***	***1975.34***	***60%***	***28%***	***8%***
Weibull	1970.97	1979.15	60%	25%	5%
Gompertz	1972.67	1980.85	60%	25%	3%
Gamma	1970.66	1978.84	60%	25%	6%
Log-normal	***1978.52***	***1986.70***	***60%***	***35%***	***19%***
Log-logistic	**1969.96**	**1978.14**	**60%**	**31%**	**16%**
Generalised gamma	1972.23	1984.50	60%	28%	8%

Notes: TA788 included a selected patient population at a subsequent point of the care pathway (those not-progressing after PBC), and OS at 2-years was reported to be 49.8%.[3] Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

Table 2 Survival model selection for OS, PBC ITT population

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 PBC KM			36%	--	--
TA788, BSC, 8 UK oncologist			--	5-15%	2-7%
Astellas clinical validation, PBC, 7 clinicians (mean, range)			35% (30-45%)	11% (5-20%)	6% (0-10%)
Exponential	***2508.00***	***2512.09***	***38%***	***9%***	***1%***
Weibull	2505.09	2513.28	38%	7%	0%
Gompertz	2509.76	2517.95	38%	10%	2%
Gamma	2501.71	2509.91	38%	7%	0%
Log-normal	***2491.22***	***2499.41***	***38%***	***14%***	***5%***
Log-logistic	**2484.83**	**2493.02**	**36%**	**13%**	**5%**
Generalised gamma	2491.04	2503.33	37%	12%	3%

Notes: TA788 included a selected patient population (those not-progressing after PBC). Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BSC, best supportive care; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

2.2.2 Cisplatin-eligible population

With the longer follow-up data available, the subgroup-specific extrapolations aligned with clinicians' expectations around the relative outcomes between the cisplatin-eligible and cisplatin-ineligible population, therefore for this update the subgroup-specific data has been used.

In this subgroup, the Weibull, Gompertz and gamma curves could be ruled out as valid options due to trends in hazards not matching observations in the EV-302 trial and, consequently, long-term extrapolations not aligning with clinical expectations. Lognormal curves had the best fit statistically. For PBC and EV+P therefore, the lognormal curve was selected for the base case, with log-logistic and generalised gamma tested in scenario analyses.

Table 3 Survival model selection for OS, EV+P cisplatin-eligible population

Model	**AIC**	**BIC**	**Time point**		
			2 years	**5 years**	**10 years**
EV-302 EV+P KM			64%	--	--
TA788, avelumab maintenance[a], 8 UK oncologist			--	20-30%	10-15%
Astellas clinical validation, EV+P[a], 7 clinicians (mean, range)			58% (50-60%)	32% (20-45%)	16% (5-35%)
Exponential	1013.45	1016.94	[redacted]	[redacted]	[redacted]
Weibull	1011.17	1018.17	[redacted]	[redacted]	[redacted]
Gompertz	1014.77	1021.76	[redacted]	[redacted]	[redacted]
Gamma	1010.11	1017.10	[redacted]	[redacted]	[redacted]
Log-normal	**1005.61**	**1012.61**	[redacted]	[redacted]	[redacted]
Log-logistic	***1007.98***	***1014.98***	[redacted]	[redacted]	[redacted]
Generalised gamma	***1007.57***	***1018.06***	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the lower limit for the cisplatin-eligible population

Notes: TA788 included a selected patient population (those not-progressing after PBC), and OS at 2-years was reported to be 49.8%.[3] Base case selection is in bold, options tested in scenario analyses are in bold italics.

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

Table 4 Survival model selection for OS, PBC cisplatin-eligible

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 gemcitabine + cisplatin KM			42%	--	--
TA788, BSC[a], 8 UK oncologist			--	5-15%	2-7%
Astellas clinical validation, PBC[a], 7 clinicians (mean, range)			35% (30-45%)	11% (5-20%)	6% (0-10%)
Exponential	930.65	934.10	[redacted]	[redacted]	[redacted]
Weibull	922.11	929.02	[redacted]	[redacted]	[redacted]
Gompertz	929.54	936.45	[redacted]	[redacted]	[redacted]
Gamma	920.05	926.96	[redacted]	[redacted]	[redacted]
Log-normal	**915.91**	**922.82**	[redacted]	[redacted]	[redacted]
Log-logistic	***917.59***	***924.50***	[redacted]	[redacted]	[redacted]
Generalised gamma	***917.90***	***928.27***	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the lower limit for the cisplatin-eligible population

Notes: TA788 included a selected patient population (those not-progressing after PBC). Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BSC, best supportive care; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

2.2.3 Cisplatin-ineligible population

Similar to the cisplatin eligible subgroup, with the longer follow up data available, the subgroup-specific extrapolations aligned with expectations around the relative outcomes and therefore the subgroup-specific data has been used. The log-logistic curve was selected for the base case, while the exponential and lognormal functions were tested in scenario analyses.

Table 5 Survival model selection for OS, EV+P cisplatin ineligible population

Model	AIC	BIC	Time point		
			2 years	**5 years**	**10 years**
EV-302 EV+P KM			55%	--	--
EV-103 Cohort K, EV+P (cisplatin-ineligible)			53.5%	--	--
EV-103 Cohort Dose esc/A, EV+P (cisplatin-ineligible)			56.4%	41.5%	
TA788, avelumab maintenance[a], 8 UK oncologists			--	20-30%	10-15%
Astellas clinical validation, EV+P[a], 7 clinicians (mean, range)			58% (50-60%)	32% (20-45%)	16% (5-35%)
Exponential	***953.94***	***957.23***	[redacted]	[redacted]	[redacted]
Weibull	955.88	962.45	[redacted]	[redacted]	[redacted]
Gompertz	955.79	962.36	[redacted]	[redacted]	[redacted]
Gamma	955.90	962.48	[redacted]	[redacted]	[redacted]
Log-normal	***964.64***	***971.22***	[redacted]	[redacted]	[redacted]
Log-logistic	**958.16**	**964.74**	[redacted]	[redacted]	[redacted]
Generalised gamma	957.71	967.57	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the upper limit for the cisplatin-ineligible population

Notes: TA788 included a selected patient population (those not-progressing after PBC), and OS at 2-years was reported to be 49.8%.[3] Base case selection is in bold, options tested in scenario analyses are in bold italics.

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

Table 6 Survival model selection for OS, PBC cisplatin-ineligible population

Model	AIC	BIC	Time point		
			2 years	**5 years**	**10 years**
EV-302 gemcitabine + carboplatin KM			28%	--	--
TA788, BSC[a], 8 UK oncologists			--	5-15%	2-7%
Astellas clinical validation, PBC[a], 7 clinicians (mean, range)			35% (30-45%)	11% (5-20%)	6% (0-10%)
Exponential	**1234.64**	**1237.98**	[redacted]	[redacted]	[redacted]
Weibull	1234.52	1241.21	[redacted]	[redacted]	[redacted]
Gompertz	1236.53	1243.22	[redacted]	[redacted]	[redacted]
Gamma	1233.13	1239.82	[redacted]	[redacted]	[redacted]
Log-normal	***1233.48***	***1240.18***	[redacted]	[redacted]	[redacted]
Log-logistic	**1225.48**	**1232.18**	[redacted]	[redacted]	[redacted]
Generalised gamma	1231.28	1241.32	[redacted]	[redacted]	[redacted]

[a] Clinicians' view was elicited over ITT population, their estimates should be considered as the upper limit for the cisplatin-ineligible population
Notes: TA788 included a selected patient population (those not-progressing after PBC). Base case selection is in bold, options tested in scenario analyses are in bold italics. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BSC, best supportive care; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom.

2.3 Progression-free survival

2.3.1 ITT population

The independently fitted standard parametric distributions along with the KM curves are shown for EV+P in

Figure **7** and in Figure 8 for PBC.

As shown in Figure 1 and Figure 2, standard parametric fits did not appropriately capture the inflection in hazards, i.e. the change between initially increasing, but then decreasing hazard pattern, for either treatment arm. Long-term predicted hazards using standard parametric fits overestimate observed hazards. As a result, for PBC, the progression-free survival extrapolations suggest that virtually no patients remain alive and progression-free at 10 years using standard parametric models. However, clinicians indicated that they expect around 5% of patients to still be alive and progression-free with PBC at year 5, and a few patients still alive and progression-free at 10 years (see Appendix P).

Regarding EV+P, clinicians indicated expecting around 20% of patients to be alive and progression-free at 10 years. Therefore, similarly to the first data cut presented in the company submission, spline fittings (piecewise polynomial functions) were used in the base case for PFS instead. Updated Appendix N provides details on the fitting of spline models to PFS.

Abbreviations: AIC, Akaike's information criterion.

Figure 7 Progression-free survival extrapolations, standard fits, EV+P in ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 8 Progression-free survival, standard fits, PBC in ITT population

Figure 9 displays the spline fits for EV+P PFS, as well as the range of estimates obtained for the three UK clinicians participating in the survey. The PFS predictions using the spline fits are better aligned to both the observed data and the clinical expert expectations than the standard parametric fits. The hazards (as shown in Figure 10) also better mirrored the observed trend in hazards from the EV-302 trial compared to the standard fits.

All spline fits aligned with the observed data as well as with clinical expert predictions, therefore the hazard with 2 knots was retained as the base case selection for EV+P.

Abbreviations: AIC, Akaike's information criterion.

Figure 9 Progression-free survival extrapolations, spline fits, EV+P in ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 10 Progression-free survival hazards, spline fits, EV+P in ITT population

For PBC, Figure 11 displays the spline fits alongside the range of estimates obtained for the three UK clinicians participating in the survey, while Figure 12 shows the hazards. The fit of the spline odds with 3 knots had lowest AIC/BIC, therefore this fit was chosen as the base case for PBC.

Abbreviations: AIC, Akaike's information criterion.

Figure 11 Progression-free survival extrapolations, spline fits, PBC in ITT population

Abbreviations: AIC, Akaike's information criterion.

Figure 12 Progression-free survival hazards, spline fits, PBC in ITT population

2.3.2 Cisplatin eligible population

A similar process was applied to select best fits for PFS in the subpopulations. All supporting information and graphs are provided in updated Appendices M and N. The subgroup-specific extrapolations aligned with clinicians' expectations around the relative outcomes between the cisplatin-eligible and cisplatin-ineligible population, therefore the subgroup-specific data was used, selecting the spline using hazards with 1 knot for EV+P and the 3 knots survival model for PBC.

2.3.3 Cisplatin ineligible population

As before, all supporting information and graphs are provided in updated Appendices M and N. The hazards spline with 2 knots was selected for EV+P PFS, while the spline for survival odds with 1 knot was selected for PBC.

2.4 Time on treatment

2.4.1 EV+P in the ITT population

EV and pembrolizumab were modelled separately to more accurately inform treatment costs in the model (refer to section 3.3.4.1 of the company submission for further details).

The independently fitted parametric extrapolations along with the KM are show in Figure 13 for EV and Figure 14 for pembrolizumab (with information on hazards over time included in updated Appendix M).

Please note that in the original model calculations a 24-month treatment stopping rule was applied for pembrolizumab, i.e. pembrolizumab use was not extrapolated further. However, some patients may have missed doses, therefore have reached the maximum allowable number of cycles later than 24 months. With the new data from the 8 August 2024 data cut, the pembrolizumab ToT KM curve is now complete. Therefore, the base case now uses the KM curve for pembrolizumab.

For EV, based on the goodness of fit statistics (Table 7), the log-logistic curve was selected for the base-case. The base-case predicts [redacted]% of patients on EV treatment in year 3, [redacted]% in year 4 and [redacted]% in year 5.

Modelled ToT for EV and pembrolizumab including treatment stopping rules is available in Figure 15.

Figure 13 Time on treatment extrapolations, EV in ITT overall safety population

Abbreviations: AIC, Akaike's information criterion; EV, enfortumab vedotin.

Figure 14 Time on treatment extrapolations, pembrolizumab in ITT overall safety population

Abbreviations: AIC, Akaike's information criterion.

Table 7 Time on treatment, goodness of fit statistics for EV and pembrolizumab

Model	EV		Pembrolizumab	
	AIC	BIC	AIC	BIC
Exponential	2648.35	2652.44	2761.08	2765.17
Weibull	2646.84	2655.02	2761.33	2769.50
Gompertz	2648.64	2656.81	2758.90	2767.07
Gamma	2642.29	2650.46	2761.34	2769.51
Log-normal	2629.67	2637.84	2785.96	2794.13
Log-logistic	***2618.79***	***2626.96***	2790.65	2798.82
Generalised gamma	2626.31	2638.57	2763.33	2775.59

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; EV, enfortumab vedotin.

Figure 15 Modelled time on treatment, EV + P in ITT population

Abbreviations: EV, enfortumab vedotin; KM, Kaplan-Meier; PFS, progression-free survival; ToT, time on treatment.

2.4.2 PBC in the ITT population

Since the KM curve was complete (see Figure 16), given that a maximum of six cycles was allowed, the KM curve was used directly to estimate proportion of patients receiving PBC each week, and fitting to standard parametric survival functions for extrapolation was not required. To align with the EV-302 protocol and

UK treatment guidelines, a treatment stopping rule of 4.14 months (i.e., maximum of six three-week cycles of therapy) was also applied.

As outlined in the company submission, a washout period of [redacted] weeks was applied after the end of gemcitabine + PBC until the start of avelumab maintenance where no costs were applied during this treatment-free interval.

Avelumab maintenance ToT as reported in EV-302 was then extrapolated from the start of maintenance therapy using standard parametric distributions.

Figure 16 ToT KM curve for gemcitabine + PBC

Abbreviations: KM, Kaplan-Meier; PBC, platinum-based chemotherapy.

The extrapolated ToT for avelumab maintenance, from the start of maintenance therapy, is shown in Figure 17 (further information can be found in updated Appendix M). The model selection process for avelumab ToT, including statistical fits and comparison of extrapolations to estimates from other sources is summarised in Table 8. Although the Gompertz curve provided the best statistical fit to the data, with log-normal and log-logistic also providing reasonable fits, these curves were all expected to potentially overestimate ToT for avelumab maintenance. Based on the model selection process, a Weibull curve was selected. It still aligned with TA788[4] in terms of expected long-term duration of avelumab maintenance therapy (predicting [redacted] of patients continuing treatment up to 5 years when clinical experts in TA788 estimated this proportion to be between 4% and 7.5%), but also provided a better statistical fit to the observed data from EV-302 compared to the only other extrapolation choice (gamma) which would have aligned with the clinical experts' expectations.

Figure 17 Time on treatment for avelumab maintenance after PBC in ITT safety population receiving avelumab maintenance

Notes: Time zero represents the start of maintenance therapy. Abbreviations: AIC, Akaike information criterion; PBC, platinum-based chemotherapy.

Table 8 Survival model selection for ToT avelumab maintenance for patients in PBC arm receiving avelumab

Model	**AIC**	**BIC**	**Timepoint**			
			6 months	**1 year**	**2 years**	**5 years**
EV-302 avelumab ToT KM			46%	38%	28%	--
TA788, avelumab maintenance ToT			--	--	--	4.0-7.5%
Exponential	642.67	645.57	65%	43%	18%	1%
Weibull	***605.55***	***611.36***	***56%***	***41%***	***26%***	***10%***
Gompertz	587.68	593.49	48%	36%	31%	30%
Gamma	612.32	618.13	58%	43%	26%	7%
Log-normal	593.07	598.88	53%	40%	28%	15%
Log-logistic	593.89	599.70	52%	38%	26%	14%
Generalised gamma	594.47	603.19	52%	40%	29%	17%

Notes: Selected curve for base case is shown in bold. Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; TA, technology appraisal; ToT, time on treatment; UK, United Kingdom.

2.4.3 Cisplatin-eligible population

Following the same process as above for ITT, but considering the subgroup-specific data only (see updated Appendix M for detailed information), the lognormal function was chosen for EV and KM curve for pembrolizumab's ToT, and, similarly to ITT, the Weibull remained the function of choice for avelumab maintenance.

2.4.4 Cisplatin-ineligible population

Based on consideration of statistical fits to the subgroup-specific ToT information as well as the slightly worse prognosis of cisplatin-ineligible patients (i.e. patients remaining on treatment are also expected to be below those predicted for the ITT and cisplatin-eligible populations), the lognormal function was chosen for ToT with EV and the KM curve for ToT with pembrolizumab. Similarly to ITT, the Weibull remained the function of choice for avelumab maintenance. All supporting information is presented in updated Appendix M.

3 Measurement and valuation of health effects

3.1 Adverse reactions

AE rates (grade ≥3 overall and grade ≥2 for peripheral neuropathy) for the ITT population are reported in Table 9. In the new data cut diarrhoea also met the inclusion criteria for AEs, therefore was included in the calculations as an additional treatment-emergent AE in both treatment arms.

Table 9 Treatment-emergent AEs included in the model (ITT population)

Adverse Events*	EV+P	PBC
Acute kidney injury	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Peripheral neuropathy (grade 2)	[redacted]	[redacted]
Peripheral neuropathy (grade 3+)	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]

Abbreviations: AE, adverse event; ITT, intention-to-treat; PBC, platinum-based chemotherapy.

AE utility decrements were applied in the base case, and Table 10 presents the values used for the calculation of the disutility associated with the newly included AE of diarrhoea.

Table 10 AE utility decrement for diarrhoea

Adverse events	Decrement	Duration (days)	QALY decrement	Source
Diarrhoea	0.047	3.42	0.0004	Decrement: Nafees et al. 2008/based on assumptions from TA772[5], duration: TA858[6]

Abbreviations: QALY, quality-adjusted life-year

3.2 Health-related quality-of-life data used in the cost-effectiveness analysis

The same approach to estimating utilities used in the original submission with the first data cut was repeated with this new data cut. Table 11 shows the results (further details in addendum to Appendix O). As per the original submission, the base-case uses treatment-dependent utilities in the pre-progression state, while the scenario analysis tests using treatment-independent utilities for the pre-progression health state and using utilities of the entire (ITT) population in the subgroup analyses.

Table 11 EV-302 health state utility values

Population		ITT	Cisplatin-eligible	Cisplatin-ineligible
Health state	**Treatment**	**Mean (SE)**		
Pre-progression	EV+P	[redacted]	[redacted]	[redacted]
	PBC	[redacted]	[redacted]	[redacted]
	Treatment-independent	[redacted]	[redacted]	[redacted]
Post-progression	Treatment-independent	[redacted]	[redacted]	[redacted]

4 Cost and healthcare resource use identification, measurement and valuation

4.1 Intervention and comparators' costs and resource use

4.1.1 Drug acquisition costs

Relative dose intensity (RDI) was taken into account for each treatment based on RDIs observed in the EV-302 trial. New information was available for EV and P from the new data cut.

Dose reductions for EV are allowed in order to manage tolerability according to individual patient needs. In EV-302, [redacted]% of patients on EV+P had treatment-related AEs leading to dose reductions of any study drug (Clinical addendum Table 7). Dose typically remains at the lower level after adjustment. Dose interruptions were also common in EV-302: [redacted]% of patients had a treatment-related AE leading to dose interruption of EV.

The new data cut provided information on the RDI of EV over time as reported in Table 12. This new information has also been incorporated into the economic model assuming the last observed RDI stays constant for the remaining time patients are on treatment, while using the original assumption of a constant RDI was tested in a

scenario analysis (see Table 13). Including RDI of EV over time in the model reflects the pattern of dose intensity more accurately than using the average RDI over the entire follow-up, hence it informs the base-case. A scenario uses the previous approach of using the average RDI over the entire follow-up.

Table 12 EV RDI over time

Time period (weeks) from	to	RDI
1	24	[redacted]
25	48	[redacted]
49	72	[redacted]
73	96	[redacted]
97	120	[redacted]
121	144	[redacted]
144		[redacted]

Note: The time -dependent EV RDI values were only available for the ITT population, therefore, the same values were used in the subgroup analyses too.

Costs were modelled on a weekly basis with the costs of wastage considered in the base case as shown in Table 13.

Table 13 Drug dosing and total acquisition costs

Regimen		Intervention	Dosing regimen	Administrations per cycle	Cycle length (days)	RDI (%)	Cost per treatment cycle (with wastage) (£)	Modelled cost per week (with wastage) (£)
EV + P		EV	1.25 mg/kg, days 1 and 8, Q3W	2	21	[redacted]	[redacted]	[redacted]
		Pembrolizumab	400 mg, day 1, Q6W	1	42	[redacted]	[redacted]	[redacted]
PBC	Gemcitabine + cisplatin	Gemcitabine	1000 mg/m^2, D1 & D8, Q3W	2	21	[redacted]	[redacted]	[redacted]
		Cisplatin	70 mg/m^2, D1 Q3W	1		[redacted]	[redacted]	
	Gemcitabine + carboplatin	Gemcitabine	1000 mg/m^2, D1 & D8, Q3W	2	21	[redacted]	[redacted]	[redacted]
		Carboplatin	AUC 4.5 (assumed dose of 450 mg), D1, Q3W	1		92.9%	44.65	

Abbreviations: AUC, area under the curve; D1, day 1; D8, day 8; EV, enfortumab vedotin; mg, milligram; P, pembrolizumab; Q2W, every 2 weeks; Q3W, every 3 weeks; PBC, platinum-based chemotherapy; RDI, relative dose intensity.

Note: * RDI for EV is the average RDI over the trial duration that has been tested in scenario analysis, thus the EV drug costs presented above reflect those used in the scenario analysis and not those used in the base-case; in the base-case, the cost per treatment cycle changes over time depending on RDI.

4.2 Subsequent treatment costs

4.2.1 Costs for subsequent lines of therapy

Avelumab maintenance costs were applied as outlined in section 3.5.2.1 of the company submission.

Following first-line therapy, it was anticipated that a proportion of the population would go on to receive subsequent systemic therapy after disease progression. Since most patients have progressed in the PBC arm in the EV-302 trial, the total proportion initiating a subsequent line of treatment in the PBC arm was assumed to represent the proportions starting a subsequent line of treatment for EV+P too. The types and distribution of therapies within this proportion was informed by observation from the EV-302 trial with the following exceptions:

- EV monotherapy is not recommended by NICE as a subsequent therapy, therefore proportions were reweighted so that the total proportion receiving subsequent therapies remained the same (as observed in the PBC arm of the trial), but those going on to receive EV monotherapy were reassigned to other treatments according to their originally observed proportions.
- Those who received pembrolizumab monotherapy in the trial were assumed to receive atezolizumab instead, as pembrolizumab monotherapy is not recommended by NICE in this indication.
- Taxane use was grouped and costed assuming the use of paclitaxel.
- Sacituzumab govitecan and erdafitinib are not recommended by NICE and have been redistributed to paclitaxel.

The distribution of subsequent therapies as included from the new data cut of EV-302 along with the estimated total cost of subsequent therapy per treatment arm are presented in Table 14. Refer to section 3.5.2.2 of the company submission for information on dosing and duration of therapies.

Table 14 Subsequent treatment distribution and total costs

		Post-progression/subsequent treatment					
		Gemcitabine + cisplatin	Gemcitabine + carboplatin	Atezolizumab	Paclitaxel	Total cost per course (£)	Total admin cost per course (£)
1L treatment	EV+P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PBC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy

4.3 Adverse reaction unit costs and resource use

The costs of treating diarrhoea as a newly included AEs is shown in Table 15. All other AE costs remained unchanged from the original submission.

Table 15 Adverse event unit costs

Adverse Event	Hospitalisation cost per event (£)	NHS reference code
Diarrhoea	696.19	FD10K non-elective short stay

Abbreviations: NHS, National Health Service

5 Severity

Following the methods described by NICE, the absolute and proportional QALY shortfall was calculated for u/mUC. The QALY shortfall aims to represent the severity of the disease by comparing the quality-adjusted life expectancy of patients when treated with standard of care in the NHS (i.e., PBC) to that of the age- and sex-matched general population.

There is uncertainty in the survival extrapolations for the PBC arm, that affects the QALY shortfall calculations, for two reasons. Firstly, the subsequent therapies used in the PBC arm of the EV-302 trial are not fully representative of the subsequent therapies available to patients in the NHS: of note, [redacted] of patients received EV monotherapy as a subsequent treatment and a further [redacted] either sacituzumab govitecan or erdafitinib. Therefore, the OS rates observed in the PBC arm may not

be representative of the OS rates of patients receiving PBC in the NHS. Given the limited data fields collected at the time that the subsequent therapies were initiated, and the various therapies, it is unlikely to be feasible to statistically adjust for their impact in the OS extrapolations. Another approach is to use real-world evidence from the NHS to estimate OS rates with PBC in the long-term. The challenge here is that the published studies refer to a period before avelumab was available, therefore are not generalisable to current times. To reflect the current treatment pathway and current OS rates, only patients treated after avelumab being recommended should be included (i.e., from May 2022), and followed for a minimum of 2-3 years to enable comparisons to the PBC arm in the EV-302 trial – such an analysis is not feasible presently but could potentially resolve this uncertainty. In summary, the implication is that the generalisability of the OS rates observed in the PBC arm in the later periods of the trial is uncertain and likely to overestimate the OS rates in the NHS.

The second source of uncertainty in the QALY shortfall calculations is in the extrapolation of OS. In five out of the seven parametric distributions, the relative QALY shortfall of 85% is reached (see Table 18). These five parametric survival distributions predict 7% - 11.8% OS rates at 5 years, corresponding to [redacted] QALYs with PBC. If the OS rate of patients treated in the NHS at 5 years is at or lower than 12%, then the criterion for the 1.2 severity modifier is met.

For these reasons, relative QALY shortfall of 85% is likely to be met, and the severity modifier of 1.2 should be applied. Furthermore, it should be noted that other treatments recently appraised in u/mUC were assessed under the 2013 NICE Methods Guide and benefitted from the end-of-life modifier (e.g., avelumab, atezolizumab). The end-of-life modifier ascribed up to 70% higher value to QALY gains at the end of life, while the moderate severity modifier that is potentially applicable to EV+P ascribes 20% higher value to QALY gains. There is a question about the fairness of appraising treatments in the same disease and similar stage but ascribing different value to QALY gains.

Table 16 Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	77% male, 23% female	Section 3.2.1, Table 20 of CS
Starting age	67.9 years	

Table 17 Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)*	Undiscounted life years
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

* Note, the model calculations also include age-related utility decrements

Table 18 Summary of QALY shortfall analysis

Scenario	Expected total discounted QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall	QALY weight based on NICE Guidelines
Base case: PBC OS log-logistic	9.80	PBC: 1.62	Absolute shortfall: 8.18 Proportional shortfall: 0.83	1
PBC OS Exponential		PBC:1.34	Absolute shortfall: 8.46 Proportional shortfall: 0.86	1.2
PBC OS Weibull		PBC:1.28	Absolute shortfall: 8.53 Proportional shortfall: 0.87	1.2
PBC OS Gompertz		PBC:1.40	Absolute shortfall: 8.41 Proportional shortfall: 0.86	1.2
PBC OS Gamma		PBC:1.28	Absolute shortfall: 8.52 Proportional shortfall: 0.87	1.2
PBC OS Log-normal		PBC:1.63	Absolute shortfall: 8.17 Proportional shortfall: 0.83	1
PBC OS Generalised gamma		PBC:1.49	Absolute shortfall: 8.32 Proportional shortfall: 0.85	1.2

6 Base-case results

6.1 Base-case incremental cost-effectiveness analysis results

Results for the ITT population with and without including the calculated 1.2 QALY weights based on the severity of the disease are shown for the ITT population in Table 19 and Table 20.

The ICERs and negative NHB shown were calculated using the list prices for pembrolizumab, avelumab and atezolizumab. Notably, the costs of EV+P are mostly

driven by the costs of pembrolizumab, given its list price (£[redacted] discounted total drug acquisition costs for EV vs £[redacted] discounted total costs for pembrolizumab over the entire treatment course means that the costs of pembrolizumab at list price account for [redacted]% of the EV+P drug acquisition costs). The ICER will reduce considerably when the confidential discounts for these treatments are taken into account. Disaggregated results, including the breakdown between cost categories and drug acquisition costs referred to above, are presented in updated Appendix J.

Table 19 Base-case results for ITT population with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-		-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.45	[redacted]
With severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-		-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.74	[redacted]

Note: All other treatments were costed using list prices. Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 20 Net health benefit of EV+P versus PBC for ITT population with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Without severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]	-	-	-	-
EV + P	[redacted]	[redacted]	[redacted]	1.45	[redacted]	[redacted]
With severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]	-	-	-	-
EV + P	[redacted]	[redacted]	[redacted]	1.74	[redacted]	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

6.2 Exploring uncertainty

Uncertainty was explored using probabilistic and deterministic sensitivity analyses, and different scenarios were also modelled. These explorations are described below.

6.2.1 Probabilistic sensitivity analysis

Results are presented as cost effectiveness acceptability curves as well as on a cost effectiveness plane. The mean probabilistic results are presented in Table 21 and align with the deterministic results.

Table 21 Probabilistic sensitivity analysis results for the base case with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-		-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.44	[redacted]
With severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]	-	-		-
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.73	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 22 Net health benefit based on probabilistic results for the base case with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Without severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.44	[redacted]	[redacted]
With severity modifier						
Gemcitabine + PBC	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	1.73	[redacted]	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

Figure 18 shows the results on cost-effectiveness plane. All of the 1,000 simulations were in the upper right-hand quadrant, indicating that EV+P is more effective although a more costly treatment option compared to PBC.

Figure 18 Base case probabilistic results on the cost effectiveness plane with no QALY weighting, but including a confidential PAS of % for EV

Note: All other treatments were costed using list prices

At the £20,000 to £30,000 threshold the probability of EV+P being cost-effective compared to PBC is % with the list prices included for pembrolizumab, avelumab and atezolizumab. However, with the confidential discounts, the probability of EV+P being cost-effective will be much higher.

6.2.2 Deterministic sensitivity analysis

With the exception of survival outcomes, major model variables in the base case for which values were uncertain were tested in a one-way deterministic sensitivity analysis to identify model drivers and examine key areas of uncertainty. Results of the deterministic sensitivity analysis without the severity modifier applied are presented as a tornado diagram (in Figure 19).

The deterministic sensitivity analysis shows that the ICER is most sensitive to the RDI for pembrolizumab and avelumab, proportion of patients receiving avelumab maintenance therapy and administration costs. However, none of the scenarios increased the ICER to above £[redacted]/QALY without the severity weighting applied.

Figure 19 Tornado diagram of impact of input parameters on base case results with no QALY weighting, but including a confidential PAS of [redacted]% for EV

Note: All other treatments were costed using list prices

Table 23: Top 20 parameters influencing the ICER with no QALY weighting, but including a confidential PAS of [redacted]% for EV

Parameter	Low value of input	High value of input	ICER at low value of input (£)	ICER at high value of input (£)	Difference (£)
RDI (%), Pembrolizumab	0.66	1.00	[redacted]	[redacted]	[redacted]
Proportion of patients receiving avelumab maintenance	0.25	0.37	[redacted]	[redacted]	[redacted]
RDI (%), Avelumab	0.66	1.00	[redacted]	[redacted]	[redacted]
Administration cost, Chemotherapy for Regimens not on the National List	318.98	472.52	[redacted]	[redacted]	[redacted]
Health state utility values, PF - EV + P	0.72	0.73	[redacted]	[redacted]	[redacted]
PFS HCRU monthly visits, Consultant led oncologist follow-up visit	0.72	1.06	[redacted]	[redacted]	[redacted]
Consultant led oncologist follow-up visit, HCRU unit cost	180.20	266.94	[redacted]	[redacted]	[redacted]
Pre-progression treatment SOC: Gemcitabine + PBC, Atezolizumab	0.31	0.46	[redacted]	[redacted]	[redacted]
Health state utility values, PF - SOC: Gemcitabine + PBC	0.70	0.71	[redacted]	[redacted]	[redacted]
Duration of sub tx (months), Atezolizumab	1.66	2.48	[redacted]	[redacted]	[redacted]
Proportion of patients receiving: Gemcitabine + carboplatin	0.40	0.59	[redacted]	[redacted]	[redacted]
Proportion of patients receiving: Gemcitabine + cisplatin	0.41	0.61	[redacted]	[redacted]	[redacted]
Age (at baseline)	67.04	68.76	[redacted]	[redacted]	[redacted]
Weight	74.23	77.55	[redacted]	[redacted]	[redacted]
Administration cost, Complex/Prolonged Chemotherapy (First Attendance)	394.80	584.84	[redacted]	[redacted]	[redacted]
Administration cost, Subsequent Elements of a Chemotherapy Cycle	312.06	462.28	[redacted]	[redacted]	[redacted]
Clinical nurse specialist, HCRU unit cost	55.33	81.96	[redacted]	[redacted]	[redacted]
PFS HCRU monthly visits, GP home consultation	0.21	0.31	[redacted]	[redacted]	[redacted]
PFS HCRU monthly visits, Clinical nurse specialist	0.50	0.75	[redacted]	[redacted]	[redacted]

GP home consultation, HCRU unit cost	144.83	214.54	[redacted]	[redacted]	[redacted]

Note: All other treatments were costed using list prices

6.2.3 Scenario analysis

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties as well as alternative input sources where available. The following scenarios were tested:

- Structural assumptions:
  - Model time horizon restricted to 20 years
  - Discount rates for costs and benefits changed to 6%, 5%, 1.5% and 0%
  - Excluding the impact of adverse events
- Survival extrapolations
  - OS: different standard parametric curves
  - PFS: next best fitting spline extrapolation
  - PFS: different standard parametric extrapolations
  - ToT: different standard parametric extrapolations
- Utilities:
  - Applying non-treatment specific, health state based utilities
  - Removing age-adjustment of utilities, i.e. trial utilities are applied throughout the model time horizon
  - Testing alternative sources for the health state utilities:
    - Utilities based on NICE TA788
    - Utilities based on NICE TA739
    - Utilities based on SMC assessment of pembrolizumab
- Drug cost calculations:
  - Pembrolizumab dosing based on trial protocol (200mg every 3 weeks)
  - EV RDI not time dependent

As seen with the base case results, the model is almost linear with probabilistic results being very close to deterministic results (a less than 0.7% difference in incremental costs and 0.8% difference in incremental QALYs). Given the alignment

between deterministic and probabilistic results, the deterministic results are displayed in Table 24.

The results are relatively stable, with most scenarios having an ICER between £[redacted]/QALY and £[redacted]/QALY including the severity modifier. The ICER is most affected by high discount rates and assumptions around dependence of OS curves. Specifically, relying on a common shape parameter between treatment arms results in the highest ICER, while applying a constant HR results in the lowest ICER. However, as noted above in section 3.3.1.3 of the CS on the assessment of proportional hazards, the PH assumption clearly does not hold for progression-free survival and is also unlikely to hold for the cisplatin-ineligible subgroup for OS. Additionally, there is a difference in the mechanism of action between EV+P and PBC, therefore it is unrealistic to assume proportionality for the survival outcomes between the treatment arms. Both of these scenarios are likely to be unrealistic.

The scenario where both treatment arms' OS were extrapolated using exponential functions also resulted in a relatively higher ICER. However, this scenario is overly conservative given that it predicts that only 8% of patients remain alive at 10 years after EV+P treatment, while the clinical validation described in section 3.3.1.2 of the CS resulted in an estimate of 16% on average. Furthermore, the clinical input obtained for TA788[4] also predicted 10-15% alive at 10 years with avelumab, despite lower OS rates at 2 years in JAVELIN 100 compared to EV-302.

The three most influential, while, at the same time, clinically plausible scenarios were the following:

- Using lognormal functions for the OS extrapolation: this alternative survival extrapolation predicts longer mean OS for both EV+P and PBC. It aligns better with the observed EV-103 data (where estimated 5-year survival rate was 41.5%, while the lognormal function predicts 35% of patients to be alive at this point and the base-case log-logistic predicts 31%), and has a major downward impact on the ICER.

- Using the best fitting standard curves to inform PFS extrapolations: although spline fits were included in the base case to better capture changes in

hazards observed over time in the trial, use of standard curves aligns with the approach taken to model all other time to event data. The scenario shows that the ICER is relatively robust to the change in survival functions.

- Using generalised gamma functions for EV+P ToT extrapolations: these functions predict shorter treatment duration for EV+P, which aligns better with observations in the EV-103 trial, where all patients discontinued treatment by year 4. This scenario reduces the predicted ICER.

Table 24 Scenario analysis results around base case, including a confidential PAS of [redacted]% for EV

Parameter	Base case	Scenario	Incremental Cost (£)	Incremental QALY (no severity modifier)	ICER (£/QALY) (no severity modifier)	ICER (£/QALY) (with severity modifier)	Difference from base case
Base Case			[redacted]	1.45	[redacted]	[redacted]	
Time horizon	Lifetime (30 years)	20 years	[redacted]	1.39	[redacted]	[redacted]	[redacted]
Annual discount rate (costs and health outputs)	3.50%	6.0%	[redacted]	1.26	[redacted]	[redacted]	[redacted]
		5.0%	[redacted]	1.33	[redacted]	[redacted]	[redacted]
		1.50%	[redacted]	1.71	[redacted]	[redacted]	[redacted]
		0.0%	[redacted]	1.84	[redacted]	[redacted]	[redacted]
Excluding impact of AEs	AEs included	AEs not included	[redacted]	1.46	[redacted]	[redacted]	[redacted]
Pembrolizumab dosing	400mg Q6W	As per trial: 200mg Q3W	[redacted]	1.45	[redacted]	[redacted]	[redacted]
EV RDI	Time dependent	[redacted]%	[redacted]	1.45	[redacted]	[redacted]	[redacted]
OS	Independent fit Both arms log-logistic	Independent fit Both arms exponential	[redacted]	1.14	[redacted]	[redacted]	[redacted]

		Independent fit Both arms log-normal	[redacted]	1.71	[redacted]	[redacted]	[redacted]
		Dependent fit: Common shape parameter, log-logistic	[redacted]	1.17	[redacted]	[redacted]	[redacted]
		Constant hazard ratio, log-logistic	[redacted]	1.86	[redacted]	[redacted]	[redacted]
PFS	Spline fits EV+P: hazard 2 knots PBC: odds 3 knots	Spline fits EV+P: normal, 2 knots PBC: normal, 3 knots	[redacted]	1.45	[redacted]	[redacted]	[redacted]
		Standard fits EV+P: generalised gamma PBC: log-logistic	[redacted]	1.46	[redacted]	[redacted]	[redacted]
		Standard fits Both arms log-normal	[redacted]	1.41	[redacted]	[redacted]	[redacted]
		Standard fits Both arms log-logistic	[redacted]	1.41	[redacted]	[redacted]	[redacted]
		Standard fits Both arms generalised gamma	[redacted]	1.46	[redacted]	[redacted]	[redacted]
Time on treatment	EV: log-logistic P: Equal to KM Avelumab: Weibull	EV: log-logistic P: log-logistic Avelumab: Weibull	[redacted]	1.45	[redacted]	[redacted]	[redacted]
		EV: generalised gamma	[redacted]	1.45	[redacted]	[redacted]	[redacted]

		P: generalised gamma Avelumab: Weibull					
		EV: log-logistic P: log-normal Avelumab: Weibull	[redacted]	1.45	[redacted]	[redacted]	[redacted]
Utilities	Treatment-specific in PFS, Age-adjustment, Source: EV-302	Health state specific, Age-adjustment, Source: EV-302	[redacted]	1.39	[redacted]	[redacted]	[redacted]
		Treatment-specific in PFS, No age-adjustment, Source: EV-302	[redacted]	1.51	[redacted]	[redacted]	[redacted]
		Health-state specific, Age-adjustment, Source: NICE TA788	[redacted]	1.50	[redacted]	[redacted]	[redacted]
		Health-state specific, Age-adjustment, Source: NICE TA739	[redacted]	1.42	[redacted]	[redacted]	[redacted]
		Health-state specific, Age-adjustment, Source: SMC pembrolizumab	[redacted]	1.32	[redacted]	[redacted]	[redacted]

Note: All other treatments apart from EV were costed using list prices
Abbreviations: AE, adverse events; EV+P, enfortumab vedotin + pembrolizumab; PBC, platinum-based chemotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks

7 Subgroup analysis

7.1 Subgroup results: Cisplatin-eligible patients

Subgroup results are presented in Table 25. As expected, the cisplatin-eligible patient subgroup has slightly longer survival and higher QALY gains than the ITT population (e.g., cisplatin-eligible patients were calculated to gain [redacted] life years with gemcitabine + PBC, and [redacted] life years with EV+P vs [redacted] and [redacted] in the ITT population, respectively). This is due to better PFS, higher subgroup-specific utilities, and the younger age of this subgroup (i.e. there is a lower impact of the application of age-adjustment of utilities and the general population mortality hazard caps).

7.2 Subgroup results: Cisplatin-ineligible patients

As expected, total costs as well as QALY gains are slightly lower in the cisplatin-ineligible subgroup compared to the cisplatin-eligible subgroup. EV+P results in a gain of [redacted] QALYs, while gemcitabine + carboplatin is predicted to generate [redacted] QALYs (versus [redacted] QALYs and [redacted] QALYs in the ITT population, respectively). The QALY difference is larger at 1.47 incremental QALYs (versus 1.45 incremental QALYs in the ITT population).

Results for the cisplatin-ineligible population are shown in Table 26.

Table 25 Base-case results for cisplatin-eligible patients, with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.50	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.80	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 26 Base-case results for cisplatin-ineligible patients, with and without including 1.2 QALY weights and a confidential PAS of [redacted]% for EV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.47	[redacted]
With severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.77	[redacted]

Note: All other treatments were costed using list prices
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

References

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2. Astellas Pharma Global Development Inc. 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: Clinical Study Report (data cut-off 8 August 2024), (2024).
3. Powles T, Park SH, Caserta C, et al. Avelumab First-Line Maintenance for Advanced Urothelial Carcinoma: Results From the JAVELIN Bladder 100 Trial After ≥2 Years of Follow-Up. *J Clin Oncol* 2023;41(19):3486-92.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy: ID6332

Summary of Information for Patients (SIP)

October 2024

File name	Version	Contains confidential information	Date
		No	

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Enfortumab vedotin (EV; Padcev®) in combination with pembrolizumab (P; Keytruda®).

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

The main population being appraised is adults with previously untreated unresectable or metastatic urothelial cancer (u/mUC) who are eligible to have platinum-containing chemotherapy (i.e. chemotherapy containing either cisplatin or carboplatin).[1] Urothelial cancer (UC) affects the cells that line the urinary system (called the urothelium), which includes the bladder, urethra (the tube that allows urine in the bladder to leave the body), ureters (tubes that carry urine from the kidneys to the bladder), and renal pelvis (the part of the kidney that connects to the ureter). Urothelial cancer that cannot be removed by surgery is called unresectable. Metastatic means the cancer has spread to other parts of the body.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Enfortumab vedotin in combination with pembrolizumab in this indication received marketing authorisation from the European Medicines Agency on 28 August 2024.[2] Approval in the UK is expected to follow the International Recognition Pathway with EMA as reference regulator (Type II variation).

- Enfortumab vedotin and pembrolizumab as monotherapies already have marketing authorisations in some settings within u/mUC. These are not covered by this appraisal.
    - EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.[1]
    - P as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.[3]
    - P as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.[3]

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

PAG: Fight Bladder Cancer
Date: August 2024
Activity: Feedback and review of patient facing material drafts
Payment: GBP £595

PAG: Fight Bladder Cancer
Date: April 2023
Activity: Above Country (Regional) Grant to support patient videos concerned with empowering the Bladder Cancer Community through videos about Shared Decision-Making project
Payment: GBP £10,000

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is urothelial cancer?

Urothelial cancer (UC) affects the cells that line the urinary system, which includes the bladder, urethra, ureters, and renal pelvis.

Bladder cancer (BC) makes up 90-95% of UC cases at diagnosis.[4] Approximately 90% of BC cases in the UK are due to UC, with the remainder of cases affecting a different type of cell within the bladder.[5] Upper tract urothelial cancer (UTUC) affects the ureters and renal pelvis, and accounts for 5-10% of UC cases.[4] However, it accounts for a higher proportion of u/mUC cases as it is typically more advanced at diagnosis than BC.[4] Almost all cancers of the ureters and renal pelvis are UC; other types are rare.[4]

UC becomes more common as people get older: 56% of BC cases in the UK were diagnosed in people aged ≥75 years in 2016-2018[6] and BC is rarely diagnosed in persons aged <40 years.[7] The peak incidence of UTUC is at 70-90 years of age.[4] UC is more common in men than women,[6] with men accounting for 75% of BC diagnoses and 65% of UTUC diagnoses in England in 2021.[8]

Symptoms and effects on quality of life

Painless blood in the urine (haematuria) is the most common presentation of BC at diagnosis.[7,9] Urinary symptoms (e.g. frequent, urgent, or painful urination) and flank pain (pain in one or both sides of the abdomen) can also occur.[7,9] UTUC can also present with blood in the urine and flank pain.[4] However, not everyone with UC gets these symptoms.

People with u/mUC may experience urinary symptoms, lower back or abdominal pain, fatigue, and a general feeling of illness.[5] People with metastatic UC can also experience weight loss, lack of appetite, and pain specific to the site of metastasis (e.g. bone pain).[4,9,10] Due to its concentration in older individuals, people with u/mUC often have other existing medical conditions that must be taken into account during their treatment.[7]

U/mUC can have a significant impact on people's physical, mental, and social quality of life.[11] Pain associated with u/mUC can affect physical and daily activities, social activities, emotional wellbeing, and overall health-related quality of life.[10] People who have previously had their bladder removed are living with surgical effects such as urostomy (where an opening has been created in the abdomen to allow urine to be collected in a bag outside the body), internal urine pouch (which is drained using a tube inserted through a hole in the abdomen), or a new reconstructed bladder.[5] Metastatic UC is also associated with a high economic

burden as a result of medical costs such as hospitalisations, emergency room visits, and end-of-life care.[12]

Prognosis

The proportion of people with BC that will be alive after five years as estimated by the National Cancer Institute in the US is approximately 39.5% for locally advanced disease and 8.8% for metastatic disease.[13] Of people diagnosed with BC in England in 2016-2020, 64.4% of those diagnosed with stage 3 were alive one year later, and 29.2% of those diagnosed at stage 4.[14] However, the outlook is individual for each person, and these numbers include people who didn't have treatment.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients with suspected UC have a variety of tests to first confirm the diagnosis, and then to find out the stage of cancer, including whether the cancer has spread.

A GP may refer patients presenting with symptoms to a hospital for tests or to see a specialist. Tests can include an ultrasound scan of the abdomen, which uses high-frequency sound waves that can create a picture of the urinary system.[15] A cystoscopy might also be carried out, which looks at the inside of the bladder to check for signs of cancer. A doctor can take samples of the bladder lining (biopsies) during this test, which will be checked for cancer cells by a laboratory. A CT/CAT (computed [axial] tomography) scan uses X-rays and a computer to create detailed pictures of the inside of the pelvis, abdomen and chest, and can be used with a special dye (contrast medium) to also look at the kidneys, bladder, and ureters (a CT urogram).

A PET-CT scan combines a CT scan with a PET scan, which uses a mildly radioactive drug to show up areas of the body where cells are more active than normal.[15] A PET-CT scan can be used to find out the size of the cancer and whether it has spread (the stage). An MRI (magnetic resonance imaging) scan uses magnetism and radio waves to take pictures of the inside of the body, and can be used to see if the cancer has grown into the deeper muscle layer of the bladder or spread to other parts of the body. Bone scans can be used to check if the cancer has spread to the bones.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Platinum-based combination chemotherapy is the current standard treatment for u/mUC in the NHS.[16]

- Cisplatin-based chemotherapy (usually cisplatin + gemcitabine) is the first choice treatment,[16] but it is not suitable for everyone because of its side effects. Around half of patients with u/mUC are not eligible to receive it due to older age, poor general health, or other conditions such as kidney problems.[17]
- Most patients who are not able to receive cisplatin receive carboplatin + gemcitabine instead, in line with NICE guidelines.[16]
- Patients whose disease responds to, or is stable after platinum-containing chemotherapy can have maintenance treatment with avelumab.[18]
- U/mUC is not currently curable, and for most patients it eventually comes back or progresses after their first treatment. Options for second-line treatment depend on the patient's health and the characteristics of their tumour. They include immunotherapy with atezolizumab, or further chemotherapy.

New guidelines from the European Society of Medical Oncology and the European Association of Urology now recommend enfortumab vedotin with pembrolizumab (EV+P) as the new first-choice first line of treatment for u/mUC.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Separate PBE has not been collected. However, a range of patient-reported outcomes were assessed in the EV-302 clinical trial: see Section 3f.

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Enfortumab vedotin targets and connects to a protein called nectin-4 on the surface of urothelial cancer cells.[1] This allows enfortumab vedotin to enter and kill the cancer cell and other cancer cells nearby. Pembrolizumab is a type of immunotherapy. It works by stimulating the immune system to fight cancer cells. It targets and blocks a protein called PD-1 on the surface of immune cells called T cells. Blocking this protein helps the T cells to find and kill cancer cells.[19] Evidence from laboratory studies suggests that the two drugs work with each other to increase the ability to kill cancer cells.[1,20]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☒Yes

☐No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

The submission is for the combination treatment of enfortumab vedotin with pembrolizumab, and all information in the SIP refers to this combination.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg body weight (up to a maximum of 125 mg for patients ≥100 kg). It is administered as an intravenous infusion (drip into a vein) over 30 minutes on Days 1 and 8 of a 21-day cycle.[1] Treatment will continue for as long as the cancer does not progress and the patient does not experience intolerable side effects.[1]

The recommended dose for pembrolizumab in combination with EV for this disease is 200 mg as an intravenous infusion on day 1 of each 3-week cycle, for a maximum of 35 cycles. if patients have adverse effects with EV, their doctor may reduce the dose.[3]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Two clinical studies have been carried out investigating the effectiveness of EV+P in treating adult patients with u/mUC.

Main clinical trial: study EV-302, registration number NCT04223856[21,22]

Title: 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

Study publications: Powles et al. 2024[21]

Locations: 25 countries around the world, including the UK

Completion date: Primary results were published by Powles et al. 2024.[21] A new data cut providing longer-term follow-up and more mature survival data is expected later and will be presented during the submission process if available.

Population: Previously-untreated patients with unresectable locally advanced or metastatic UC that are eligible to receive platinum-based chemotherapy.

Objective: to compare the efficacy and safety of EV+P with that of platinum-based chemotherapy in this population.

Number of participants: 886 adults with locally advanced/metastatic UC, who were randomised to receive either EV+P (442 patients) or chemotherapy (444 patients).

Trial design: Patients were randomly assigned to receive either EV+P or platinum-based chemotherapy. They were regularly evaluated to see their response to treatment, whether their cancer had progressed, the side-effects they had, and how long they lived. They also completed questionnaires about their pain levels and their quality of life (e.g. their symptoms, their ability to carry out their usual activities, and their emotional wellbeing). Treatment with EV+P continued until the cancer progressed, the patient had intolerable side-effects, or the patient or clinician made the decision to stop. Treatment with platinum-based chemotherapy was for 6 cycles.

Earlier-stage clinical trial: study EV-103, registration number NCT03288545[23]

This earlier-stage trial looked at several different groups of patients with UC and several different combinations of treatments. Some of the groups (cohorts A and K) had u/mUC and received EV+P; however, only patients who were not eligible for cisplatin treatment took part. Information from this trial provides supporting information on the efficacy of EV+P in part of the patient group covered by the NICE appraisal.

Title: A Study of Enfortumab Vedotin Alone or With Other Therapies for Treatment of Urothelial Cancer

Study publications: Initial results were published by Hoimes et al. 2023.[23] The latest update (cohort A) was presented by Rosenberg 2024.[24]

Locations: United States, Canada, France, Italy, Puerto Rico, Spain

Completion date: Estimated 2026.

Population: Patients with u/mUC or muscle invasive BC

Main objective: To determine the safety and tolerability of enfortumab vedotin alone and in combination with pembrolizumab and/or chemotherapy for the treatment of locally advanced/metastatic UC and muscle invasive BC.

Number of participants: 191 adults with u/mUC, were assigned to cohort A (40 patients) to receive EV+P, or cohort K (151 patients) to receive either EV+P or EV monotherapy

Key eligibility criteria: To be eligible for cohort A or K, participants had to have confirmed locally advanced or metastatic urothelial cancer that they have not had prior treatment for, or no prior adjuvant/neoadjuvant platinum-based therapy in at least 12 months. They also had to be ineligible to receive cisplatin-containing chemotherapy.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The EV-302 clinical trial found that EV+P almost doubled progression-free survival and overall survival, compared with platinum-based chemotherapy. Progression-free survival is the time from randomisation into the trial to first documentation of disease progression or death due to any cause (whichever comes first). Overall survival is the time from randomisation into the trial to date of death due to any cause. Treatment with EV+P also resulted in a significantly higher response rate (percentage of patients whose cancer reduced [partial response] or disappeared [complete response] following treatment) compared with chemotherapy. Details are given below.

- Patients in the EV+P group had a significantly longer progression-free survival compared with chemotherapy. The median (average) progression-free survival with EV+P was 12.5 months, compared with 6.3 months with chemotherapy. This means there was a 55% reduction in the risk of the disease progressing (Hazard ratio (HR): 0.450; 95% confidence interval (CI): 0.377, 0.538; 2-sided p-value <0.00001).
- Median overall survival was longer in patients treated with EV+P compared with chemotherapy, at 31.5 months in the EV+P group and 16.1 months in the chemotherapy group. This means a 53.2% reduction in the risk of death with EV+P vs. chemotherapy (HR: 0.468; 95% CI: 0.376, 0.582; 2-sided p-value <0.00001).
- EV+P was associated with a significantly higher response rate than chemotherapy (67.7% [95% CI: 63.1, 72.1] vs. 44.4% [95%CI: 39.7, 49.2]), and a higher rate of complete response (disappearance of all signs of cancer in the body) (29.1% vs. 12.5%).[21]
- Responses lasted longer in patients treated with EV+P than with chemotherapy: median duration of response was not reached with EV+P (95% CI: 20.2, NE), compared with a median of 7.0 months (95% CI: 6.2, 10.2) in the chemotherapy arm.[21]

Longer-term follow-up of 45 cisplatin-ineligible patients is available from study EV-103 (dose escalation + cohort A). After a median follow-up of 62 months:[24]

- 47% of the 33 patients who responded to treatment maintained a response at 2-5 years.
- The progression-free survival rate remained at 38.2% at 3-5 years.
- 41.5% of patients were still alive at 5 years after starting treatment.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life scores during the EV-302 clinical trial showed that the benefit in progression-free and overall survival seen from treatment with EV+P was achieved without negatively affecting quality of life, pain or functioning compared with chemotherapy.[25] This included scores from the EORTC QLQ-30 questionnaire, which specifically addresses quality of life in cancer.

Looking specifically at the quality of life measure preferred by NICE for use in cost-effectiveness modelling (the EQ-5D), additional analyses suggested that before disease progression, the quality of life of patients treated with EV+P was higher than those patients treated with chemotherapy.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

EV+P can cause side effects like all medicines, some of which can be serious. Adverse events (any undesirable experience associated with the use of a medical product in a patient) in trials are graded on a scale of 1 (mild) to 5 (leading to death).

The percentages of patients with treatment-related adverse events were similar between the EV+P and chemotherapy arms in the EV-302 trial, despite a longer duration of treatment with EV+P.[21]

- Treatment-related adverse events of grade 3 or higher occurred in 55.9% of patients treated with EV+P and in 69.5% of those treated with chemotherapy in the EV+P study.
    - After adjustment of the data based on how long patients were exposed to treatment, the rate was 1.273 adverse events per patient-year in the EV+P group and 5.358 events per patient-year in the chemotherapy group.
- The most common treatment-related adverse events of any grade in patients treated with EV+P in the EV-302 clinical trial were peripheral sensory neuropathy (damage to the nerves that carry messages of sensations to the brain; in 50.0% of patients), pruritis (itching; in 39.8%), and alopecia (hair loss; in 33.2%).[22]
    - In the chemotherapy group, the most common such adverse events were anaemia (in 56.6%), neutropenia (low levels of a type of white blood cells; in 41.6%), and nausea (in 38.8%).

- The most common treatment-related adverse events of grade 3 or higher in the EV+P group were maculopapular rash (a skin reaction; in 7.7% of patients), hyperglycaemia (high blood sugar; in 5.0%), and neutropenia (in 4.8%).[21,22]
    - The most common such events in the chemotherapy group were anaemia (in 31.4%), neutropenia (in 30.0%), and thrombocytopenia (low blood levels of thrombocytes, cells which play a role in blood clotting; in 19.4%).

During the trial, 40.7% of patients in the EV+P group had their dose reduced because of treatment-related AEs, as did 37.9% in the chemotherapy group. Treatment-related AEs resulting in discontinuation of any treatment occurred in 35.0% and 18.5%, respectively.[21]

More information on adverse effects with EV and pembrolizumab as standalone treatments can be found in their respective patient information leaflets.[26,27]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefit of EV+P is that compared with the current standard treatment (platinum-based chemotherapy), it significantly extends both the length of time patients have before their cancer progresses, and how long they live after starting treatment.[21]

In the EV-302 study, both of these times were almost doubled with EV+P compared with the chemotherapy arm. The median time until disease progression was 12.5 months with EV+P versus 6.3 months with chemotherapy, and the median overall survival was 31.5 months in the EV+P group vs. 16.1 months in the chemotherapy group.[21]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Both EV+P and platinum-based chemotherapy are given by IV infusion, so patients have to travel to hospital to be treated. Although EV+P is significantly more effective than platinum-based chemotherapy (based on the EV-302 study), patients have to stay on treatment for longer with EV+P. This is because

chemotherapy is given as a fixed-length course of 6 cycles, whereas EV+P (like many non-chemotherapy cancer treatments) is taken until the patient has disease progression or intolerable side-effects. The continuing need for regular treatment visits might be seen as a disadvantage by some patients and/or their caregivers. However, EV and P infusions take 30 minutes each,[1] whereas cisplatin infusions take several hours.[28]

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

What are economic models?

Economic models are a way of capturing the benefits and costs associated with different medical treatments over a patient's lifetime. This allows NICE to estimate how cost-effective a new treatment is compared with existing treatments, and to decide whether paying for a new treatment is good value for money for the NHS. In most cases models look at the overall population of patients who will be using the treatment, rather than looking at individuals.

Models take their information from clinical trials whenever possible. However, clinical trials only last a limited amount of time, so that results can be obtained within a reasonable timescale. This means that models have to extrapolate (project forward) beyond what was seen in the trial, in order to estimate lifetime

costs and benefits. Extrapolation involves making some assumptions, and by its nature involves some uncertainty.

How the economic model reflects u/mUC

The type of model used in this appraisal is termed a partitioned survival model. This is a well-established method that is often used in the modelling of cancer. It divides the hypothetical patients into three possible 'health states': either alive without disease progression (i.e., the cancer is stable or responding to treatment), alive with disease progression, or dead. It uses data from the trial on progression-free and overall survival to estimate the proportion of patients who are in each of the health states over time. Beyond the time period of the trial, statistical methods are used to extrapolate the curves until the time when the whole patient group can be expected to have died (even patients whose disease didn't come back).

The model reflects u/mUC by reflecting information from the experience of patients in the EV-302 clinical trial. The model structure and inputs were also discussed with expert clinicians to ensure that the disease and patient journey were being properly captured. Inputs were also compared against published values in the scientific literature and previous NICE appraisals. Further information on how life extension, quality of life and treatment cost were modelled is given below.

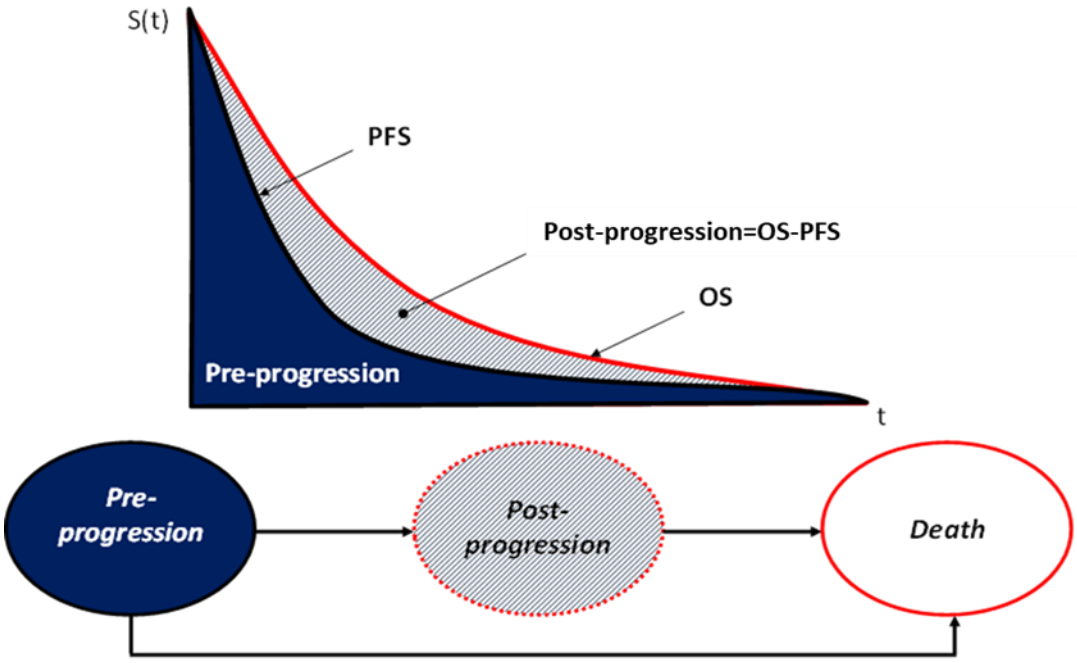

Figure 1: schematic of a partitioned survival model
Key: S(t), survival time; OS, overall survival; PFS, progression-free survival

Modelling how much EV+P extends life

The EV-302 trial showed that, compared with patients receiving platinum-based chemotherapy, patients treated with EV+P had a longer time before their disease progressed (progression-free survival), and lived longer (overall survival; see Section 3e). At the time of modelling, patients in the EV-302 trial had been

followed for an average of 17.2 months (some for less time and some for longer, depending on when they joined the trial). At this cut-off (which was at a pre-specified point set out when the trial was planned), 530 of the 886 patients had had a PFS event (either progressed or died), and 359 of the 886 had died. The trial is continuing, but longer-term data will not be available until the next pre-specified cut-off point is reached.

As discussed above, established statistical methods were used to extrapolate (i.e. project forward) from the progression-free and overall survival results seen in the trial, in order to predict progression-free and overall survival over the lifetime of the entire group of hypothetical patients with u/mUC. The projections were calculated using several different methods and were checked against findings from other studies and with UK clinicians to see which were the most realistic.

Modelling quality of life

To reflect patients' quality of life whilst in the pre-progression and progressed states, each state is assigned a 'utility value'. This is a value between 0 and 1, where 1 corresponds to perfect health and 0 corresponds to death. The utility values are based on the EQ-5D quality of life questionnaires filled out by patients during the EV-302 study, so they reflect patients' experience of being in each state. While the patients are 'on treatment', i.e. in the pre-progression state, the utility values are taken from the separate treatment arms, to reflect any treatment-related differences. In the progressed state, when patients are no longer on the trial treatments, the same (lower) utility value is used for everyone. However, it is possible that the EQ-5D questionnaire (which is the standard quality of life measure for economic modelling) did not fully capture all of patients' experience with u/mUC and its treatment.

The model also takes into account the negative effects of adverse events on quality of life, and the cost of treating them. Rates of adverse events of grade 3 and above (or grade 2 and above for neuropathy) are taken from the trial. For each event, a deduction is made to the quality of life (utility), and the cost of treating the event is added.

Modelling treatment costs

The model looks at the cost to the NHS of buying and administering the different drugs, and treating the side-effects that arise. EV+P is more expensive to the NHS than platinum-based chemotherapy, mainly because EV and P cost more. The drugs used in platinum-based chemotherapy cost less than innovative specialist treatments, because they have been available for many years and are widely used across many different cancers.

Model results

The model found that treatment with EV+P improved patient outcomes, resulting in greater life expectancy and more quality-adjusted life-years (QALYs) than platinum-based chemotherapy. It also increased healthcare costs compared with

platinum-based chemotherapy. These findings remained when different methods were used to calculate the benefits of EV+P.

Uncertainty

The main areas of uncertainty are as follows:

- The length of progression-free and overall survival beyond the time span of the trial. In particular, it possible that a minority of patients may go into long-term remission after treatment with EV+P, but this is difficult to predict.
- The amount of time patients will stay on treatment with EV+P. This affects the cost of treatment.

To address uncertainty, different scenarios were modelled and presented to NICE. Expert clinicians were consulted to check whether the model inputs and assumptions were realistic and applicable to UK patients.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Currently, the first line of treatment for u/mUC is standard chemotherapy drugs. Chemotherapy drugs kill all cells that multiply quickly, regardless of whether they are cancerous. EV+P is an innovative combination of two relatively new drugs that have been specifically developed to target specific differences found in cancer cells which help the cancer to survive and grow.

EV+P represents an important advance in the treatment of u/mUC, because it almost doubles average progression-free and overall survival compared with platinum-based chemotherapy. It is the first treatment to provide a major improvement over platinum-based chemotherapy.[21] Treatment guidelines from the European Society of Medical Oncology (ESMO) and the European Association of Urology (EAU) now recommend EV+P as the new first-line treatment of choice for u/mUC for patients who are considered platinum-eligible.[4,9,29]

The model and resulting QALY calculation captures the main benefits of EV+P over platinum-based chemotherapy. However, it does not take into account the potential benefits to quality of life for patients' caregivers and families that may result from extended progression-free and overall survival with EV+P.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Decisions on the funding of treatments for BC disproportionately affect people living with the consequences of socioeconomic deprivation. In England, estimates by Cancer Research UK indicate that the European age-standardised incidence rate in the most deprived Index of Multiple Deprivation (IMD) quintile compared with the least is 47% higher in females and 23% higher in males (2013-2017).[6] There are an estimated 980 more cases/year than there would be if every quintile had the same age-specific crude incidence rates as the least deprived quintile.[6]

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

- Information on bladder cancer and its treatment in the UK can be found on Cancer Research UK's website:
  - https://www.cancerresearchuk.org/about-cancer/bladder-cancer
- Information of upper urinary tract urothelial cancer and its treatment in the UK can be found on Cancer Research UK's website:
  - https://www.cancerresearchuk.org/about-cancer/upper-urinary-tract-urothelial-cancer

Further information on NICE and the role of patients**:**

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Adverse event: any undesirable experience associated with the use of a medical product in a patient

BC: bladder cancer

Complete response: there are no signs of cancer on scans or tests

Haematuria: blood in the urine

Median: the middle number in a sorted list of numbers

Metastatic: cancer that has spread to other parts of the body

Overall survival: time from randomisation into the trial to date of death due to any cause

Partial response: the cancer has shrunk by at least one third (30%) and there are no signs the cancer has grown anywhere else in the body

Progression-free survival: time from randomisation into the trial to first documentation of disease progression or death due to any cause (whichever comes first)

QALY (quality-adjusted life year): A measure in which length of life is adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.

Renal pelvis: the part of the kidney that connects to the ureter

Response rate: percentage of patients whose cancer met the criteria for response (i.e. reduced or disappeared) following treatment

u/mUC: unresectable/metastatic urothelial cancer

UC: urothelial cancer

Ureters: tubes that carry urine from the kidneys to the bladder

Urethra: tube that allows urine in the bladder to leave the body

Urothelium: the cells that line the urinary system

UTUC: upper tract urothelial cancer

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

Clarification questions v2

Redaction adjusted in response to NICE request; content otherwise unchanged

February 2025

File name	Version	Contains confidential information	Date
ID6332 Clarification responses_redacted_28Feb2025	2	Yes	28 Feb 2025

Section A: Clarification on effectiveness data

Background

A1. In Table 1 in the comparator row, the company quotes Jones et al (2024) who state that subsequent results from randomised trials have cast doubt on the relative efficacy of 1L ICI [immune checkpoint inhibitor] monotherapy treatment. This is mentioned as a justification for not including atezolizumab as a comparator. Please could the company elaborate on the results of the trials and their implications for efficacy. Jones et al 2024 does not discuss this, and the cited RCT publication for atezolizumab does not report final survival analyses. Hence it is unclear why the results are under question.

In January 2024, final results of the IMvigor130 study (NCT02807636) of atezolizumab monotherapy versus investigator's choice of platinum-based chemotherapy in untreated locally advanced or metastatic UC were published by Bamias et al (study groups B vs C).[1] The final analysis did not show a significant improvement in overall survival with first-line atezolizumab monotherapy vs chemotherapy. As of data cut off Aug 31 2022, after a median follow-up of 13·4 months (IQR 6·2-30·8), median overall survival was 15·2 months (95% CI 13·1-17·7; 271 deaths) in group B [atezolizumab monotherapy] and 13·3 months (11·9-15·6; 275 deaths) in group C [chemotherapy] (stratified hazard ratio 0·98 [95% CI 0·82-1·16]).[1] Previous interim analyses of the atezolizumab + chemotherapy (group A) vs placebo + chemotherapy (group C) had also not found a significant OS benefit, and neither did the final analysis of the A vs C comparison (published January 2024).[2]

The position of atezolizumab was downgraded in the 2024 update of the ESMO clinical guidelines. Like the Jones paper, the guideline update does not cite references. In the 2022 ESMO guideline, atezolizumab had a class IIIB recommendation as 1L treatment for cisplatin-ineligible PD-L1-positive patients with the caveat that results final OS results from the RCT were awaited. In the 2024 update, in the 'EV+P not unavailable or contraindicated' pathway, atezolizumab is only recommended as 2L treatment for carboplatin-eligible patients, after progression on carboplatin – and not as a 1L option. It is given a grade IIIB

recommendation in this position: III indicates level of evidence (with level I the highest), and B indicates “Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.” The guideline states that “Single-agent ICIs [immune checkpoint inhibitors; the class to which atezolizumab belongs] have a limited role in first-line advanced disease and should not be routinely recommended.”

The company also notes that in November 2022 atezolizumab’s US license was voluntarily withdrawn by Genentech for the treatment of adults with locally advanced or metastatic urothelial carcinoma (mUC, bladder cancer) who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1, or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This was because the IMvigor130 trial did not meet the co-primary endpoint of overall survival (OS) for atezolizumab plus chemotherapy compared with chemotherapy alone.[3]

Systematic Literature Review

A2. Could the company please provide a rationale for combining enfortumab vedotin with pembrolizumab i.e. why was pembrolizumab chosen to be the drug in combination with enfortumab vedotin and not any other PD-1 inhibitor?

Section 1.3 and section 1.4 of the study protocol for EV-103 (supplied with this document) provides the rationale for the mechanistic mode of action for EV and P. Further, details of preclinical and clinical trial data are described to support the value of a checkpoint inhibitor (CPI) when used in combination with an antibody drug conjugate (ADC). In section 1.5 of the study protocol, details are described for EV and P in combination; importantly observations are stated for CPI and other ADC and CPI combinations “Brentuximab vedotin and CPI Nivolumab” and that based on the potential enhancement of immune response, it is hypothesised that combining EV with a CPI will result in improved response rates and may be synergistic, with the potential to prolong PFS and OS in patients with locally advanced or metastatic urothelial carcinoma. This section also details both products (EV and P) adverse event profiles; with the hypothesis stated that there may be minimal overlapping toxicity between EV and P. As such, it was reasonable to combine these agents in a phase 1 dose escalation and expansion study, and based on the results the combination was taken forward to phase 3 trials.

A3. The literature searches for the SLR are designed to retrieve RCTs and controlled trials, yet the SLR eligibility criteria allows for single-arm studies for cisplatin-ineligible patients and studies of PD-1/PD-L1 inhibitors and EV. Could the company please clarify why the searches did not specifically search for single-arm studies such as cohort or other observational studies?

The objective of this SLR was to be comprehensive enough to capture data on potential emerging therapies. As noted in the report, “Single-arm studies also are not designed to test for statistical superiority. However, to capture all of the emerging evidence for potentially relevant comparators, single-arm studies were included for PD1/PD-L1 inhibitors, EV-containing regimens, and all studies in the cisplatin-ineligible population”. The rationale was that PD-1/PD-L1 inhibitors and EV were emerging therapies often studied first in single-arm studies; and in addition, agents often were studied first in the cisplatin-ineligible population before being studied in the full population (reflective of EV-302). Cohort and other observational studies were not included because these studies are typically on licensed treatments, whereas the rationale for including single-arm trials was specifically to capture evidence on emerging therapies.

EV-302 study

A4. Priority question: CS Document B section 2.11 states “A further, event-driven data cut from the ongoing EV-302 study is expected in 4Q 2024. This will provide longer-term PFS and OS data. The Company hopes to be in a position to present this additional data to NICE, together with updated modelling results, as soon as possible”. Could the company please clarify whether this long-term data will be submitted to NICE and when?

Efficacy and safety results of the new data cut (of 8 August 2024) are presented in the addendum to the company’s responses to clarification questions, supplied with this document, together with Kaplan-Meier curves showing comparison of model predictions based on the originally submitted data cut to the efficacy results available from the new data cut.

The company is currently working on the health economic analyses and updating the cost-effectiveness model with the new data cut (all other inputs remain the same),

and plans to submit an addendum to the economic section of the company submission on 29 November.

EV-103 study

A5 Could the company please supply a clinical study report, protocol and statistical analysis plan (SAP) for study EV-103?

The items requested are supplied with this document. The CSR reflects the data cut-off of June 2022. Please note that the long-term data from the cohort A publication is based on a post-hoc analysis for the purpose of publication, without an updated CSR.

A6. With the exception of cisplatin eligibility, the inclusion and exclusion criteria and of cohorts A and K of study EV-103 appear to be the same as that of study EV-302. Furthermore, the same dose regimen of enfortumab vedotin + pembrolizumab is used and the same key outcomes (PFS, OS etc) are measured. Could the company therefore please further clarify why results from study EV-103 were not included in the model but only used to validate survival extrapolations? Specifically, what would the likely advantages and disadvantages be of including data from this study in the model?

The results from study EV-103 were used only to validate survival extrapolations because pooling EV-103 cohorts A and K data with EV-302 data would potentially introduce bias. The EV-103 study did not include a comparator arm and only included cisplatin-ineligible patients. Therefore, if it were to be pooled with data from EV-302, it would only add patients to the cisplatin-ineligible population in the EV+P arm, and therefore it would break randomisation. Although the inclusion/exclusion criteria were similar, patients in EV-103 cohorts A and K had higher prevalence of some observed prognostic factors associated with poorer survival compared to EV-302 patients, such as age, ECOG PS and visceral metastases (see Document B page 90). Furthermore, the EV-103 cohorts A and K are relatively small compared to EV-302, hence their impact on the extrapolation is also likely to be small.

The advantage of formal incorporation would have been that the pooled EV-302 and EV-103 data could have directly informed the estimation of the survival model and associated parameter uncertainty. However, there is no guidance from NICE DSU or

from consensus in the methodological literature on the most appropriate method to incorporate external data in survival extrapolation.

- NICE DSU TSD 21 concludes: "*Incorporation of other external information. Other external information, such as registry data, may be useful to incorporate within survival models. However, research is ongoing in this area and we cannot make firm recommendations*." (page 89); and "*There are many ways in which external data sources could be incorporated into survival analyses and extrapolation. Further research is required exploring the most appropriate for specific situations. Bayesian methods would appear to offer a means by which both expert opinion and external data sources, together with model uncertainty, could be explored and integrated into health technology assessment*." (page 92).[4]

- Similarly, Palmer et al noted: "*Several approaches have been proposed to formally use information from different sources for survival extrapolation modeling.14-19 Nevertheless, these methods have not been standardized and the most appropriate method to use in any situation remains an area of ongoing research.18*" (page 2).[5]

On the other hand, since the relevant EV-103 cohorts (cohorts A and K) included only cisplatin-ineligible patients, the formal incorporation in the extrapolations of the ITT population would overweight the distribution of cisplatin-ineligible patients relative to cisplatin-eligible, reducing the generalisability of the predictions to the patient population in clinical practice.

References

A7. *Could the company please supply the following references*:

CS document B reference 35: Astellas Pharma Europe. Adelphi mUC Disease Specific Programme (EVEREST study), Data December 2023 to May 2024: Report in development, (2024).

CS document B reference 96: Astellas Pharmaceuticals Inc. Post hoc analyses of EV-302 individual patient data. Data on File, (2024).

The requested items are supplied with this document. Ref 96 is a spreadsheet including the additional analyses informing duration of subsequent treatments (file name: AST66194 EV-302 subsequent trt duration v1, values highlighted within the respective worksheets). The duration of gemcitabine + cisplatin or carboplatin treatment was based on the class duration of platinum therapy treatment. The durations of pembrolizumab and atezolizumab treatment were based on the class duration of PD-1 or PD-L1 treatment. The duration of docetaxel and paclitaxel were based on class duration of taxane treatment.

Section B: Clarification on cost-effectiveness data

B1. The CS (p127) states that the mixed model treatment coefficient was statistically significant, and so the base case uses treatment-specific pre-progression utility values. Could the company please provide a graph of mean patient health-related quality of life over time, by treatment arm for the EV-302 ITT population.

Figure 1 and Figure 2 below present graphs of the observed mean EQ-5D-3L index over time and change from baseline over time (using the first data cut dated 8th August 2023).

The results of the observed EQ-5D-3L data should be interpreted with caution because the proportion of completed questionnaires is lower in the chemotherapy arm than the in the EV+P arm. For example, the compliance rate in the EV+P arm was below 50% only from week [redacted], where [redacted] patients filled in the EQ-5D-5L questionnaire; at this time point, the compliance rate of the chemotherapy arm was [redacted]% and [redacted] patients filled in the questionnaire. The compliance rate in the chemotherapy arm was below 50% from week [redacted] ([redacted] ([redacted]%) patients filled in the EQ-5D-5L questionnaire); data from the first data cut of 8th August 2023.[6]

If patients who did not fill in the questionnaire experienced worse health-related quality of life than patients who did, then the higher the proportion of patients who did

not complete the questionnaires, the larger the difference between the experienced ('true') EQ-5D-3L index and observed EQ-5D-3L index. As the compliance rate is lower in the chemotherapy arm than in the EV+P arm, the impact of non-completed questionnaires is larger in the chemotherapy arm. Therefore, the apparent difference in the observed mean EQ-5D-3L index scores over time between the trial arms would be an artifact of the differential completion rates rather than reflecting differences in patients' HRQoL, and the observed EQ-5D-3L indexes are not necessarily representative of the experience of all patients in the trial.

Therefore, the appropriate approach is to analyse the data with a method that can handle the missing data, such as the mixed effect model which was used to estimate EQ-5D-3L utility indexes by health state.[7] A mixed effect model uses all the observed data to estimate the effect of each observed characteristic on the EQ-5D-3L index over time.

Figure 3 and Figure 4 show the predicted mean utility and mean change from baseline utility over time, based on the mixed effects model used to estimate utilities by health state to inform the model. The mixed effects model estimated that EV+P treatment had a positive coefficient for utilities. When using the mixed effect model to predict mean utility over time for the two trial arms, it predicts that the mean utility is slightly [redacted] in the EV+P arm up to approximately week [redacted], then [redacted] subsequently. This is aligned with the observed data, as shown in Figure 1, and supports the validity of the mixed effects model in not only reflecting the observed data but also handling the missing data.

Figure 1: Mean utility over time in overall PRO FAS population of EV-302, UK 3L tariff

Notes: *Values at the bottom of the figure represent number of patients at each time point.* ***Abbreviations:*** *3L, three level; EV, enfortumab vedotin; PRO FAS, patient-reported outcome full analysis set; SE, standard error; UK, United Kingdom.*

Figure 2: Mean change from baseline utility over time in overall PRO FAS population of EV-302, UK 3L tariff

Notes: *Values at the bottom of the figure represent number of patients at each time point.* ***Abbreviations:*** *3L, three level; EV, enfortumab vedotin; PRO FAS, patient-reported outcome full analysis set; SE, standard error; UK, United Kingdom.*

Figure 3: Predicted mean change from baseline utility over time by treatment in overall PRO FAS population of EV-302, UK 3L tariff

Notes: *Figure generated based on predictions from mixed-effect model using DCO1.*

Figure 4: Predicted mean utility over time by treatment in overall PRO FAS population of EV-302, UK 3L tariff

Notes: *Figure generated based on predictions from mixed-effect model using DCO1.*

B2. Could the company please provide a) the completion rates for the EQ-5D-5L, and b) the total number of EQ-5D-5L questionnaires completed, in the EV-302 PRO FAS for both treatment arms post-progression. Could the company please also state how long after post-progression was health related quality of life measured?

Health-related quality of life was measured as detailed in Table 13 Electronic Patient-Reported Outcomes Schedule of Events in the EV-302 study protocol.[8] This was weekly until week 14, and every 3 weeks through disease progression and survival follow-up. That is, there was no protocol-mandated time-point at which EQ-5D-5L data collection needed to stop.

The completion and compliance rates for the EQ-5D-5L are presented in Appendix O of the company submission (see Figures O.1 and O.2 in Appendix O). As noted in Section 2.6.6 of the Company Submission, overall, 731 of the 886 randomised patients completed baseline PRO questionnaires and patient compliance with PRO assessments remained >70% through week 17 in the chemotherapy arm and week 29 in the EV+P arm.[9] As discussed in CS Section 2.12.2 (p.78), post hoc analysis of individual patient-level data found that in both treatment arms, completion rates were [redacted] 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 [redacted] for EV+P than for chemotherapy. Beyond Week 86, the completion rate for all health states and treatment arms were less than [redacted]%.[10]

Since patients in worse health states [redacted] to complete the questionnaires, the PRO data could be biased in favour of chemotherapy, particularly post-progression, i.e. the HRQoL benefits of EV+P over chemotherapy may be greater than suggested by the primary PRO analysis.

Based on the EV-302 data cut dated 8th August 2024, the follow-up period for post-progression HRQoL on average was [redacted]days (median [redacted]days, range [redacted]days).

B3. We checked the company's base case results and note a discrepancy between the ICERs reported in the CS (Table 59 and Table 61) and the values

produced by the model obtained by the EAG (Table 1) for the cisplatin-eligible and the cisplatin-ineligible patients. Could the company please explain this discrepancy?

Table 1 Base case results without severity modifier, including EV PAS

Population	**ICER (£/QALY)**	
	CS result	**EAG result**
Cisplatin-eligible	[redacted]	[redacted]
Cisplatin-ineligible	[redacted]	[redacted]

The base case curve selections for OS, PFS and time on treatment (ToT) differ between the subgroups, and these need to be changed manually in the Excel spreadsheet. All other inputs update to subgroup-specific inputs when the population selection is made on the Settings sheet. Please use the settings presented below to align with the base cases applied in the company submission.

		Population		
Variable	**Excel reference**	**ITT**	**Cisplatin-eligible**	**Cisplatin-ineligible**
PFS EV+P	Efficacy_PFS E14	Hazards, 2 knots	Hazards, 1 knot	Hazards, 2 knots
PFS SOC	Efficacy_PFS E16	Odds, 3 knots	Normal, 3 knots	Odds, 1 knot
OS EV+P	Efficacy_OS E13	Log-logistic	Log-logistic	Log-logistic
OS SOC	Efficacy_OS E14	Log-logistic	Log-normal	Log-logistic
TOT EV+P	Efficacy_ToT F8	Log-logistic	Log-normal	Log-normal
TOT SOC	Efficacy_ToT F9	Log-normal	Log-normal	Log-normal

B4. CS Table 40 shows that the relative dose intensity (RDI) for enfortumab vedotin is 80.1%. Could the company please comment on the reasons why RDI is so low, including the reasons for treatment interruption or dose reduction.

Dose reductions are allowed in order to manage tolerability, both in the trial protocol

and the prescribing information for EV[11] (see CS Table 2). Thus, the license allows for dose adjustment according to individual patient needs. In EV-302, 40.7% of patients on EV+P had treatment-related AEs leading to dose reductions of any study drug (CS Table 16). Dose typically remains at the lower level after adjustment. Dose interruptions were also common in EV-302: 60.5% of patients had a treatment-related AE leading to dose interruption of EV.[12] (NB Dose interruption includes dose elimination and dose delay as collected on the CRF. Dose elimination is when a scheduled dose is skipped. Dose delay is when a dose does not occur on the scheduled dosing day.[6])

The EV SmPC provides information on the most common AEs leading to dose interruption and dose reduction for EV when administered in conjunction with P (information relates to 564 patients who received at least one dose of EV 1.25 mg/kg in combination with P in either EV-103 or EV-302; Table 2).[11] Of note, a similar RDI ([redacted]%) for EV was seen with EV monotherapy in the EV-301 study.

Table 2 Adverse reactions (≥ 2%) leading to dose interruption or reduction of EV when administered in combination with P (EV-103 and EV-302)

Most common adverse reactions (≥ 2%) leading to dose interruption of EV	Peripheral sensory neuropathy (17%) Rash maculo-papular (6.9%) Diarrhoea (4.8%) Fatigue (3.7%) Pneumonitis (3.7%) Hyperglycaemia (3.4%) Neutropenia (3.2%) Alanine aminotransferase increased (3%) Pruritus (2.3%) Anaemia (2%)
Most common adverse reactions (≥ 2%) leading to dose reduction of EV	Peripheral sensory neuropathy (9.9%) Rash maculo-papular (6.4%) Fatigue (3.2%) Diarrhoea (2.3%) Neutropenia (2.1%)

Source: SmPC[11]

B5. Could the company please clarify whether any adverse events for neutropenia reported in CS Table 36 were for febrile neutropenia, and, if so, report a corresponding disutility and cost to treat this adverse event.

The neutropenia events reported in CS Table 36 refer to any neutropenia, and not febrile neutropenia specifically. This table is based on Table 37 of the EV-302 CSR, which summarised events from the CSR Table 12.6.1.3.1 (Grade 3-5 Treatment-Emergent Adverse Events by Preferred Term).[6] For this table, the term neutropenia refers to any reportable terms of neutropenia based events: Neutrophil count decreased, Neutropenia, Febrile neutropenia, Band neutrophil count decreased, Band neutrophil percentage decreased, Cyclic neutropenia, Idiopathic neutropenia, Neutropenic infection, Neutropenic sepsis and Neutropenic colitis. The incidence of febrile neutropenia was [redacted] patients ([redacted]%) with EV+P vs [redacted] patients ([redacted]%) with chemotherapy.

Clinician 2 in the consultation exercise described in response B6 below was asked how neutropenia is managed in clinical practice. They said that neutropenia is a common chemotherapy side effect. It should be managed according to guidelines (e.g. ASCO guidelines[13]) by giving granulocyte colony stimulating factor (G-CSF) and reducing drug doses. Patients are not hospitalised (due to infection risk) – patients are managed at home/outpatient. They said that neutropenic sepsis (febrile neutropenia) is a severe complication of chemotherapy and requires 2-5 days in hospital with IV antibiotics, and is associated with high fatality (about 5-10%).

The model currently uses code WJ11Z: Other Disorders of Immunity, to represent the cost of neutropenia. All other codes within the WJ category are associated with higher unit costs. Due to the difference in the incidence of febrile neutropenia events between the treatment arms, inclusion of costs and disutilities associated with febrile neutropenia would result in a more favourable ICER for EV+P versus PBC than the current base case.

B6. Could the company please explain which health care resources would typically be used to treat fatigue in clinical practice and show how the cost of these resources would be similar to that reported in CS table 47.

The cost of managing fatigue was based on the committee papers for NICE TA788 (avelumab for maintenance treatment of locally advanced or metastatic urothelial

cancer after platinum-based chemotherapy,[14] see CS Table B.3.20 page 100). Therefore the healthcare resources align with those used in a previous NICE appraisal, thereby ensuring consistency across appraisals within the same disease area.

To better understand the applicability of this assumption, two expert clinicians were consulted via videoconference interviews (Clinicians 1 and 2, who are Professors and Consultants in Medical Oncology in two different large cancer centres in England). Clinician 1 explained that Grade 3 fatigue means that the patient struggles with daily activities. They indicated that management of treatment-related severe fatigue is to delay the next treatment cycle (i.e. delayed dose for example for 1 week then reevaluate). They noted that it is important to distinguish if fatigue is due to treatment or disease, i.e. fatigue may be because of disease progression rather than the treatment. Clinician 2 said that there is no real 'treatment' for Grade 3 fatigue. It does not require hospitalisation, and is managed by treatment holiday i.e. dose interruption.

In light of this, we have now undertaken a scenario analysis where the cost of treating fatigue as an adverse event was set to zero. Total AE costs were estimated to be £[redacted] and £[redacted] for the EV+P and PBC arms, respectively with the original assumptions. If the cost of treating fatigue as an adverse event is reduced to £0, the total AE costs reduce to £[redacted] for the EV+P arms and to £[redacted] for the PBC arm. Table 3 presents the original base case results for reference, while **Error! Reference source not found.** shows the results of the scenario where cost of fatigue is assumed to be zero. The impact on the incremental costs is minor (difference of £[redacted] per patient; less than 0.1% of the incremental costs).

Table 3. Original results with cost of fatigue equal to £4,072

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.60	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.92	[redacted]

Table 4. Scenario results with cost of fatigue equal to £0

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.60	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.92	[redacted]

B7. The total AE costs reported in the CS (p141) (£[redacted] and £[redacted] for the EV+P and PBC respectively) differ from those values used in the model (£[redacted] and £[redacted] for the EV+P and PBC respectively). Could the company please confirm which values are correct.

Apologies for this mistake. The values reported in the model are the correct values, i.e. total AE costs are £[redacted] and £[redacted] for the EV+P and PBC respectively. These values were also reported in Table J.4. of Appendix J, providing the disaggregated results of the cost-effectiveness analysis.

Please note that on CS p.141, the values were not marked as CIC, but this was an error (in the model and in appendix J they were marked CIC). The values should be CIC as together with information on other cost items (e.g. health state costs) they would allow back-calculation of total drug costs, therefore the confidential discount. Therefore we have marked the values in the response as CIC and will upload updated versions of the CS with this information correctly marked as CIC when submitting the updated economic model with the new data cut.

Section C: Textual clarification and additional points

No questions

References

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3. Genentech. Genentech Provides Update on Tecentriq U.S. Indication for Previously Untreated Metastatic Bladder Cancer (2022). https://www.gene.com/media/statements/ps_112822 (accessed 8 November 2024).
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12. Powles T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. *N Engl J Med* 2024;390(10):875-88.
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

1. Pembrolizumab with enfortumab vedotin for untreated metastatic urothelial cancer [ID6332]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	**Jeannie Rigby**
2. Name of organisation	Action Bladder Cancer UK
3. Job title or position	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	Action Bladder Cancer UK is a national registered charity dedicated to providing information and support to those with bladder cancer and their families and carers; raising awareness; improving outcomes; providing health professional learning and funding research. ABC UK is governed by a trustee board (10 members) and has full time Chief Executive and core staff, and many patient volunteers, and a network of patient support groups. ABC UK is funded mainly by public donations, legacies, grants and fundraising, together with a smaller amount of corporate arms length grants.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	Not in the last 12 months.

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NONE
5. How did you gather information about the experiences of patients and carers to include in your submission?	A core remit of ABC UK is to provide support and information for those with bladder cancer and their carers. We work closely with many patients (or family members) every year by providing direct support by phone helpline and email – many of these contacts with patients will concern treatment choices (or lack of), the effects of treatment and the impact of bladder cancer on daily life and coping with this disease along what can be a long, and sometimes complicated, treatment pathway. We set up and sustain patient support groups across the UK. We run a programme of patient support events. We also collect information about patient experience through our extensive education programme for specialist urology/cancer nurses. We conduct patient surveys to gather information on the direct impact of bladder cancer, impacts of treatments and on-going surveillance and monitoring and potential recurrence of bladder cancer. We provide patient views and input to many clinical trials and research projects. We also encourage many research projects to include PROMS aspect to their research, sometimes funding this work or providing patient participants for this research. As part of our core Governance, patients make up 50% of our Trustee board (together with clinicians forming the other 50%). We have many patient volunteers who help us to deliver our work and programmes.

	We work closely with patients on the production, and regular updating, of all of our ABC UK information materials and web content. Patients also input into all submissions to both NICE and SMC regarding use of medicines for the treatment of bladder cancer, and have reviewed and inputted into this submission.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A common psychological impact is patients struggling to come to terms with the very poor outcomes presented on their diagnosis. It is also very distressing to realise that treatment options are extremely scarce. Many of the calls we get from these patients (or a family member) ask whether there are any other treatment options available for them. In addition to coming to terms with the very poor outlook they must also endure the adverse side effects of currently available treatments, leaving patients both emotionally and physically exhausted. This can have a toll on more general health, including mental health. Family members and carers struggle between providing optimistic support and hoping that the ordeal they are forced to witness gets no worse, or lasts too long, giving rise in many cases to feelings of guilt at their own mixed emotions. They can also feel anger or helpless at the lack of availability of alternative treatments and the poor quality of life the patient is having to endure. There can be a considerable carer burden due to quality of life for the patient together with common negative side effects from existing treatments. Our patient groups, our patient survey responses and patient support helpline enquiries all reflect these views and similar experiences for patients with this condition. ABC UK are often asked by these patients (or a carer/family member) what else can be done – if there are other treatment options, or treatments which may have less adverse treatment effects than already undergone. Of significant concern to these patients is the lack of any progress in new treatment options over very many years, especially compared with most other forms of cancer. 62 yr old male - now deceased: ‘It was a shock to be told my cancer had gone through the [bladder] wall … I had chemotherapy and that made me really ill so they had to stop it. Then I was told they couldn’t do much more. That’s it.’

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The aim of treatment for most patients in this group is to control the cancer, relieve symptoms and maintain quality of life. However, treatment options for this type of bladder cancer are very limited, patients and families can be shocked by the limited treatment options are available. It can be difficult to decide which treatment to try or whether to have treatment at all, issues which also have to be considered are how the treatment might affect your quality of life. The current treatment options for this patient group can adversely affect quality of life. This includes the possible serious side effects as well as the process of any treatment. A patient might undergo one, or more, of the treatments below for metastatic bladder cancer: • chemotherapy • immunotherapy or targeted cancer drugs (there are very few immunotherapy treatments widely available in the UK) • radiotherapy to the site where the cancer has spread • surgery to remove cancer tumour in the bladder • surgery to unblock the ureters or urethra • a clinical trial. Chemotherapy is a common treatment offered for metastatic bladder cancer – however side effects include: sickness; loss of appetite; losing weight; extreme tiredness; increased risk of getting an infection; bleeding and bruising easily; diarrhoea or constipation; hair loss. It is common for patients to be unable to continue chemotherapy due to the impact of serious treatment effects. Some patients may also not be eligible for further chemotherapy due to co-morbidities, the percentage of treatment-related adverse events or longer-term tolerability with chemotherapy.

8. Is there an unmet need for patients with this condition?	There is an urgent unmet need for treatment for this patient group following chemotherapy or where chemotherapy has proved unsuitable. There is little other treatment choice available and currently outcomes are poor. New treatments are required to meet this pressing need, and to be processed in a timely manner to a wider use within the NHS. Treatment options for locally advanced or metastatic bladder cancer are very limited; a large percentage of this patient group are not eligible for current treatment options due to other conditions or comorbidities; other existing treatments can show high levels of lack of tolerability and adversely affect quality of life. It is of particular appropriateness given the trial results for Pembrolizumab plus Enfortumab Vedotin therapy which demonstrate improved survival versus the current most common treatment available for this patient group.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**Treatment options** for locally advanced or metastatic bladder cancer are very limited; a large percentage of this patient group are not eligible for current treatment options due to other conditions or comorbidities; other existing treatments can show high levels of lack of tolerability and adversely affect quality of life. Clinical trial evidence clearly and compellingly demonstrates significant improvements in not only progression free survival but also overall survival compared to traditional chemotherapy. This evidence demonstrates the first significant improvement in survival rates for this patient group for many years. This treatment has considerable advantages over existing treatments given the trial results for Pembrolizumab plus enfortumab vedotin therapy which demonstrate **improved survival** versus the current most common treatment available for this patient group. It should also be noted that clinical trial results have shown comparable benefit for Pembrolizumab plus Enfortumab Vedotin in all subgroups including cisplatin and carboplatin eligible, visceral metastases and PDL-1 positive and negative patients groups. Due consideration should be given to the **quality of life** for patients with existing recommended common treatment (chemotherapy), and also to the percentage of treatment-related adverse effects with chemotherapy and the impact on quality of life for this patient group as well as survival. • A significant percentage of patients with locally advanced or metastatic urothelial cancer (c50%) are ineligible for first-line cisplatin-based chemotherapy because of other comorbidities or impaired renal function etc. • Gemcitabine plus Carboplatin can be used to treat cisplatin-ineligible patients, but has shown lower activity and poor tolerability for the patient. • In addition, of the cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who receive first-line treatment, a significant percentage do not receive a second-line treatment. • This underlines the need for, and gives a greater urgency to, effective and tolerable first-line therapies. • Other treatment options are limited, or are not available to this patient group via the NHS.

	Positive response to immunotherapies may be triggered later, however this response is likely to be durable, bringing longer-term survival benefits for patients. Improvement in quality of life for these patients, both in terms of improvements in physical health and in mental well-being, will also provide significant benefits for carers. Improvements in negative side effects from current treatment options, would mean less hospital appointments and less hospital time taken to alleviate these side effects.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Lack of access to this new treatment.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with locally advanced or metastatic bladder cancer might benefit most due to evidence of improved survival and less impact of serious side effects with Pembrolizumab plus Enfortumab Vedotin. Treatment options for locally advanced or metastatic bladder cancer are very limited; a large percentage of this patient group are not eligible for current treatment options due to other conditions or comorbidities; other existing treatments can show high levels of lack of tolerability and adversely affect quality of life. Those patients who have been unable to continue chemotherapy due to the impact of serious treatment effects – which is common. Those patients may also not be eligible for further chemotherapy due to co-morbidities, the percentage of treatment-related adverse events or longer-term tolerability with chemotherapy. Clinical trial evidence has shown that the benefits of Pembrolizumab plus Enfortumab Vedotin extend across a range of levels of PD-L1 expression, thus evidencing efficacy across a wide patient demographic and range of sub groups, regardless of PD-L1 status.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality of access to treatments: Patients expressed concern that it would not be made widely available through the NHS, equally across the UK, leading to inequality of access to treatments. There is an inequality within bladder cancer in that female patients are often diagnosed at a more advanced stage than male patients.

Other issues

13. Are there any other issues that you would like the committee to consider?	There is a lack of treatment options for those patients with bladder cancer. It is of some concern, that new emerging therapies should be given proper consideration, particularly where there is such an acute patient need. Pembrolizumab plus Enfortumab Vedotin has shown to be of great impact – not only in terms of clinical efficacy but also in terms of impact on patients across the patient sub groups. Results have shown considerable benefit in terms of quality of life and treatment side effects, particularly when compared with chemotherapy. The use of Enfortumab Vedotin plus Pembrolizumab, and the impressive results shown, is a significant advance in the treatments available for locally advanced or metastatic urothelial carcinoma. Enfortmab Vedotin plus Pembrolizumab has the potential to set a new standard of care. It is also of pressing concern that new therapies such as Enfortumab Vedotin plus Pembrolizumab are given wider clinical use in order to gather and collate further data to support potential wider use of this combination. The NICE Guideline NG2 is referenced within the terms of this Appraisal. We feel obliged to raise the issue that this Guideline was published in February 2015 (nearly 10 years ago), has had no substantial update since then and is thus out of date in many key areas particularly regarding treatments or treatment methods and the care pathway as recommended within this Guideline. We feel this is a matter of some imperative which should be considered within any review of available evidence regarding the treatment of bladder cancer, particularly in relation to newer therapies vs existing therapies. This necessary update of the Guideline is currently being advocated for strongly by patient organisations and clinical experts with NICE and an evidence surveillance review is currently in progress, however with no indication of any update.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is an urgent need for treatments for this patient group, to improve current poor outcomes and lack of treatment options. • Enfortumab Vedotin plus Pembrolizumab has clearly demonstrated in clinical trials significantly improved survival vs common current treatments. • Enfortumab Vedotin plus Pembrolizumab has clearly demonstrated in clinical trials significantly improved quality of life and significant benefits in terms of treatment side effects when compared with current common treatments. • New emerging therapies should be given proper consideration particularly where there is such an acute patient need. Enfortumab Vedotin plus Pembrolizumab is a significant advance in the treatment of bladder cancer and should be given the wider access which these patients merit. • Evidence from clinical trials is compelling both for clinical efficacy and patient quality of life and improvement in side effects - Enfortumab Vedotin plus Pembrolizumab should be considered and approved for first line treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

1. Pembrolizumab with enfortumab vedotin for untreated metastatic urothelial cancer [ID6332]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Fight Bladder Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight Bladder Cancer is a registered Charitable Incorporated Organisation in Scotland (SC051881), England and Wales (1198773), and was initially established as an unincorporated charity in England and Wales (1157763). It also operates in Northern Ireland. Fight Bladder Cancer is a patient-led charity dedicated to supporting individuals affected by bladder cancer, raising awareness of the disease, and advocating for improved research and treatment options. The charity provides information, support, and resources for patients, carers, and healthcare professionals, as well as facilitating peer-to-peer support through online forums and local groups. Fight Bladder Cancer is funded through a combination of donations, fundraising events, and grants from trusts and the pharmaceutical industry. The organisation has a community of thousands, including patients, carers, healthcare professionals, and supporters.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Patient Information Booklets & National Cancer Patient Experience Survey (02/11/2023) Amount: £10,000.00 Company: Roche UK Global RFP Request for Proposals (RFP) Engaging the Bladder Cancer Patient Community in Research and Publications (22/11/2023) Amount: £15,552.36 Company: Pfizer Charity Leaders Forum (31/01/2024) Amount: £1,200.00 Company: Pfizer Look. And You Will C Us. Translations (30/04/2024) Amount: £10,000.00 Company: Gilead Awareness - Conferences & Events (30/04/2024) Amount: £9,000.00 Company: Janssen J&J Johnson & Johnson Innovative Medicine Policy - Exemplar (30/04/2024) Amount: £30,000.00 Company: Janssen J&J Johnson & Johnson Innovative Medicine Patient and Carer Information Booklets (09/05/2024) Amount: £9,094.80 Company: Janssen J&J Johnson & Johnson Innovative Medicine

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information about the experiences of patients and carers through several methods. Surveys were distributed to patients and carers affected by metastatic or unresectable bladder cancer, capturing their experiences with the condition, current treatments, and quality of life. Feedback was also collected from online bladder cancer support communities. Lastly, we collaborated with other bladder cancer patient organisations to gather insights from their members, especially regarding unmet needs and the impact of current treatments.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with metastatic urothelial cancer is an intensely challenging and emotionally exhausting journey for both patients and carers. Patients undergo continuous treatments like chemotherapy, radiotherapy, and clinical trials, all of which carry debilitating side effects such as fatigue, infections, and significant changes in bodily functions. These interventions often leave patients in constant pain, while the disease relentlessly progresses, leading to a rapid decline in quality of life. Metastatic urothelial cancer carries a grim prognosis, with few treatment options available. The treatments that do exist are highly invasive and come with severe side effects, further diminishing quality of life in a person's final months. The primary focus is on slowing the cancer's spread, rather than achieving a cure. This leaves many patients feeling frustrated and disheartened by the limited efficacy of treatments and delays in care, compounding their fear and anxiety as they confront the lack of viable options. The impact on daily life is profound, with patients often struggling to work, travel, or maintain physical activity. The emotional and physical toll is immense, with many realising that the goal is to extend life rather than to cure the disease. "My cancer has spread to my lungs and bones, and the treatments are just delaying the inevitable." "I've had 3 cycles of chemo and the side effects are unbearable, leaving me in constant pain and unable to move around as I used to." The World Bladder Cancer Patient Coalition Global Survey on Bladder Cancer found that patients with metastatic / advanced cancer experience greater hardships in certain aspects of life, outlined below:[1] - Respondents with advanced/metastatic cancer were more likely to be **impacted financially** (severely, to some extent or slightly/) (57%) compared to all other respondents (49%) - Advanced/metastatic respondents were **more vulnerable to changes in employment** status. Advanced and/or metastatic cancer patients were significantly more likely to voluntarily leave their job (19%) or take an early retirement (26%) compared to all other respondents (3% and 12% respectively) - Respondents with advanced/metastatic bladder cancer felt **less able to live a full life** – with 39% saying they could not life a full life following their diagnosis and treatment. This was three times higher compared to all other survey respondents (13%).

- Advanced/metastatic patients were more likely to say that the **long-term emotional impact** of their treatment for bladder cancer has not been addressed (60%) compared to other survey respondents (46%).

The World Bladder Cancer Patient Coalition survey highlights the crucial role carers play in supporting bladder cancer patients, facing both emotional and practical challenges. Most carers (91%) experience significant emotional distress, including fear of relapse (65%) and ongoing anxiety (60%). Many feel unprepared, with only 21% finding adequate information on how to care, while 43% need more guidance. Emotional support is the most common yet difficult role (49%) for carers, who also manage appointments and research treatment. With most carers (71%) providing long-term support, they often prioritise the patient's needs over their own, underscoring the need for better resources and support[1].

"I'm exhausted, physically and emotionally. Between hospital visits and managing his care at home, I hardly have time to take a breath."

"I feel like I'm drowning in responsibility. Every day brings something new, and I'm constantly afraid of what's next."

Both patients and carers frequently describe the experience as isolating, exhausting, and fraught with fear and frustration. The emotional toll is amplified by feelings of injustice as they confront the limitations of medical care. While some find solace in support groups or online communities, the journey through metastatic urothelial cancer is marked by profound pain and emotional turmoil for both those living with the disease and those caring for them.

"I feel like we're battling this alone, and the healthcare system is just dragging its feet."

"The lack of clear communication from doctors only adds to our stress and uncertainty. It feels like we're constantly left in the dark."

[1]The World Bladder Cancer Patient Coalition (2023). Patient and carer experiences with bladder cancer: findings from a global survey. https://worldbladdercancer.org/patient-and-carer-experiences-with-bladder-cancer/

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers express a range of emotions about the care provided by the NHS for metastatic urothelial cancer, though they unanimously agree on the need for more treatment options. Some feel fortunate and appreciative of the quality of care, especially given that it is free of charge. "I feel incredibly lucky to have access to treatment through the NHS. The care I've received has been top-notch, and I can't imagine going through this without it." "The nurses and doctors have been amazing. They've been there every step of the way, making sure I understand my treatment and what's next." However, many express frustration with delays in diagnosis, long treatment wait times, and poor communication with healthcare providers. "The communication, or lack of it, from Urology is awful. It's causing so much stress and anxiety for my husband." "I thought that waiting was too long, but I was told the secretary was on holiday. I've never waited this long in 11 years of treatment." Access to alternative treatments and clinical trials is another major concern. While some patients benefit from therapies like immunotherapy or chemotherapy, many feel there are limited and untailored options available. "We had to push for advanced genomic testing after standard treatments stopped working. Why isn't this offered earlier?"

8. Is there an unmet need for patients with this condition?	The situation for metastatic or unresectable bladder cancer patients is dire, with glaring gaps in care that leave many struggling in uncertainty and fear. Communication with healthcare providers is woefully inadequate, often leaving patients in the dark about their treatment plans. The lack of clear, consistent updates exacerbates the emotional toll, as patients face the terrifying prospect of battling an aggressive cancer without knowing what lies ahead. Delays in treatment are a critical failure, with life-saving procedures postponed or cancelled at alarming rates. Patients with metastatic and unresectable bladder cancer are left waiting in anguish, knowing that every lost day could allow their cancer to advance. The system's inability to respond urgently to these high-risk cases leaves many feeling abandoned and powerless as they watch their condition deteriorate. Even more alarming is the limited access to alternative treatments. Patients have few options. The promise of clinical trials or personalised treatments like advanced genomic testing remains out of reach for many, leaving them to endure treatments that are ineffective or not tailored to their needs. The lack of innovation and personalised care in the face of such a deadly disease is nothing short of devastating. "We were told the treatment was only to buy time. It's devastating to feel like there's no real solution." "My dad's been on a clinical trial, but the side effects are brutal, and it feels like the options are so limited." "We've heard so much about trials and new treatments, but they feel out of reach. We don't know what's even available to us." "I feel like there's no clear path forward, and every option feels like a stopgap…" "I keep asking about other treatments, but we're just told to wait. It's hard not to feel like there's nothing left for us."

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The EV-302 clinical trial showed a significant increase in overall survival for patients treated with enfortumab vedotin and pembrolizumab (31.5 months vs. 16.1 months with chemotherapy). This highlights the potential for extended life expectancy in patients with advanced bladder cancer. The combination therapy also delayed disease progression (12.5 months vs. 6.3 months with chemotherapy), allowing patients to live longer without their cancer worsening. The overall response rate—complete or partial tumour shrinkage—was markedly higher in those receiving the combination treatment (68%) compared to chemotherapy (44%), demonstrating a greater likelihood of tumour reduction. Many patients also experienced prolonged periods of remission, with responses lasting 12 to 18 months, showing the potential for sustained disease control (Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in advanced urothelial cancer. N Engl J Med. 2024;390:875-888. doi:10.1056/NEJMoa2312117.) In the EV-302 study, the median time for pain to worsen was 14.2 months for patients on pembrolizumab with enfortumab vedotin, compared to 10 months for those on chemotherapy. By week 26, patients on pembrolizumab with enfortumab vedotin experienced a greater reduction in worst pain than those on chemotherapy. Among those with moderate-to-severe pain at the start, noticeable improvements were seen between weeks 3 and 26 with pembrolizumab with enfortumab vedotin (Gupta S, Loriot Y, Van Der Heijden MS, et al. PROs from a phase 3 trial of enfortumab vedotin plus pembrolizumab vs. chemotherapy in advanced urothelial cancer. J Clin Oncol. 2024;42(16_suppl):4502. doi:10.1200/JCO.2024.42.16_suppl.4502.) In the EV-302 study, for the overall quality of life, pembrolizumab with enfortumab vedotin patients had a brief decline at week 3 but returned to normal afterward. In contrast, patients on chemotherapy experienced a steady decline from week 1 to week 17, with scores dropping between -1.2 and -7.1 below baseline. Although their condition stabilised at week 17, it remained at a worse level compared to patients on pembrolizumab with enfortumab vedotin, who had already recovered by then (Gupta S, Loriot Y, Van Der Heijden MS, et al. PROs from a phase 3 trial of enfortumab vedotin plus pembrolizumab vs. chemotherapy in advanced urothelial cancer. J Clin Oncol. 2024;42(16_suppl):4502. doi:10.1200/JCO.2024.42.16_suppl.4502.) In the EV-302 study, although side effects were reported, they were generally more manageable than those experienced with chemotherapy. Patients faced fewer severe side effects, such as reduced cases of anaemia and neutropenia, which often accompany chemotherapy. Enfortumab vedotin and pembrolizumab allowed many patients to maintain a better quality of life, with side effects like neuropathy and skin reactions often being milder than the more debilitating effects of chemotherapy, such as anaemia and nausea (Powles T, Valderrama BP,

	Gupta S, et al. Enfortumab vedotin and pembrolizumab in advanced urothelial cancer. N Engl J Med. 2024;390:875-888. doi:10.1056/NEJMoa2312117.) For the patients that we spoke with, many reported significant tumour shrinkage with the enfortumab vedotin and pembrolizumab combination. Some saw an extension in survival, even with metastatic disease. "The combination has given me more time with my family. It shrunk my cancer significantly, which we didn't expect at this stage." "I feel like the treatment is targeting my cancer more effectively than chemo alone. The side effects are tough, but the results have been worth it." "This combo has given us hope and more time." "This treatment has slowed the progression of my disease, and I'm able to do more day-to-day activities without as much pain." "We had to push for this combination, but I'm glad we did. It feels like it's giving me a fighting chance."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The EV-302 clinical trial found that while the combination therapy is generally better tolerated than chemotherapy, it still poses risks of serious side effects. Neuropathy was one of the most common issues, significantly impacting daily activities. Skin reactions were also prevalent, ranging from mild rashes to severe conditions requiring medical intervention, with 16% of patients reporting serious skin issues. High blood sugar, particularly in patients with pre-existing diabetes, added to the list of complications that required careful management. Pembrolizumab contributed its own set of immune-related side effects, including pneumonitis, hepatitis, and thyroid dysfunction, which could be severe enough to require discontinuation or adjustment of the treatment. A substantial portion of patients (35%) had to stop treatment due to adverse effects, particularly peripheral neuropathy and severe skin reactions (Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in advanced urothelial cancer. N Engl J Med. 2024;390:875-888. doi:10.1056/NEJMoa2312117). In the EV-302 trial, patients received pembrolizumab infusions every three weeks (on day 1 of each 21-day cycle), administered intravenously. Enfortumab vedotin was also delivered intravenously on days 1 and 8 of each 21-day cycle. Patients discontinued pembrolizumab when they experienced disease progression, unacceptable toxicity, or after completing the maximum 35 treatment cycles. Enfortumab vedotin was discontinued upon confirmed disease progression, unacceptable toxicity, or patient choice, with no set maximum number of cycles. Frequent hospital visits for these infusions posed an additional burden for patients (Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in advanced urothelial cancer. N Engl J Med. 2024;390:875-888. doi:10.1056/NEJMoa2312117). For the patients that we spoke with, they said that managing side effects, such as neuropathy (nerve damage), skin reactions, and fatigue, was a common challenge for patients on enfortumab vedotin and pembrolizumab. Neuropathy, causing pain, numbness, or tingling in the hands and feet, frequently led to dose reductions or stopping treatment altogether. Some patients experienced limited or no tumour shrinkage, resulting in disappointment. Severe fatigue was another prominent side effect, along with immune-related complications like arthritis and joint pain. "I do have a lot of appointments, but it's not too many. I go to the hospital more frequently than before, I look forward to it. It's like a day out. I like seeing familiar faces — people who understand. It's not the end of the world."

	"The only difference with enfortumab vedotin is - I've got to be on it forever. There's no end date. They'll stop it when it affects me too much. This is pure maintenance to keep me going. My life has been saved, but I don't know for how long. How long until it damages an organ? What will it do then? If I asked, they'd give me an answer, but I don't want a due date." "The neuropathy has been really difficult to manage. I've had to stop treatment a couple of times due to the pain in my hands and feet." "It's frustrating that the treatment works for some but not for everyone. We didn't get the results we were hoping for, and now we're out of options." "The costs of managing side effects, like neuropathy and skin reactions, add up, and the emotional toll of constant hospital visits is exhausting."

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who may benefit more include those ineligible for cisplatin-based chemotherapy. Cisplatin remains the standard treatment for advanced bladder cancer, but many, especially older adults or those with kidney issues, cannot tolerate it. For these patients, pembrolizumab combined with enfortumab vedotin offers a viable alternative, providing effective treatment for those unable to undergo platinum-based therapy. Patients who may benefit less include those with severe pre-existing neuropathy. Enfortumab vedotin carries a significant risk of peripheral neuropathy. Individuals with existing nerve damage may see their symptoms worsen, potentially requiring dose reductions or stopping treatment, which can reduce its effectiveness. Additionally, patients with autoimmune conditions such as rheumatoid arthritis, lupus, or inflammatory bowel disease may experience immune-related complications triggered by pembrolizumab, making this combination less suitable for them. Patients with diabetes may also face challenges, as enfortumab vedotin can cause hyperglycaemia, complicating blood sugar management and possibly leading to interruptions in treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The new NICE severity modifier may not fully address the needs of people with metastatic urothelial cancer. This group, often older and with limited treatment options, faces significant barriers to accessing innovative therapies like erdafitinib. The severity modifier, which replaced the end-of-life modifier, was designed to increase the value of treatments for severe conditions. However, it may fail to capture the full impact of therapies for patients in advanced cancer stages. For example, while erdafitinib clearly extends survival and improves quality of life, the weighting applied under the severity modifier might undervalue its benefits for this patient group. Older individuals with shorter life expectancy often achieve a lower QALY gain, potentially resulting in a lower score in NICE's cost-effectiveness assessments. This shift could reduce access to life-extending treatments that would have previously qualified for higher weighting under end-of-life criteria. Adjustments to the severity modifier's application are needed to ensure equitable access to innovative treatments like erdafitinib, addressing health inequalities and improving outcomes for vulnerable patients. Ethnic diversity in clinical trials is another area of concern. Urothelial cancer trials, including those for erdafitinib, frequently underrepresent Black and minority ethnic populations. This lack of representation limits the available data on how this combination performs across diverse groups, potentially impacting its broader application and effectiveness in real-world settings. Geographic disparities also play a significant role. Access to advanced cancer treatments tends to be more available in large urban centres with specialised oncology services, while patients in rural or under-resourced areas face greater difficulties. This disparity risks exacerbating existing inequalities in cancer care across England. Similarly, those in remote areas may find it challenging to access centres offering therapies like pembrolizumab with enfortumab vedotin, especially given the frequent hospital visits required. Gender disparities in bladder cancer outcomes must also be addressed. Women with bladder cancer often present at more advanced stages, experience worse quality of life post-treatment, and suffer from higher cancer-specific mortality compared to men. (Hart ST, Woods ME, Quek ML. Gender disparities in bladder cancer management. Urology Times, February 20, 2019, Volume: 47, Issue: 2)

Other issues

13. Are there any other issues that you would like the committee to consider?	Urothelial cancer has long been overlooked, consistently ranking near the bottom in the NHS cancer patient experience survey since its inception. For patients facing this aggressive disease, the lack of progress in treatment options has been deeply frustrating. Urothelial cancer carries a high risk of recurrence and progression, contributing to one of the highest suicide rates among cancer patients, driven by the emotional burden of treatment and diminished quality of life. Despite the urgent need for innovation, few groundbreaking treatments for bladder cancer have been reimbursed. Many new therapies reviewed by NICE have been rejected, leaving patients with limited hope. Access to innovative treatments is essential for these patients, who often face limited options and grim prognoses. Nivolumab was rejected by NICE in July 2018 (ID995). It was not recommended for patients who had previously undergone platinum-based chemotherapy. Similarly, pembrolizumab, another immunotherapy, was also rejected in April 2021 (ID1019, TA692)—for treating patients who had received prior platinum-containing chemotherapy. Atezolizumab offers a glimmer of hope for some. In October 2021, it was recommended for patients with advanced urothelial cancer who were unsuitable for cisplatin-containing chemotherapy (ID939, TA739). However, efforts to secure reimbursement for the combination of atezolizumab with platinum-based chemotherapy were halted when the company notified NICE in November 2022 that they would not submit evidence for its appraisal (ID1206). Avelumab has been approved as a maintenance treatment for urothelial cancer patients whose disease has not progressed after platinum-based chemotherapy. However, the recommendation, issued in May 2022 (ID3735), comes with limitations, including stopping treatment after five years or earlier if the disease progresses. Enfortumab vedotin was met with disappointment in March 2022. The company, like others before it, informed NICE that they would not submit evidence for its appraisal (ID3845).

	The lack of access to innovative treatments leaves bladder cancer patients in a precarious position, highlighting the need for change in how these therapies are evaluated and approved. For patients battling this much-ignored cancer, access to new treatments is not just a matter of better care - it's a matter of hope.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Metastatic urothelial cancer causes significant pain, fatigue, and a reduced quality of life, with few effective treatments available. • Patients and carers endure emotional, financial, and physical hardships due to long treatment times and invasive therapies. • There is a pressing need for better communication, personalised treatment options, and quicker access to care in the NHS. • Pembrolizumab with enfortumab vedotin improves survival, delays disease progression, and enhances pain management compared to chemotherapy. • Access to innovative treatments remains a challenge, with many patients unable to benefit from new therapies due to regulatory barriers.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Emma Maund critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator; Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the guarantor.

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1L	First-line
2L	Second-line
ADC	Antibody drug-conjugate
AE	Adverse event
AIC	Akaike information criterion
AUC	Area under the curve
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group,
EMC	Electronic Medicines Compendium
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
EV	Enfortumab vedotin
EV+P	Enfortumab vedotin with pembrolizumab
FAS	Full analysis set
Gem	Gemcitabine
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICR	Independent central review
IPD	Individual patient level data
ITT	Intent to treat

MMAE	Microtubule-disrupting agent monomethyl auristatin E
mITT	Modified intent to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
P	Pembrolizumab
PBC	Platinum-based chemotherapy
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RoB	Risk of bias
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
ToT	Time on treatmenbt
TSD	Technical Support Document
u/mUC	Unresectable or metastatic urothelial carcinoma
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Overview of key issues

ID	Summary of issue	Report sections
1	Severity modifier	7
2	Avelumab time on treatment	4.2.6.4

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

The ICER is presented with and without a severity multiplier of 1.2 and the ICER is [redacted] and [redacted] per QALY, respectively, for enfortumab vedotin with pembrolizumab versus platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine for the company's new data cut. There is a QALY gain of 1.45 and an additional cost of [redacted]. The company base case results are shown in Table 2

Table 2 Company base-case results for ITT population with and without including a severity modifier (applying 1.2 QALY weights) and a confidential PAS of [redacted]% for EV.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Without severity modifier							
PBC+gem	[redacted]	[redacted]	[redacted]				
EV+P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.45	[redacted]
With severity modifier of 1.2 applied to QALYs							
PBC+gem	[redacted]	[redacted]	[redacted]				
EV+P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.74	[redacted]

Source: CS addendum (November 2024) Table 19
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; QALY quality adjusted life year

1.3 The decision problem: summary of the EAG's key issues

The EAG could identify no keys issues relating to the decision problem.

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 1 Severity modifier

Report section	Section 7
Description of issue and why the EAG has identified it as important	According to the NICE Health Technology Evaluations manual section 6.2.12,[1] severity of the condition can be calculated as a proportional QALY shortfall between the general population and someone with this condition and may lead to applying a QALY weighting. A proportional QALY shortfall of more than 85% leads to a QALY weight of x1.2. The company argues that, even though their calculated proportional QALY shortfall is 83% i.e. slightly less than the necessary 85%, a severity modifier of 1.2 should be applied.
What alternative approach has the EAG suggested?	The EAG calculated the proportional QALY shortfall using the EAG base case assumptions and obtained a QALY shortfall of 84%. However, we agree with the company that there may be uncertainty around the estimates for QALYs for PBC+gem. The company states that the OS rates observed in the PBC+gem arm may not be representative of the OS rates of patients receiving PBC+gem in the NHS, due to

	different treatments being used in the trial that are not available in the NHS. They also note that using alternative parametric distributions for OS leads to a QALY shortfall of more than 85%.
What is the expected effect on the cost-effectiveness estimates?	Using the severity modifier reduced the ICER from [redacted] to [redacted] per QALY in the company base case.
What additional evidence or analyses might help to resolve this key issue?	The CS addendum (29th November 2024) states that [redacted] of patients received EV monotherapy as a subsequent treatment and a further [redacted] of patients received either sacituzumab govitecan or erdafitinib. These treatments are not available in the NHS. Some adjustment of the OS extrapolation by removing the effect of these treatments may help to provide a more accurate estimate of the proportional QALY shortfall.

Abbreviations: EV, enfortumab vedotin; OS, overall survival; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine

Issue 2 Avelumab time on treatment

Report section	Section 4.2.6.4
Description of issue and why the EAG has identified it as important	The company use the Weibull parametric curve to extrapolate time-on-treatment for avelumab for patients originally receiving PBC+gem. One of our experts thought than the mean avelumab treatment duration ([redacted] months), and the proportion of patients on avelumab at one year (41%) and two years (26%), was high. Our expert commented that avelumab is usually given for less than a year (about 9 months).
What alternative approach has the EAG suggested?	We prefer to use the exponential parametric curve for avelumab time on treatment in our base case, because this results in the shortest time on treatment: mean of [redacted] months; the proportion of patients on avelumab at one year is 43% and at two years is 18%.
What is the expected effect on the cost-effectiveness estimates?	The company base case is [redacted] (no modifier); [redacted] (with modifier). Using the exponential curve to model avelumab treatment increases the ICER to [redacted] (no modifier); [redacted] (with modifier).

What additional evidence or analyses might help to resolve this key issue?	Further clinical expert advice concerning time on avelumab treatment for patients with unresectable or metastatic urothelial cancer receiving PBC+gem.

Abbreviations: PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine

We also disagree with the company regarding the following issues:

- Discounting, which we apply from the start of the model time horizon in our base case (discussed in section 4.2.5)
- Pre-progression utilities (discussed in section 4.2.7.3 and shown in Table 28): the company use treatment-specific utilities for the entire pre-progression period. In our base case, we use:
  - The health state-specific utility for enfortumab vedotin with pembrolizumab
  - The treatment-specific utility for chemotherapy for the first 6 months, then the health state-specific utility for the remaining time in pre-progression
- The choice of parametric curve to model progression-free survival (discussed in section 4.2.6.3). We use the loglogistic for both arms in our base case, rather than spline fits.

However, each of these issues has only a minor effect on the ICER, so we do not regard them as key issues.

1.5 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG critique of the company's model discussed in Table 33, we have identified several key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

For EAG base case

- Discounting: we use the standard form of discounting starting at the beginning of the first cycle, rather than starting at the end of the first year (section 4.2.5).
- Pre-progression utilities: we use treatment specific for platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine for the first six months (u=[redacted]) and then treatment independent utility thereafter (u=[redacted]). We use treatment independent utility for enfortumab vedotin with pembrolizumab (u=[redacted]) (section 4.2.7).
- Progression-free survival for enfortumab vedontin with pembrolizumab and platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine: Use the loglogistic distribution, rather than splines (section 4.2.6.3)
- Time on treatment for avelumab maintenance therapy: use the exponential curve, rather than the Weibull distribution (section 4.2.6.4).

The EAG base case results are shown in Table 3 using the EAG's preferred assumptions. When using these assumptions, the ICER increases to [redacted] and [redacted] per QALY for enfortumab vedotin with pembrolizumab vs platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine with and without the severity modifier. The model results are most sensitive to using the exponential distribution for avelumab maintenance treatment.

Table 3 EAG's preferred model assumptions, cumulative results with PAS for enfortumab vedotin

				Cumulative ICER £/QALY.	
Preferred assumption	Treatment	Total costs	Total QALYs	No severity modifier	Severity modifier of 1.2.
Company base-case	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
+ Discounting applied at start of model time horizon	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC	[redacted]	[redacted]	[redacted]	[redacted]
+ Pre-progression utilities: EV+P [redacted]; PBC+gem [redacted] for the first 6 months, then [redacted].	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
+PFS: Use the loglogistic for EV+P and PBC+gem	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
+ToT for avelumab maintenance: Exponential curve	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAG created table
Abbreviations: EAG, evidence assessment group; EV+P, enfortumab vedotin with pembrolizumab; OS, overall survival; PFS, progression-free survival; HRQoL, health-related quality of life; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; PD, progressed disease, ToT time on treatment. Severity multiplier of 1.2 applied to incremental QALYs.

For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.1.1.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Astellas Pharma Ltd on the clinical effectiveness and cost effectiveness of enfortumab vedotin with pembrolizumab for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 28th October 2024. A response from the company via NICE was received by the EAG on 19th November 2024 and another on 29th November 2024. This can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on urothelial cancer

The CS provides key background information on urothelial cancer, covering: definitions and classifications, incidence and prevalence, diagnosis, risk factors, symptoms and burden of disease, and prognosis.

Also discussed in the CS is the current care pathway for people with unresectable or metastatic urothelial cancer (Figure 1). The CS notes that platinum-based combination chemotherapy is the current standard of care for unresectable or metastatic urothelial cancer in the NHS, received by approximately 84% of treated patients. About 10% of patients are estimated as being unsuitable for platinum-based therapy (see below).

The type of platinum-based therapy given depends on whether patients are suitable to take cisplatin. The Galsky criteria[2] were developed to assess cisplatin eligibility, considering factors such as age, cancer performance status, and comorbidities such as renal impairment. The CS estimates that around 50% of patients eligible for platinum-based therapy can tolerate cisplatin and are eligible for cisplatin-based chemotherapy, comprising **cisplatin and gemcitabine**. The remaining 50% of patients would be eligible for **carboplatin and gemcitabine,** or **atezolizumab** if their tumours express programmed cell death ligand 1 (PD-L1) at a level of 5% or more (based on NICE TA739).[3] In contrast, one of the EAG's clinical experts suggested that around two-thirds of platinum-eligible patients would be treated with cisplatin in practice. The higher proportion of patients considered for cisplatin-based chemotherapy is due to regimen variations in clinical practice (e.g. spitting

the cisplatin dose) designed to make cisplatin more tolerable for patients who otherwise would not be fit enough to withstand its toxicity.

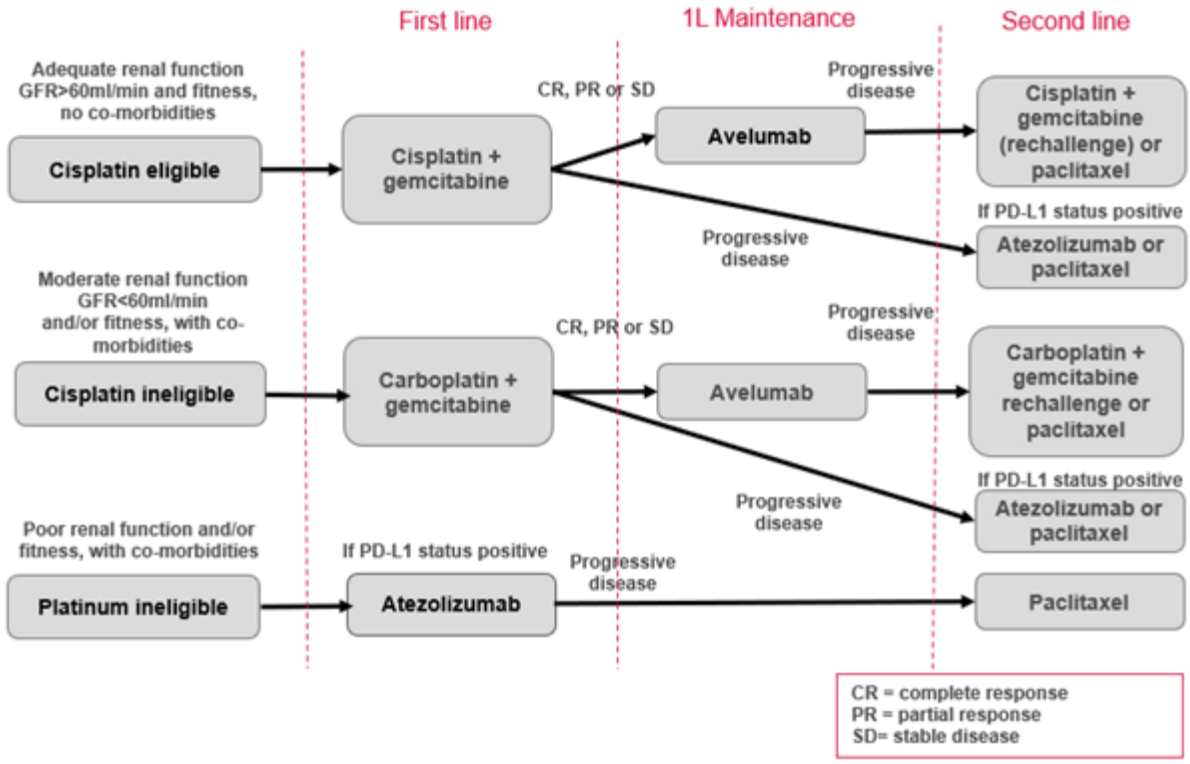

Figure 1 Current treatment of unresectable or metastatic urothelial cancer in NHS practice in England

Source: reproduced from CS Figure 2

Clinical experts advising the EAG agree with the description of current clinical practice in the CS (Figure 1). The experts commented that platinum-eligible patients would typically receive six three-week cycles (18 weeks in total) of **gemcitabine and cisplatin / carboplatin** (as appropriate) with a CT scan after every third cycle to check for progression. If the patient is responding to treatment or is considered to have stable disease they would likely commence first-line maintenance treatment with **avelumab** (a checkpoint inhibitor), given every two weeks. Alternatively, avelumab treatment may be substituted for close monitoring for progression. Some patients may opt for the second of these two options because avelumab's two-week dosing schedule can be burdensome, requiring regular hospital visits for treatment. Also, some patients, particularly the more elderly, may need a treatment break after enduring chemotherapy.

On disease progression, patients who are fit enough would commence second-line treatment with atezolizumab (also a checkpoint inhibitor). The experts noted that, contra to

CS Figure 1, at second line atezolizumab is not restricted to patients who are PD-L1 positive, it can be given regardless of this biomarker. **Pembrolizumab** was previously an option at second-line during the Covid-19 pandemic, and this was the clinicians preferred treatment compared with atezolizumab due to better response rates. However, pembrolizumab is not recommended for use as a second-line treatment based on a NICE technology appraisal in 2021 (NICE TA692).[4] If pembrolizumab became available at this stage of the care pathway the clinicians would revert to giving pembrolizumab rather than atezolizumab.

Only a minority of patients survive to third-line therapy. If they are fit enough, they would be offered a **taxane (e.g. paclitaxel)**. However, patient take-up is low and treatment response rates are modest. Our clinical experts commented that chemotherapy re-challenge would be offered to only a minority of patients.

The NICE scope includes the treatment regimen **methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF])** (hereafter referred to as MVAC) as a comparator to first-line enfortumab in combination with pembrolizumab in patients eligible for cisplatin. However, MVAC does not feature in the company's care pathway diagram (Figure 1). As we will discuss below (section 2.3), the CS excludes MVAC as a comparator claiming it is rarely used in this indication. The EAG experts concur with the company, commenting that they do not use MVAC in the metastatic setting due to its toxicity. MVAC is more likely to be used earlier in the pathway, specifically in the neoadjuvant treatment setting. Clinicians use an accelerated 'dose dense' MVAC formulation in this setting, given over 2 weeks instead of 3 or 4 weeks. This regimen, they suggest, is better tolerated by patients than standard MVAC.

The NICE scope also includes **atezolizumab** as a comparator treatment to first-line enfortumab in combination with pembrolizumab in patients ineligible for cisplatin. However, in the company's care pathway diagram (Figure 1) at first-line, atezolizumab is restricted to platinum-ineligible patients. As we will discuss below (section 2.3), the company contend that atezolizumab is rarely used at first-line in the platinum-eligible population and this justifies its exclusion as a comparator in the CS. Clinical experts advising the EAG commented that they rarely use atezolizumab as a first-line treatment in cisplatin-ineligible patients. Their preference is to give carboplatin and gemcitabine first-line, even at a reduced dose in less healthy patients, rather than atezolizumab.

Our clinical experts noted that there is general uniformity in clinical practice around the country.

2.2.2 Background information on enfortumab vedotin

Section 1.2 of the CS gives a summary description of enfortumab vedotin and pembrolizumab. Enfortumab vedotin is an antibody drug-conjugate (ADC) targeting a protein called Nectin-4, located on the surface of urothelial cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE), via a linking molecule that is broken by protease enzymes. The anti-cancer activity of EV is thought to be due to binding of the ADC to Nectin-4 expressing cells, then internalisation of the ADC Nectin-4 complex into the cell, and the release of MMAE which triggers a series of cell responses resulting in cytotoxic cell death (see CS Table 2).

Pembrolizumab is a PD-1 inhibitor immunotherapy which potentiates T-cell responses, including anti-tumour responses, through blockade of programmed cell death protein 1 (PD-1) binding to programmed cell death-ligands 1 and 2 (PD-L1 and PD-L2). The CS states that the combination of these two drugs results in enhanced anti-tumour activity in vivo.

The marketing authorisation was granted in October 2024 by the Medicines and Healthcare products Regulatory Agency (MHRA), as follows: 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.

The treatment is given via intravenous infusion on days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity.

The CS regards enfortumab vedotin with pembrolizumab as addressing unmet clinical need for more efficacious first-line treatments for unresectable or metastatic urothelial cancer. The company describes enfortumab vedotin with pembrolizumab as a ‘step change’ in the treatment of urothelial cancer, based on encouraging clinical trial results. They also consider it an innovative treatment due to the complementary mechanisms of action of the two constituent drugs.

2.2.3 The position of enfortumab vedotin in the treatment pathway

CS section 1.3.5.4 discusses the company’s proposed position of enfortumab vedotin with pembrolizumab in the care pathway. CS Figure 5 (reproduced in Figure 2 below) illustrates this positioning. The company’s favoured position for enfortumab vedotin with pembrolizumab accords with the marketing authorisation, which permits the combination to be used as a first-line treatment of adult patients with unresectable or metastatic urothelial cancer eligible for platinum-containing chemotherapy (Section 2.2.2 of this report).

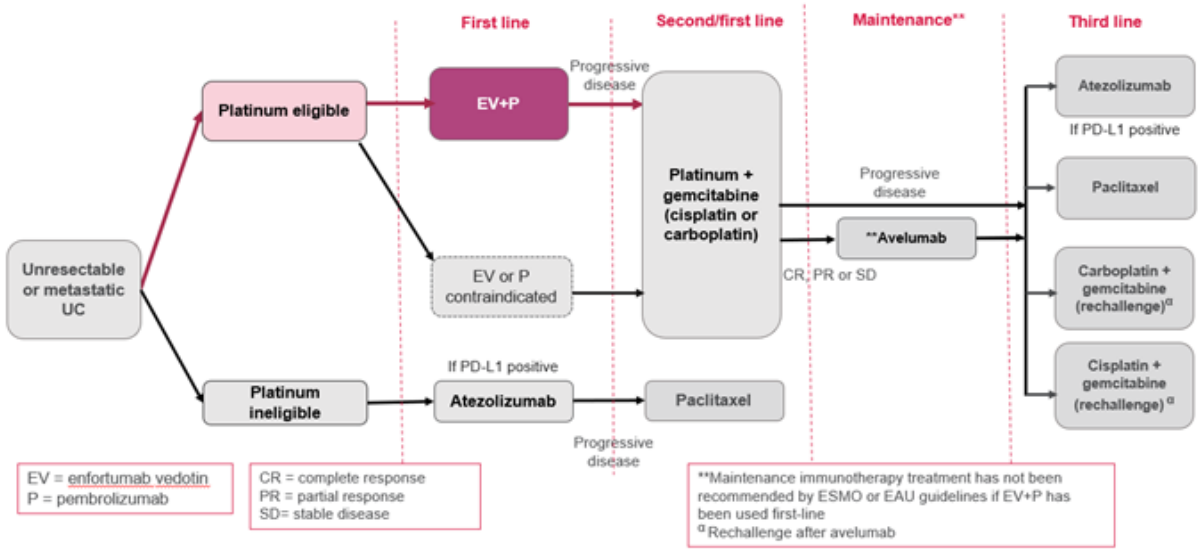

Figure 2 Proposed position of enfortumab vedotin combined with pembrolizumab in the treatment pathway

Source: Reproduced from CS Figure 5

Given the company's decision not to include atezolizumab and MVAC as comparators in their submission, the main comparator treatment at first-line is platinum-based treatment (i.e. cisplatin or carboplatin with gemcitabine). The company suggests that if enfortumab vedotin with pembrolizumab is recommended by NICE, first-line platinum-based treatment would potentially be displaced, becoming the standard of care at second-line in patients who progress. This is reflected by latest updated European clinical guidelines on bladder cancer/upper urinary tract urothelial carcinoma by the European Association of Urology and the European Society of Medical Oncology (ESMO). These guidelines all recommend enfortumab vedotin with pembrolizumab as the standard of care at first line advanced urothelial carcinoma. Platinum-based chemotherapy plus gemcitabine is now recommended by guidelines as second-line treatment unless enfortumab vedotin is unavailable or contraindicated.

The EAG's clinical advisors were supportive of using enfortumab vedotin as a first line treatment in patients with unresectable or metastatic urothelial cancer. They were familiar with the results of clinical trials of enfortumab vedotin and the European clinical guideline recommendations, and perceived there to be much clinical interest in this treatment. One expert suggested that enfortumab vedotin is likely to change the treatment paradigm in unresectable / metastatic urothelial cancer.

One of the experts reported clinical experience of enfortumab vedotin from treating patients in clinical trials (in a different indication to this current NICE technology appraisal). The

expert observed good efficacy with the treatment and noted that clinical management of patients treated with enfortumab vedotin appears to be generally similar to that of current standard care. Over time they are increasing their familiarity with enfortumab vedotin's side effect profile (for example, cases of peripheral neuropathy, impaired glycaemic control, skin rashes) and knowing when to anticipate the need for dose adjustments, dose interruptions and other interventions. This clinical expert noted that this is a process clinicians go through with any novel treatment.

EAG conclusion

The CS provides a detailed and comprehensive background description of advanced urothelial cancer and current clinical practice, drawing on the latest European clinical guidelines and NICE technology appraisals. The EAG's clinical experts generally agree with the company's assertions regarding current standard of care and the likely implications for the care pathway if enfortumab vedotin with pembrolizumab were to be recommended by NICE as a first-line treatment in the advanced disease setting. Its potential introduction is unlikely to require significant changes to clinical practice, but time and experience will enable clinicians to increase their familiarity with its side effect profile and necessary clinical management.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. The main observation from Table 4 is that, generally, the decision problem matches the scope of the appraisal, and in the instances where they differ, a clinically justified explanation is provided. Specifically, the company exclude two of the comparator treatments (Methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF] in people whom cisplatin-based chemotherapy is suitable; and atezolizumab in people whom cisplatin-based chemotherapy is unsuitable), citing evidence that they are rarely used in clinical practice. The sources include the Delphi mUC Disease Specific Programme™, (A real world clinical practice survey);[5] the IQVIA tracker (prescribing data from 50 UK clinicians);[6] and the Systemic Anti-Cancer Therapy (SACT) database (containing data on the use of cancer medicines in the NHS in England). The company's exclusion of MVAC and atezolizumab as comparators was supported by the EAG clinical experts who commented that they do not use them as first-line treatments in the metastatic setting for reasons such as excessive toxicity (MVAC) and poor efficacy (atezolizumab).

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People with untreated unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.	As NICE scope.	Note: the pivotal trial (EV-302) population was described as 'locally advanced or metastatic' urothelial cancer (UC), whereas the wording in the licensed indication and the NICE scope is	The CS states that "urothelial cancer that has spread to the pelvic or nearby lymph nodes and/or to the wall of the pelvis or abdomen and is not resectable is referred to as unresectable or locally advanced disease" (CS page 17).

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			'unresectable or metastatic' UC. However, as noted by the EMA (EPAR p. 1103) unresectable disease was an inclusion criterion for the trial (see Section 2.3.1, Table 8). There is therefore no misalignment between the trial population and the licensed indication or the scope	One of the EAG's clinical experts suggested that locally advanced urothelial cancer is not clearly defined generally in clinical practice. Their interpretation is that locally advanced, as stated in the CS, is referring to incurable local disease (T4 or heavy burden of nodes) and this is the same as unresectable disease. The other expert commented that locally advanced urothelial cancer is as big, bulky bladder cancer, that is not metastatic and has no node involvement (T3B). In their view distinctions between resectable disease and

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				metastases is a 'grey area'. Some clinicians would consider any pelvic lymph node involvement to be metastatic, not just pelvic nodes outside the pelvis. Lymph nodes within the pelvis are considered resectable by surgeons. Whether a tumour is resectable or not is defined by whether the surgeon can or cannot operate on it. Most surgeons cannot operate on a cancer that is attached to another organ or the pelvic wall or pelvic bones.
Intervention	Enfortumab vedotin in combination with pembrolizumab.	As NICE scope: Enfortumab vedotin (EV; Padcev®) in combination with pembrolizumab (P; Keytruda®). The	As NICE scope.	Decision problem matches the NICE Scope

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		combination is referred to in this document as EV+P.		
Comparators	For people whom cisplatin-based chemotherapy is suitable: • Gemcitabine plus cisplatin • Methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF]) For people whom cisplatin-based chemotherapy is unsuitable: • Gemcitabine plus carboplatin	For people whom cisplatin-based chemotherapy is suitable: • Gemcitabine + cisplatin For people whom cisplatin-based chemotherapy is unsuitable: • Gemcitabine + carboplatin	MVAC rarely used in practice (only ~2% of 1L pts in UK based on market research). Atezolizumab now infrequently used in 1L treatment (8-10% of all patients and 3% of platinum-eligible patients); Clinical advice is that carboplatin + gemcitabine (followed by avelumab maintenance in eligible patients) is now preferred over atezolizumab in patients	EAG clinical experts consider it reasonable to exclude standard MVAC. They do not use it in the metastatic setting as it is considered quite a toxic regimen. The data in support of MVAC is more robust in the perioperative setting where they use an accelerated 'dose dense' formulation given over two weeks instead of 3 or 4 weeks, which is better tolerated. One expert noted that clinical trial data in the neoadjuvant setting showed that dose dense MVAC is superior to gemcitabine and cisplatin, and they speculated whether in the metastatic setting it would also

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	• Atezolizumab (people whose tumours express PD-L1 at a level of 5% or more)		who are eligible for carboplatin but not cisplatin. This position is supported by EMSO guidelines (2022) and British Uro-Oncology Group and Fight Bladder Cancer in their comments on the NICE scoping consultation	be superior to enfortumab vedotin combined with pembrolizumab. Both experts agree with the exclusion of atezolizumab as a comparator. Clinicians favour gemcitabine plus carboplatin, rather than atezolizumab, as a first-line treatment in metastatic patients unsuitable for cisplatin. They consider atezolizumab to be less efficacious.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment	As NICE scope (Note: Response rates are presented in the submission but are not used in the economic model)		Decision problem matches the NICE Scope

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	• Health-related quality of life			
Subgroups	If the evidence allows the following subgroups will be considered: • People for whom cisplatin containing chemotherapy is unsuitable • People whose tumours express PD-L1	Analyses will be presented for platinum-eligible patients as a whole, reflecting the ITT population of the EV-302 trial and the licensed indication for EV+P. In addition, subgroup analyses will be presented for cisplatin-eligible and cisplatin-ineligible subgroups since the comparator treatment is defined based on cisplatin-eligibility.	The Company do not believe that subgroup analysis based on PD-L1 status is relevant. This is because EV+P significantly improved relative outcomes regardless of PD-L1 status (see Section 2.6.2 and 2.6.3). PD-L1 status did not impact absolute outcomes either for platinum-containing chemotherapy, nor for EV+P OS (see Appendix E). Although there is some indication of PD-L1 status influencing	EAG clinical experts do not regard PD-L1 as a useful biomarker in urothelial cancer. They noted that measurement of PD-L1 is not standardised and has been measured in different ways in many clinical trials. It is prognostic in some clinical trials but not in all. The evidence that it is predictive and a companion diagnostic for CKI is poor and unvalidated.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			EV+P PFS, any such effect is highly uncertain. Lastly, the licensed indication for EV+P covers all eligible patients and does not differentiate by PD-L1 status.1	
Special considerations including issues related to equity or equality	None specified	Decisions on the funding of treatments for bladder cancer (which accounts for 90-95% of UC cases at diagnosis[7]) disproportionately affect people living with the consequences of socioeconomic deprivation. In England, the European age-standardised incidence rate/100,000 in the most	Socioeconomic status (IMD quintile) has not been included in the economic modelling. However, the disproportionate impact on people with greater socioeconomic deprivation may be relevant to NICE's decision making given that reducing health	We acknowledge the points made. The NICE evaluation committee will take into consideration impact on equality in their deliberations.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		deprived Index of Multiple Deprivation (IMD) quintile was 10.5 in females and 32.3 in males, compared with 7.1 in females and 26.2 in males the least deprived quintile (2013-2017, as reported by Cancer Research UK).[8] Cancer Research UK estimated that there are 980 more cases/year than there would be if every quintile had the same age-specific crude incidence rates as the least deprived quintile.	inequalities is a priority under the NHS England Core20PLUS5 programme.[9]	

Source: Partly reproduced from CS Table 1
Abbreviations: EAG, evidence assessment group; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; EV+P, enfortumab vedotin with pembrolizumab; OS, overall survival; PFS, progression free survival; UC, urothelial carcinoma

EAG conclusion

The company's decision problem generally matches the scope of the appraisal. In the instances where they differ, the company provides a clinically justified explanation. Exclusion of two of comparator treatments, MVAC and atezolizumab, is based on evidence showing minimal use in clinical practice. This seems reasonable.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

In CS Appendix D the company describe their systematic literature review (SLR) to identify clinical evidence relevant to enfortumab vedotin with pembrolizumab in the first-line treatment of unresectable or metastatic urothelial carcinoma. The EAG's appraisal of the company's systematic review methods is summarised in Appendix 1. Briefly, the company carried out a SLR with broader eligibility criteria for the population and intervention than those specified in NICE final scope (CS Appendix D Table 4). With respect to study design, eligible for inclusion were phase 2 and phase 3 RCTs that assessed the efficacy and safety of first-line regimens in locally advanced/metastatic urothelial cancer. Single-arm studies were also included "to capture all of the emerging evidence" for PD-1/PD-L1 inhibitors and enfortumab vedotin containing regimens and all studies in the cisplatin-ineligible population (CS Appendix D section 3.1). Company clarification response A3, elaborated on the rationale for including single arm studies, namely that "PD-1/PD-L1 inhibitors and enfortumab vedotin were emerging therapies often studied first in single-arm studies; and in addition, agents often were studied first in the cisplatin-ineligible population before being studied in the full population". Overall, the EAG does not consider there are any issues in relation to eligibility criteria for the SLR.

The EAG did, however, identify an issue with the company searches, which may result in relevant evidence being missed. The searches are designed to retrieve RCTs and controlled trials, yet, as stated above, the SLR eligibility criteria specify single-arm studies for cisplatin-ineligible patients and of PD-1/PD-L1 inhibitors and enfortumab vedotin containing regimens would be included. However, the searches did not specifically search for single-arm studies, such as cohort or other observational studies (Company clarification response A3). The EAG did note the searches identified a multi-cohort study for this category. Some single-arm studies could be found from terms for 'clinical trial' and as relevant arms within a multiple arm trial. With respect to the SLR, which had broader eligibility criteria for intervention then the NICE scope, relevant single arm trials may have been missed. However, with respect to the NICE scope, the EAG scrutinised the overview of the complete trial programme for enfortumab vedotin and enfortumab vedotin with pembrolizumab provided in CS document B Table 5, and the studies included as evidence of clinical efficacy in the EPAR.[10] The EAG identified as relevant only those included in this appraisal. The EAG therefore do not consider that relevant single arm trials have been missed.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation

3.2.1 Included studies

The SLR identified 264 records reporting 75 unique clinical studies (CS Appendix D.4.2 and CS Appendix D Figure 2). Of these studies, two were relevant. These were study 'EV-302' (an RCT) and study EV-103 (a multi-cohort study). Study EV-103 comprised of eight cohorts of patients of which three cohorts (two single arm ("dose escalation" and "cohort A") and one randomised ("cohort K")) investigated enfortumab vedotin with pembrolizumab and were therefore considered relevant to this appraisal (CS sections B.2.1 and B.2.2, CS Appendix D.4.2). After assessing CS document B Table 5 ("Overview of the trial programme for enfortumab vedotin and enfortumab vedotin with pembrolizumab in urothelial cancer") and CS Appendix D Table 13 ("List of studies by treatment under investigation") the EAG agree that only study EV-302 and the three cohorts from study EV-103 are relevant to the appraisal.

3.2.1.1 Study characteristics

3.2.1.1.1 EV-302

The EV-302 study (KEYNOTE-A39, NCT04223856) is an ongoing phase III, multicentre, randomised, open-label controlled trial comparing the efficacy and safety of enfortumab vedotin with pembrolizumab to platinum-based chemotherapy (cisplatin if eligible, or carboplatin) in combination with gemcitabine, hereafter referred to as chemotherapy, in adult patients with previously untreated unresectable locally advanced or metastatic urothelial carcinoma. The trial results **support the company's regulatory approval** for enfortumab vedotin with pembrolizumab. Evidence from the trial **directly inform the economic model** (CS Document B Table 6).

The trial has two primary outcomes: progression free survival (PFS), based on blinded-independent central review (ICR), and overall survival (OS). Patients were enrolled from 25 countries, including the UK ([redacted]; EV-302 updated Clinical Study Report (CSR) Table 12.1.1.3). Approximately 42% of patients were enrolled from Europe and 21% from North America. Table 5 below summarises the EV-302 trial methodology.

Table 5 Summary of EV-302 trial methodology

Study characteristics	
Trial design	RCT Open label (response and progression were assessed by blinded-IRC) 2 arm: Arm 1: **EV+P** (n=442) Arm 2: **PBC+gem** (n=444)
Randomisation	1:1 Stratified by: eligibility to receive cisplatin (eligible or ineligible), PD-L1 expression status (high or low), and liver metastases (present or absent). N=886 patients randomised (including [redacted] from the UK).
Study status	Trial start date 30/03/2020 – ongoing. Data cut of **08 August 2023 (median follow-up 17.2 months)** used in the CS (including initial CS health economic model), the EV-302 CSR and the primary journal publication of the trial (Powles et al, 2024)[11] Data cut of 08 August 2024 **(median follow up** 29.1 months**)** provided in CS addendum (15 November 2024) and updated CSR tables and figures only. Used in CS new data cut health economic model (CS addendum (29 November 2024)).
Duration of treatment (months) in data cut 08 Aug 2024	**EV+P** (n=440): median [redacted] ([redacted]) **PBC+gem** (n=433): median [redacted] ([redacted])
Location	185 sites in 25 countries: **Europe** (Belgium, Czech Republic Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Russia, Spain, Switzerland, United Kingdom) **Asia** (China, Israel, Japan, Singapore, South Korea, Taiwan, Thailand, Turkey) **North America** (Canada, United States) **Other** (Argentina, Australia)
Included population	Patients aged ≥ 18 years with histologically documented unresectable locally advanced or metastatic urothelial carcinoma with no prior systemic therapy for locally advanced

Study characteristics	
	or metastatic disease (with exception of neoadjuvant chemotherapy if recurrence was >12 months from completion of therapy or adjuvant chemotherapy following cystectomy if recurrence was >12 months from completion of therapy) who were considered by the investigator eligible to receive cisplatin- or carboplatin-containing chemotherapy, had archival tumour tissue (muscle-invasive urothelial carcinoma or a biopsy of metastatic urothelial carcinoma) for PD-L1 testing prior to randomization and an ECOG PS of 0, 1 or 2.
Excluded population	Patients who had previously received: enfortumab vedotin or other MMAE-based antibody-drug conjugate; a PD-L1 inhibitor for any malignancy, including earlier stage urothelial cancer, defined as a PD-1 inhibitor or PD-L1 inhibitor; an agent directed to another stimulatory or co inhibitory T-cell receptor; any other anti-cancer treatment with chemotherapy, biologics, or investigational agents that is not completed 4 weeks prior to first dose of study treatment. Patients with uncontrolled diabetes, an estimated life expectancy of less than 12 weeks, or active central nervous system metastases.
Intervention (EV+P)	**EV:** 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle**, until disease progression or unacceptable toxicity**. **P:** 200 mg IV on day 1 of each 3-week cycle, as above to a **maximum of 35 cycles**.
Comparator (PBC+gem)	**Gemcitabine**: 1000 mg/m^2 body surface area on days 1 and 8 of a 3-week cycle as IV infusion, **in combination with either**: • **Cisplatin**: 70 mg/m^2 on day 1 as IV infusion or • **Carboplatin**: AUC equivalent to 4.5 or 5 mg/ml/min (Calvert formula) day 1 Chemotherapy given for a **maximum of 6 cycles.** Cisplatin ineligibility determined using Galsky criteria[a]
Maintenance therapy	Use of maintenance therapy **permitted in the chemotherapy group** in geographic regions in which the maintenance therapy was available.[b]

Study characteristics	
Concomitant medications	**Allowed:** palliative radiotherapy on stable non-target bone lesions; surgical resection with curative intent in subjects with favourable response may be permitted after discussion; anti-emetics; granulocyte-stimulating growth factors; insulin; therapies to manage EV-associated toxicity; antimicrobial prophylaxis. **Prohibited:** medications or vaccinations prohibited by the exclusion criteria; systemic antineoplastic therapy; radiation therapy except as noted above.
Primary outcomes	Progression free survival, based on blinded-IRC assessment per RECIST version 1.1, and overall survival (both inform the economic model)
Secondary outcomes informing the economic model	Adverse events HRQoL (EQ-5D-5L)
Other secondary outcomes reported in the CS	**Efficacy:** Response rate (blinded-IRC assessed ORR and DOR), time to pain progression, mean change from baseline in worst pain at week 26 **HRQoL:** EORTC QLQ-C30 **Safety:** Type, incidence, relatedness, severity and seriousness of adverse events (AEs), adverse events of special interest, treatment discontinuation due to adverse events **Other:** Receipt of subsequent anti-cancer therapies

Source: Partly reproduced from CS document B Tables 6 and 8; EV-302 CSR Table 12.1.1.3
Abbreviations: AUC, area under the curve CSR, clinical study report; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L, EuroQoL Five-dimension Five-level; EV, enfortumab vedotin; EV+P, enfortumab vedotin with pembrolizumab; HRQoL, health-related quality of life; IRC, imaging review committee; IV, intravenous; max, maximum; min, minimum; MMAE, monomethyl auristatin E; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours;
[a] Galsky criteria, defined by a glomerular filtration rate of 30 to < 60 ml per minute per 1.73 m2 of body-surface area; hearing loss of grade 2 or higher, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 2, or New York Heart Association class III heart failure at enrolment
[b] Trial amendment made to define the use of maintenance therapy after discontinuation or completion of chemotherapy, such that it was not considered to be subsequent anticancer therapy.

3.2.1.1.2 EV-103

Study EV-103 (KEYNOTE-KN-869, NCT03288545) is an ongoing phase Ib/II, multicentre, multi cohort, open-label, study (CS Table 7, CS section B.2.3.2). The trial started on 26 October 2017 with long-term follow-up ongoing (EV-103 CSR section 6). The purpose of the study is to evaluate the safety and antitumor activity of the combination of enfortumab vedotin with pembrolizumab and/or chemotherapy in patients with locally advanced or metastatic urothelial cancer and to inform the dosing and design of study EV-302. The combination regimens are evaluated in eight separate cohorts (dose escalation, A, B, D, E, F, G and K, see Table 6). Planned efficacy analyses were by cohort and dose level and by arm with cohort K. Patients treated with the same regimen and the same dose level and setting were permitted to be pooled. Safety endpoints were analysed by cohort/arm (EV-103 SAP version 4 sections 6.1, 7 and 7.5). Of the eight cohorts, three (dose escalation, A and K) evaluated enfortumab vedotin with pembrolizumab and are therefore of relevance to this appraisal. All three cohorts only included patients who were **cisplatin ineligible,** which is a subgroup of the population of relevance for the appraisal. In cohort A and K, 40 and 76 participants respectively received enfortumab vedotin with pembrolizumab as first-line therapy. By default, the dose of enfortumab vedotin with pembrolizumab was the same as in study EV-302. In the dose escalation cohort, 5 participants received the same dose of enfortumab vedotin with pembrolizumab as in study EV-302 as first-line therapy. Only data from these 121 participants is of relevance to the appraisal.

Table 6 Cohorts of patients with locally advanced or metastatic urothelial cancer in study EV-103

Cohort[a]	Treatment; population, treatment line
Dose escalation	**EV+P; cisplatin-ineligible; 1L** or as 2L if they previously progressed on PBC
A	**EV+P; cisplatin-ineligible; 1L**
B[b]	EV+P; disease progression/recurrence; 2L
D	EV+cisplatin; cisplatin eligible; 1L
E	EV+carboplatin; cisplatin ineligible, 1L
F[b]	EV+gemcitabine; PBC ineligible;1L and 2L
G	EV+P+PBC; PBC eligible; 1L
K[c]	EV monotherapy or **EV+P; cisplatin ineligible; 1L**

Source: Partly reproduced from EV-103 CSR Figure 1
Abbreviations: 1L, first-line treatment; 2L, second line treatment; EV+P, enfortumab vedotin with pembrolizumab; PBC, platinum-based chemotherapy (cisplatin or carboplatin)
Bold signifies cohorts/arms that evaluated enfortumab vedotin with pembrolizumab and are therefore of relevance to this appraisal.
[a] There is no cohort C
[b] Cohorts B and F did not open to enrollment
[c] Treatment allocated by randomisation

The company have combined results of participants (n=5) from the dose escalation cohort who were assigned the same dose of enfortumab vedotin with pembrolizumab as first line therapy as in study EV-302 with those of cohort A (n=40). This combined cohort is referred to in the CS and in the EAG report as "Cohort A + dose escalation" (n=45). Results from cohorts A+ dose escalation and cohort K were used to **support the company's regulatory approval** for enfortumab vedotin with pembrolizumab (CS Table 7), but were **not used to directly inform the economic model** (CS section B.2.2.1). They were, however, **used to validate the survival extrapolations** (CS document B Table 7). CS section B.2.2.1 states results were not used to directly inform the economic model because the population, cisplatin-ineligible patients, only represents a subgroup of the submission (CS section B.2.2.1). Company clarification response A6, provides a more detailed explanation: as cohorts included cisplatin-ineligible patients, their incorporation in the model would overweight the distribution of cisplatin-ineligible patients relative to cisplatin-eligible thereby reducing the generalisability of the predictions to the patient population in clinical practice. Furthermore, there was no relevant comparator arm, and patients in the cohorts had a higher prevalence of some observed prognostic factors associated with poorer survival i.e a greater proportion of patients aged ≥75 years, with a ECOG PS of 2 and with visceral

metastases and fewer with an ECOG PS 0 (see section 3.2.1.1.4 for further details). The EAG agree with the company's reasons.

The CS presents baseline characteristics for study EV-302 (CS section B.2.6.1 and CS Table 10) and for cohort A + dose escalation (CS section B.2.6.8.1 and CS Table 13) only. The EAG found baseline characteristics for cohort K reported in the EV-103 CSR (EV-103 CSR Tables 10,11 and 12).

3.2.1.1.3 EV-302 baseline characteristics

The CS states baseline characteristics for study EV-302 were generally well balanced between study arms. Briefly, the median age of participants was 69 years (range 22 to 91), with approximately one quarter aged ≥ 75 years, and most were male (77%). Approximately two thirds (68%) identified themselves as White. Randomised participants were from Europe (42%), North America (21%) and rest of the world (37%; EV-302 CSR Table 11). Specifically, [redacted] were from the UK (EV-302 updated CSR Table 12.1.1.3) One EAG clinical expert commented that in UK clinical practice patients were a little older (median age in the early 70s) and more than 97% were White.

Approximately 50% of participants had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (indicating the participant is fully active with no restriction on activities) while 3% had an ECOG PS of 2 (indicating they were able to walk and manage self-care, but unable to work). Both of the EAG clinical experts commented that in terms of ECOG PS, participants were fitter than those seen in clinical practice.

Most participants had a mild decrease (creatinine clearance (CrCl) ≥ 60 and < 90 mL/min; 37%) or moderate decrease (CrCL ≥ 30 and < 60 mL/min; 41%) in renal function (EV-302 CSR Table 12). A severe decrease in renal function was seen in approximately 2% of participants (EV-302 CSR Table 12).

There was a slight imbalance between the enfortumab vedotin with pembrolizumab arm and the chemotherapy arm in the proportion of participants with lower tract urothelial cancer (69% versus 76.4%) and conversely upper tract urothelial cancer (30.5% versus 23.4%), which has a worse prognosis. As stated in CS section B.2.12.2, the effect of this imbalance on trial results would be conservative in terms of enfortumab vedotin with pembrolizumab efficacy i.e. would favour chemotherapy. Both of the EAG clinical experts agreed with this statement. Both EAG clinical experts commented that the proportions with upper tract urothelial cancer was higher than that seen in clinical practice, with one expert quantifying that 5 to 10% of patients in the UK have upper tract disease.

With respect to histology type, 85% of participants had urothelial carcinoma. One EAG clinical expert commented this is lower than that seen in the UK, which is >90% of cases.

Most participants (95%) had metastatic disease at randomisation. Approximately 72% of participants had visceral metastases and 23% lymph node only disease. One EAG clinical expert commented that the proportion with lymph node only disease, which has better prognosis, was higher in the trial population than that seen in UK clinical practice, which is <20%.

With respect to cisplatin eligibility, 54% of participants were eligible for cisplatin and 46% were not. One EAG clinical expert commented that in UK clinical practice 60% of patients are cisplatin eligible and 40% are cisplatin-ineligible.

PD-L1 expression was categorised as high (combined positive score (CPS) ≥ 10) in 58% of participants and low (CPS < 10) in 42%. Both of the EAG clinical experts commented that PD-L1 is not used in clinical practice as a prognostic marker.

Overall, both of the EAG clinical experts considered the EV-302 trial population to be a "standard trial population", in that it was fitter, had fewer comorbidities and better prognosis than real world cohorts. However, they did believe it was generalisable to real world practice.

3.2.1.1.4 Cohort A + dose escalation and cohort K baseline characteristics

Baseline characteristics of Study EV-302 and cohort A + dose escalation and the enfortumab vedotin with pembrolizumab arm of cohort K were similar with the following exceptions:

- Compared with study EV-302, a greater proportion of patients in cohort A + dose escalation were aged ≥75 years (35.6% vs 23.7%), had EGOG PS 2 (17.8% vs 2.9%), and had visceral metastases (84.4% vs 71.8%), while fewer had ECOG PS 0 (33.3% vs 49.4%). The company caution that since the sample size in EV-103 is small (N=45), comparisons should be treated with caution (CS section B.2.6.8.1).
- Compared to study EV-302, as with cohort A + dose escalation, a greater proportion of patients in the enfortumab vedotin with pembrolizumab arm of cohort K were aged ≥ 75 years ([redacted] vs 23.7%), had ECOG PS2 ([redacted] vs 2.9%) and visceral metastases ([redacted] vs 71.8%). Unlike cohort A + dose escalation, the proportion of patients with ECOG 0 were similar between study EV-302 and the enfortumab vedotin with pembrolizumab arm of cohort K (49.4% vs [redacted]). Both cohort A + dose escalation and cohort K predominately recruited patients from the USA ([redacted]), while study EV-302 recruited only [redacted]% from the USA.

EAG conclusion

The EV-302 trial is a large ongoing phase III, multicentre, randomised, open-label, controlled trial comparing the efficacy and safety of enfortumab vedotin with pembrolizumab to platinum-based chemotherapy in combination with gemcitabine, in adult patients with previously untreated unresectable locally advanced or metastatic urothelial carcinoma. It was used as the pivotal trial in the granting of the marketing authorisation and is the sole source to directly inform the economic model for this appraisal. The trial is generally representative of patients with previously untreated unresectable locally advanced or metastatic urothelial carcinoma, though the trial patient population is younger and fitter than would be seen in practice.

3.2.2 Risk of bias assessment

The company's methodological quality assessment (also referred to as risk of bias assessment) of study **EV-302** and **cohort K** of study **EV-103** was conducted using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2),[12] and for cohort A + dose escalation using the Cochrane ROBINS-I tool (CS Appendix D sections 3.6 and 5.0).[13] An overview of the company's judgements for each bias domain and an overall risk of bias, for EV-302 and cohort K is presented in CS Appendix D Tables 53 and 54 and for cohort A + dose escalation in CS Appendix D Table 52.

The company assessed that all three studies were at low risk of bias for each domain of judgement and for overall risk of bias. The EAG note that only one person performed the risk of bias assessment of each study, without apparent checking by a second reviewer for errors (CS Appendix D section 3.6), and the CS did not include any justifications for risk of bias judgements.

The EAG independently appraised study EV-302. RoB 2 provides a framework for assessing the risk of bias in a single randomised trial for *one or more individual outcome measures(s)*.[12] The company assessed the risk of bias for the two primary outcomes of EV-302, PFS and OS, as these were deemed most critical for informing the economic model. Although the study was open-label, PFS was assessed by blinded-IRC, and OS is a considered a 'hard endpoint' with a low risk of measurement error or bias. The EAG agree with the company's RoB 2 judgements for PFS and OS i.e. low risk of bias for each domain of judgement and for the overall risk of bias.

The company did not formally assess risk of bias for health-related quality of life outcomes, specifically EQ-5D-5L which informs the economic model. However, the CS discusses the disparity in the study arms between the number of participants who completed the questionnaires (CS sections B.2.6.6 and B.2.12). Furthermore, post-hoc analysis showed that completion rates were [redacted] in the chemotherapy arm due to more participants having progressed. Participants who completed the questionnaires may therefore not be representative of participants who did not (CS sections B.2.6.6 and B.2.12.2 and company clarification response B2), which would bias the data in favour of chemotherapy.

3.2.3 Outcomes assessment

All outcomes included in the NICE scope (OS, PFS, response rate, adverse effects of treatment and HRQoL) were measured in the EV-302 trial.[14] CS document B, CS Appendices E and F, and CS addendum (15 November 2024) present results of these outcomes for trial EV-302. Results for the EV-302 trial were also reported in the main trial publication (Powles et al., 2024),[11] in the CSR and updated CSR tables and figures provided by the company. Table 7 provides a summary of the NICE scope and decision problem related outcomes reported in the EV-302 trial.

Table 7 List of NICE scope and decision problem related outcomes reported in the EV-302 trial

Endpoint	Outcome	Definition
Co-Primary outcomes informing the model	Blinded-independent central review (ICR) assessed progression free survival (PFS)	Time from randomisation to the first occurrence of disease progression as assessed by Blinded-ICR according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or death from any cause, whichever occurred first (CS document B Table 8)
	Overall survival (OS)	Time from date of randomisation to date of death due to any cause (CSR Table 8)
Secondary outcomes informing the model	Adverse effects	A TEAE was defined as a newly occurring or worsening AE after the first dose of study treatment through 30 days after the last dose of study treatment, or through 90 days after the last dose of

Endpoint	Outcome	Definition
		study treatment for SAE in arms utilising pembrolizumab (CSR section 5.6.3.6.1) SAEs leading to death, hospitalisation, or prolonged hospitalisation, persistent or significant incapacity or disruption to normal daily life, congenital anomaly/birth defect, were life-threatening or required intervention to avoid one of the above (trial protocol (version amendment 08) section 7.8.1.1) Severity of AEs were graded according to the NCI CTCAE version 4.03 (Grade 1, mild; Grade 2, moderate; Grade 3, severe but not life-threatening; Grade 4, life-threatening; Grade 5, death) (trial protocol (version amendment 08) section 7.8.1.1) Adverse events of special interest for EV: skin reactions, peripheral neuropathy, hyperglycaemia, ocular disorders, and infusion-related reactions (CSR section 5.6.3.6.2)
	Health-related quality of life (EQ-5D-5L)	Data collection via an electronic questionnaire. Baseline assessment at clinic up to 24 hours prior to first dose of study treatment and before any study procedures or assessments conducted. Subsequent assessments completed at home prior to clinic visit (once weekly for the first 12 weeks, on Week 14 and once every 3 weeks for the remainder of the study through disease progression and survival follow-up; CS section B.3.4.1)

Endpoint	Outcome	Definition
Secondary outcomes *not* informing the model	Objective response rate (by blinded-ICR and by investigator)	Proportion of patients achieving a confirmed CR or PR per RECIST v1.1. (SAP v4 section 7.5.2.1)
	Duration of response (by blinded-ICR; and by investigator)	Time from the first objective response (CR or PR that is subsequently confirmed) to the first documented PD per RECIST v1.1 or death from any cause, whichever occurs first. DOR will only include subjects with a confirmed response (CR or PR per RECIST v1.1; SAP v4 section 7.5.2.1)
	Health related quality of life (EORTC QLQ-C30)	Questionnaire developed to assess the quality of life of cancer patients, including global health status/QoL, functional scales, symptom scales, symptom items and financial impact (CSR Table 9)

Source: Partly reproduced from CS section B.3.4.1, CS document B Table 8, CSR section 5.6.3.6.1 and 5.6.3.6.2, CSR Table 8 and 9, SAP v4 section 7.5.2.1, trial protocol (version amendment 08) section 7.8.1.1
Abbreviations: AE, adverse event; CR, complete response; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-5L, EuroQoL Five-dimension Five-level; IRC, imaging review committee; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumours; SAE, serious adverse event; TEAE, treatment-emergent adverse event

The CS reports results from a data cut of 08 August 2023. CS addendum (15 November 2024) reports results from the latest available data cut (08 August 2024), and these are used to inform the latest version of the economic model (clinical addendum (29 November 2024)).

Outcomes specified in the NICE final scope and decision problem informing the economic model were:

- Progression free survival (CS addendum (15 November 2024) section 2.3)
- Overall survival CS (CS addendum (15 November 2024) section 2.4)
- HRQoL via the EQ-5D-5L (mapped to the EQ-5D-3L; CS addendum (29 November 2024) Appendix O).
- Adverse events grade ≥3 overall and grade ≥2 for peripheral neuropathy for any treatment regimen in the EV-302 trial (CS addendum (29 November 2024) section 3.1).

In addition, time on treatment also informed the economic model (see section 4.2.6.4).

The trial protocol (version amendment 08), published as an appendix to the primary trial publication (Powles et al.,2024),[11] and CSR section 5.4.1 show that overall methods, frequency and timing of all outcome assessments were identical between trial arms, reducing the risk of evaluation time bias.

EAG conclusion

Overall, we consider the efficacy, HRQoL and safety outcomes to be appropriate to the decision problem and scope.

3.2.4 Statistical methods of the included studies

The CS (Section 2.4) reports the statistical methods used in the EV-302 study, with further detail available in the trial statistical analysis plan (SAP) available as an appendix to the primary trial publication (Powles et al. 2024).[11] In Table 8 below we summarise and critique the trial's statistical procedures. In brief, the trial was powered to detect a statistically significant difference in PFS and OS (dual primary outcomes) for enfortumab vedotin with pembrolizumab versus platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine. Pre-specified secondary outcomes included measures of tumour response, adverse events and patient reported outcomes (PROs). In addition, the trial included a small number of exploratory endpoints (e.g. investigator-assessed outcomes, exploratory biomarkers) which were not tested statistically.

Table 8 Statistical methods of the EV-302 study

Analysis populations
The SAP (Version 4.0; 22-Jun-2023)[11] lists several analysis populations, including: *Efficacy analyses* • Intention to treat (ITT) population – all randomised patients, analysed in the trial arm they were randomised to, irrespective of which treatment they received. *Safety analysis* • Safety population – all enrolled patients who received any dose of the trial treatment, according to actual treatment received *Response related endpoints* • Response Evaluable Set – all pts with measurable disease at baseline, analysed in the trial arm of original random assignment *Patient Reported Outcomes (PROs)* • Patient Reported Outcomes Full Analysis Set (PRO FAS) - all randomised pts who received any amount of study treatment and completed a PRO at baseline;

EAG comment: The analyses sets are clearly defined and align with methodological standards for clinical trials. Importantly a 'true' ITT population is used for the co-primary outcomes OS and PFS.

Sample size calculations

The main components of the sample size calculations are tabulated below, for the co-primary endpoints OS and PFS.

End-point	Power	Alpha level (2-sided)	Events required (n)	HR	Median duration (months)	Patients required (n)
OS	93%	0.045	489	0.73	15.3	860
PFS	90%	0.005	526	0.7	7	

Assumptions include:

- (OS / PFS, respectively) Kaplan Meier curves follow piecewise exponential distribution with a reduced hazard rate (50% / 20% of initial rate) from 24/15 months; enrolment period of 30 months; yearly drop-out rate of 5%.

Data-cuts:

- Single planned (final) analysis of PFS: when approx. 526 events or 356 OS events occurred
- Two planned analyses of OS: (i) interim analysis coinciding with the PFS final; (ii) final OS analysis when approx. 489 events occur.

EAG comment: The sample size calculation is clearly defined but justifications for certain assumptions are not explicit in the CS or the SAP (e.g. the size of the expected treatment effect). The required number of patients randomised was exceeded (n=886 randomised, n=860 required), therefore statistical power is sufficient.

Methods to account for multiplicity

Dual primary outcomes PFS and OS, with a family-wise type I error rate, 2-sided initial alpha allocation of 0.005 and 0.045, for PFS and OS respectively. If one of the co-primary outcomes was statistically significant the alpha was then applied to the other outcome. If both PFS and OS were statistically significant, then selected secondary outcomes were tested statistically in sequence using a pre-specified "gatekeeping" strategy. Each of the selected secondary outcomes were only tested if the preceding outcome was significant at the 5% threshold.

EAG comment: Appropriate safeguards were used to lower the probability of false positive results arising due to testing multiple outcomes and at multiple timepoints.

Analysis of outcomes

- Log rank tests of statistical significance for OS and PFS hazard ratios.

• Kaplan Meier method used to estimate time to event outcomes (OS and PFS), • Log-log transformation of 95% confidence intervals. • Censoring rules for PFS were revised so that chemotherapy arm patients who received maintenance therapy as the first subsequent therapy were not censored.
EAG comment: The statistical tests are appropriate to the outcome measures used.
Handling of missing data
Imputation of missing data was done only for certain outcomes, including duration of AEs, treatment emergent status of AEs; for estimating dates of certain key events such as time from diagnosis to randomisation, death, and commencement of subsequent anti-cancer therapy.
EAG comment: The EAG has no specific concerns
Sensitivity & post-hoc analyses
• "Supportive" subgroup analyses reported for PFS, OS and overall response (CS Appendix E), for pre-specified factors including, stratification factors (inc: cisplatin eligibility), demographics, and disease status (e.g. ECOG performance status, type of metastases and renal function). • Sensitivity analyses of OS and PFS explored alternative assumptions, such as unstratified analyses; censoring of patients using subsequent therapy; non-proportional hazards.
EAG comment: he EAG has no specific concerns
Source: Table contains amalgamated text from CS Section 2.4 and the SAP (Version 4.0; 22-Jun-2023)[5]

EAG conclusion on study statistical methods

The statistical methods used in the EV-302 trial are clearly described in the CS with further detail available in the trial SAP. The trial was adequately powered to detect statistically significant differences between enfortumab vedotin with pembrolizumab compared with chemotherapy. The overall statistical design is appropriate for the clinical evaluation of cancer treatments.

3.2.5 Efficacy results of the intervention studies

Here we present a summary of the key efficacy and safety results from the EV-302 trial, focusing on PFS, OS, HRQoL and adverse effects. The outcome data in the CS is based on the primary results of the EV-302 trial data cut of 8 August 2023, with a median follow-up for survival of 17.2 months. This was planned to be triggered when approximately 526 PFS or 356 OS events occurred. This represents the final PFS results and the interim OS results.

Subsequently, a further data cut was done on 8 August 2024 (median follow-up 29.1 months) and is presented in CS addendum (15 November 2024). This was planned to be triggered when approx. 489 OS events occurred. This represents the final results for OS and an update to the final PFS results. Of note, the company refers to this data cut as being “an exploratory ad hoc analysis”.

Below we present the results from the 8 August 2024 data-cut. The results are generally consistent with the results from the primary analysis and show a statistically significant survival benefit for enfortumab with pembrolizumab over chemotherapy.

3.2.5.1 Progression free survival (PFS)

Median PFS in the EV+P arm was almost double that in the chemotherapy arm, at 12.5 months (95% CI, 10.4 to 16.6) with enfortumab with pembrolizumab, versus 6.3 months (95% CI, 6.2 to 6.5) with chemotherapy. Patients in the enfortumab with pembrolizumab arm had a 52% lower risk of disease progression or death compared the chemotherapy arm (HR 0.48; 95% CI, 0.41 to 0.57; P<0.001). This is based on the stratified analysis in the ITT population.

3.2.5.2 Overall survival (OS)

Median OS was almost twice as long in the enfortumab with pembrolizumab arm compared to the chemotherapy arm, at 33.8 months (95% CI, 26.1 to 39.3) versus 15.9 months (95% CI, 13.6 to 18.3). The risk of death was 49% lower in the enfortumab with pembrolizumab arm than in the chemotherapy arm (HR 0.51; 95% CI, 0.43 to 0.61; P<0.001).

Estimated survival at 24 months was 60.1%[redacted]) in the EV+P arm and 35.4%[redacted]) in the chemotherapy arm.

3.2.5.3 HRQoL outcomes

CS section B.2.6.6.2 briefly reports on the EQ-5D-5L Health State Index Scores (utility scores) and Visual Analogue Scale (VAS) scores for the 08 August 2023 data cut for study EV-302. At baseline, [redacted] of patients in the enfortumab vedotin with pembrolizumab arm and [redacted] in the chemotherapy arm completed at least one component of the EQ-5D-5L questionnaire. The mean baseline utility scores were [redacted] in the enfortumab vedotin with pembrolizumab arm and [redacted] in the chemotherapy arm, and the VAS scores were [redacted] and [redacted] respectively. During the treatment period, both utility and VAS scores were reported to have remained stable, with little to no change from baseline throughout the study period.

CS addendum (15 November 2024) section 2.7 (data cut 08 August 2024) states that EQ-5D-5L completion rates (the proportion of participants who completed at least one question

of the instrument among the ITT analysis set; updated CSR Figure 12.3.9.2) and compliance rates (the proportion of participants who completed at least one question of the instrument among those expected to complete at each visit. Participants are expected to complete the instrument if the scheduled visit occurred; updated CSR Figure 12.3.9.1) were consistently higher in the enfortumab vedotin with pembrolizumab arm from approximately week 8, but only reports results for EQ-5D-5L VAS score.

However, updated CSR Table 12.3.9.3 (data cut 08 August 2024) provides a summary of EQ-5D-5L utility scores at each visit, which showed that utility scores changed little from baseline. For illustrative purposes only, the EAG have provided mean change from baseline for a range of study visits in Table 9.

Table 9 EQ-5D-5L Health State Index Over Time

Week	EV+P N	EV+P mean change from baseline (SD)	PBC+gem N	PBC + gem mean change from baseline (SD)
Baseline	377	N/A	356	N/A
4	317	[redacted]	297	[redacted]
8	306	[redacted]	282	[redacted]
17	279	[redacted]	241	[redacted]
29	243	[redacted]	158	[redacted]
50	178	[redacted]	93	[redacted]
74	145	[redacted]	58	[redacted]
107	91	[redacted]	26	[redacted]

Source: Partly reproduced from updated CSR Table 12.3.9.3
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; N/A, not applicable; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; SD, standard deviation

These results, however, should be interpreted with caution as there is disparity in the study arms between the number of participants who completed the questionnaires. Furthermore, post-hoc analysis showed that participants who completed the questionnaires may not be representative of participants who did not (CS sections B.2.6.6 and B.2.12.2 and company clarification response B2), and this is likely to favour the chemotherapy arm (see section 3.2.2)

3.2.5.4 Subgroup analyses

CS section B.2.7 and CS Appendix E report subgroup analyses of study EV-302 for the 08 August 2023 data cut. CS addendum (15 November 2024) section 2.9 reports forest plots of

prespecified subgroup analyses for the two primary outcomes, blinded-IRC assessed PFS (CS addendum (15 November 2024) Figure 5) and OS (CS addendum (15 November 2024) Figure 6), of the 08 August 2024 data cut, which are reported here.

Subgroups included:

- **Baseline demographic characteristics** (age (<65 years, ≥ 65 years), race, region, sex)
- **Measure of baseline disease status** (ECOG PS (0, 1-2), primary disease site, liver metastases, PD-L1 expression, cisplatin eligibility, metastatic disease site, renal function)

The company states that the benefit of enfortumab vedotin with pembrolizumab for PFS and OS was consistent between the ITT population and all predefined subgroups. The EAG agree that confidence intervals for the hazard ratios for all subgroup analyses were less than one, signifying a benefit for enfortumab vedotin with pembrolizumab, with one exception. For the subgroup analysis of region for OS, the upper 95% confidence interval for the North America subgroup was [redacted].

3.2.5.5 Safety outcomes

Data on adverse events were reported in CS section B.2.10 (for study EV-302 (data cut 08 August 2023) and cohort A + dose escalation only) and CS Appendix F. Updated adverse event data with a data cut of 08 August 2024 for study EV-302 was reported in CS addendum (15 November 2024) section 2.10 and updated CSR tables and is reported here.

For adverse events leading to discontinuation, dose interruption or reduction or that occurred in ≥20% of patients in either treatment arm (any grade), or ≥5% in either arm (grade ≥3) CS addendum (15 November 2024) section 2.10 only reports treatment-related adverse events i.e. adverse events assessed by the investigator as related to any study drug treatment. However, the health economic model, albeit in the ITT population rather than safety population, and the summary of safety of enfortumab vedotin with pembrolizumab published in the SmPC,[15] use treatment-emergent adverse events i.e. adverse events that occurred irrespective of their assessed relatedness to any study drug.

The EAG have therefore augmented data from CS addendum (15 November 2024) Table 7 with treatment-emergent adverse events leading to discontinuation, dose interruption or reduction of study drug (see Table 10) and present data for treatment-emergent adverse event in ≥20% of patients in either treatment arm (any grade), or ≥5% in either arm (grade ≥3) in Table 11. This data was obtained from updated CSR tables 12.6.1.1.1, 12.6.1.1.2,

12.6.1.1.3, 12.6.1.1.4, 12.6.1.2.1 and 12.6.1.3.1. The EAG preferentially report data on treatment-emergent adverse events in this section.

The EV-302 safety population (all patients who received any dose of the trial treatment according to the actual treatment received) include a total of 873 of 886 randomised patients. Table 10 gives a summary of key safety results of the 08 August 2024 data cut. Given the longer treatment duration in the enfortumab vedotin with pembrolizumab arm compared to the chemotherapy arm, event rates were adjusted for treatment exposure. Adverse events by patient incidence rate and adjusted for exposure are shown in below. Both exposure-adjusted treatment-emergent event rates and exposure-adjusted treatment-related adverse were lower in the enfortumab vedotin with pembrolizumab arm than in the chemotherapy arm in all categories shown in Table 10

Table 10 Overview of adverse events in study EV-302

Adverse event	Patient incidence rate		Event rate adjusted for exposure	
	EV+P (N=440) N (%)[a]	PBC+gem (N=433) N (%)[a]	EV+P (PY=[redacted]) Events (Events/PY) [a]	PBC+gem (PY=[redacted]) Events (Events/PY [a])
Any TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to discontinuation of any study drug	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to discontinuation of EV	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to discontinuation of P	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to interruption of any study drug	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to interruption of EV	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to interruption of P	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to dose reduction of any study drugs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from CS addendum (15 November 2024) Table 7 and CSR updated CSR Tables 12.6.1.1.1, 12.6.1.1.2, 12.6.1.1.3, 12.6.1.1.4
Abbreviations: E, events; EV, enfortumab vedotin; EV+P, enfortumab vedotin with pembrolizumab; NA, not applicable; P, pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; PY, patient-years; TEAEs, treatment-emergent adverse events
[a]Data are from the latest data cut of 08 August 2024

Almost all patients in both the enfortumab vedotin with pembrolizumab and chemotherapy arms experienced treatment-emergent adverse events ([redacted]) or treatment-related adverse events [redacted]; see Table 10). The most common treatment-emergent adverse events for

patients receiving enfortumab vedotin with pembrolizumab arm was peripheral sensory neuropathy ([redacted]), pruritus ([redacted]) and diarrhoea ([redacted]) while for those receiving chemotherapy it was anaemia ([redacted]), neutropenia ([redacted]) and nausea ([redacted]; see Table 11). One EAG clinical expert had experience of treating patients admitted to accident and emergency as a result of side effects from enfortumab vedotin with pembrolizumab. They considered these side effects similar to those observed with chemotherapy.

The proportion of patients experiencing a treatment-emergent adverse event that led to death was similar between enfortumab vedotin with pembrolizumab and chemotherapy ([redacted] versus [redacted]), including those considered treatment-related ([redacted] versus [redacted]). Serious adverse events, however, were more common in the enfortumab vedotin with pembrolizumab arm compared to chemotherapy ([redacted] versus [redacted]), including those considered treatment related ([redacted] versus [redacted])

The proportion of patients experiencing any treatment-emergent adverse event with a severity grade ≥3 was similar between enfortumab vedotin with pembrolizumab and chemotherapy. The EAG note that proportion of patients experiencing a treatment-related adverse event with a severity grade ≥ 3 was less in the enfortumab vedotin with pembrolizumab arm compared to the chemotherapy arm ([redacted] versus [redacted]). The most common treatment-emergent adverse events with a severity grade ≥3 for patients receiving enfortumab vedotin with pembrolizumab was rash maculopapular ([redacted]), anaemia ([redacted]) and hyperglycaemia ([redacted]), while for those receiving chemotherapy it was anaemia ([redacted]), neutropenia ([redacted]) and thrombocytopenia ([redacted]).

More than twice as many patients in the enfortumab vedotin with pembrolizumab arm experienced a treatment-emergent adverse event leading to discontinuation of any study drug compared to the chemotherapy arm ([redacted] versus [redacted]). The most common reason for discontinuing any study drug in the enfortumab vedotin with pembrolizumab arm was peripheral sensory neuropathy ([redacted]updated CSR Table 12.6.1.4.4) while in the chemotherapy arm it was anaemia ([redacted]; updated CSR Table 12.6.1.4.4). In the enfortumab vedotin with pembrolizumab arm, treatment-emergent adverse events led to the discontinuation of enfortumab vedotin in [redacted] of patients and to the discontinuation of pembrolizumab in [redacted] of patients.

A greater proportion of patients in the enfortumab vedotin with pembrolizumab arm experienced a treatment-emergent adverse event leading to interruption of any study drug compared to the chemotherapy arm ([redacted] versus [redacted]). However, the proportion of patients experiencing adverse events leading to dose reduction of any study drugs was similar between enfortumab vedotin with pembrolizumab and chemotherapy.

Table 11 Treatment-emergent adverse events in study EV-302 occurring in ≥20% of patients in either treatment arm (any grade), or ≥3% in either arm (grade ≥3)

	EV+P (N=440)		PBC+gem (N=433)	
Adverse event	**Any grade[a]**	**Grade ≥3[a]**	**Any grade[a]**	**Grade ≥3[a]**
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from updated CSR Tables 12.6.1.2.1 and 12.6.1.3.1
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine
[a]Data are from the latest data cut of 08 August 2024[redacted]

3.2.5.5.1 Adverse events of special interest

Treatment-emergent adverse events of special interest for enfortumab vedotin that occurred in study EV-302 are shown in Table 12. The two most common adverse events of special interest were skin reactions ([redacted]) and peripheral neuropathy ([redacted]). Apart from infusion-related reactions, the proportion of patients with specific adverse events of special interest for enfortumab vedotin were at least [redacted] in the enfortumab vedotin with pembrolizumab arm compared to the chemotherapy arm. The most marked difference was seen in the proportion of patients with ocular disorders, which was nearly [redacted] in the enfortumab vedotin with pembrolizumab arm compared to the chemotherapy arm. One

EAG clinical expert commented that the use of enfortumab vedotin would require additional clinical management in the form of input from ophthalmology.

Table 12 Treatment -emergent adverse events of special interest for enfortumab vedotin in study EV-302

Adverse event	EV+P (N=440)	EV+P (N=440)	PBC+gem (N=433)	PBC+gem (N=433)
	Any grade[a] n (%)	Grade ≥3[a] n (%)	Any grade[a] n (%)	Grade ≥3[a] n (%)
Peripheral Neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Skin reactions	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
SCAR	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Ocular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]
Corneal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reactions	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from CS Addendum (15 November 2024) Table 9
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; SCAR, severe cutaneous adverse reaction.
[a]Data are from the latest data cut of 08 August 2024

3.2.5.5.2 Long-term safety outcomes

A post-hoc analysis of cohort A + dose escalation of study EV-103, which included cisplatin-ineligible patients only, provided longer-term adverse event data for enfortumab vedotin with pembrolizumab (median follow up of 62.1 months (range 0.66 to 69.55); CS section B.2.10.2, company clarification response A5). The company state that no new safety concerns were identified. For adverse events of special interest for enfortumab vedotin, only data for treatment-related adverse events were reported (Table 13). However, as with study EV-302, the two most common events of special interest for enfortumab vedotin were skin reactions (66.7%) and peripheral neuropathy (62.2%). The company state the majority of treatment-related adverse events of special interest for enfortumab vedotin improved or resolved. The safety of pembrolizumab was also reported to be consistent with previously observed results, except for severe skin reaction, which were reported at a higher incidence in this study ([redacted] (any grade), 22.2% (grade ≥3). Both EAG clinical experts commented they

had no concerns regarding the higher incidence of severe skin reactions with pembrolizumab specifically.

Table 13 Treatment-related adverse events of special interest for enfortumab vedotin in cohort A + dose escalation of study EV-103

Adverse event	Dose escalation[a]/cohort A (N=45)	
	Any grade n (%)	Grade ≥3 n (%)
Skin reactions	30 (66.7)	10 (22.2)
Peripheral neuropathy[b]	28 (62.2)	2 (4.4)
Ocular disorders	18 (40.0)	0
Dry eye	16 (35.6)	0
Blurred vision	5 (11.1)	0
Corneal disorders	1 (2.2)	0
Hyperglycaemia	5 (11.1)	4 (8.9)
Infusion-related reactions	3 (6.7)	1 (2.2)

Source: Reproduced from CS document B Table 18
[a] Dose escalation patients who assigned to EV+P 1.25 mg/kg IV on Days 1 and 8, and P 200 mg IV on Day 1 of every 3-wk cycle and for whom study treatment was administered as 1L therapy;
[b] Peripheral neuropathy Standardized MedDRA queries (broad scope). 8 patients had pre-existing peripheral neuropathy and 37 did not have pre-existing peripheral neuropathy. Pre-existing condition includes medical history and conditions ongoing at baseline

Both EAG clinical experts expressed concerns over the cumulative toxicity of enfortumab vedotin over time, with one encouraging research into optimal scheduling and dosing i.e. effective lower doses or shorter schedules.

3.2.6 Pairwise meta-analysis of intervention studies

CS section B.2.8. states that a meta-analysis is not applicable since EV-302 is the only study comparing enfortumab vedotin with pembrolizumab versus platinum based chemotherapy in first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy (i.e. eligible for either cisplatin or carboplatin). The EAG concurs with this assertion.

3.3 Critique of studies included in the indirect comparison and/or multiple treatment comparison

Atezolizumab was included in the NICE scope as a comparator for a subgroup of unresectable or metastatic urothelial carcinoma patients. The Company does not consider atezolizumab to be a relevant comparator in this (or any) subgroup because of low usage in current NHS clinical practice and therefore did not present an indirect treatment comparison (ITC) with atezolizumab (CS section B.2.9). The EAG concurs with this assertion.

3.4 Additional work on clinical effectiveness undertaken by the EAG

None

3.5 Conclusions on the clinical effectiveness evidence

3.5.1 Decision problem

The company's decision problem generally matches the scope of the appraisal. Exclusion of two of comparator treatments, MVAC and atezolizumab, is appropriate given evidence showing minimal use in clinical practice. The only comparator of interest was therefore platinum-based chemotherapy (cisplatin if eligible, or carboplatin) in combination with gemcitabine.

3.5.2 Treatment pathway

The company's favoured position for enfortumab vedotin with pembrolizumab, is as first-line treatment of adult patients with unresectable or metastatic urothelial cancer eligible for platinum-containing chemotherapy, which accords with its marketing authorisation. Platinum-based chemotherapy plus gemcitabine would therefore become a second-line treatment. This reflects the latest European clinical guidelines on bladder cancer/upper urinary tract urothelial carcinoma. Both of the EAG clinical experts were supportive of using enfortumab vedotin with pembrolizumab as first-line treatment, and agreed with the company's assertions regarding likely implications for the care pathway if enfortumab vedotin with pembrolizumab were to be recommended by NICE. Its potential introduction is unlikely to require significant changes to clinical practice, but time and experience will enable clinicians to increase their familiarity with its side effect profile and necessary clinical management.

3.5.3 Clinical effectiveness of enfortumab vedotin with pembrolizumab

The results from the pivotal trial, EV-302, at both the primary (primary PFS, interim OS) data cut August 2023 and the updated data cut on 8 August 2024 (final OS, updated PFS) show a statistically significant survival benefit for enfortumab vedotin with pembrolizumab compared to cisplatin- based chemotherapy. Clinical experts advising the EAG regard the results as highly clinically significant. However, they noted the adverse effect profile of enfortumab and did have some concerns over potential cumulative toxicity.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review for economic models for interventions used for local advanced or metastatic urothelial cancer on 13 December 2022 (and updated on 03 June 2024). The inclusion and exclusion criteria are shown in CS Appendix G Table 1. The searches were conducted in Medline, Embase and EconLit and the search strategy is outlined in CS Appendix G. Health Technology Assessment agencies were also searched.

The review identified 25 economic evaluations, of which 22 were cost-effectiveness / cost-utility assessment. Seven HTA submissions were identified, including two Technology Assessments from NICE. A summary of the studies is shown in Appendix G(b). No studies were identified for enfortumab vedotin with pembrolizumab.

The EAG identified three studies that assessed the cost-effectiveness of enfortumab vedotin with pembrolizumab by Li et al.[16] and You et al.[17] which were published in September 2024 and Rieger et al.[18] (in press at the time of writing of this report).

The study by Li et al.[16] conducted a cost-effectiveness analysis of enfortumab vedotin with pembrolizumab as a first-line treatment for patients with metastatic urothelial cancer from the perspective of US payers. The study by You et al.[17] conducted a cost-effectiveness analysis of enfortumab vedotin with pembrolizumab versus platinum-based chemotherapy with gemcitabine as a first-line treatment for advanced urothelial cancer from the perspective of the Chinese healthcare system. Both of these studies included a Markov model, each with three health states. Rieger et al.[18] conducted a cost-effectiveness analysis of enfortumab vedotin with pembrolizumab as a first-line treatment for patients with metastatic urothelial cancer from the perspective of Germany and the USA. A Markov model was developed with multiple states with three lines of treatment. The results of all the studies are shown in Table 14.

Table 14 Results from the published cost-effectiveness studies for enfortumab vedotin with pembrolizumab for urothelial cancer

Study	Treatment comparison	Costs (incremental)	QALYs (incremental)	ICER (£ per QALY gained)
Li et al.(2024)[16]	EV+P vs PBC+gem	$962,241	1.72	$558,973
You et al. (2024)[17]	EV+P vs PBC+gem	$352,050	1.52	$232,256
Rieger et al.(2024)[18]	EV+P vs Nivolumab + PBC+gem[a]	€194,317	0.60	€323,861

Source: EAG created table
[a] Also compared against standard of care.
EV enfortumab vedotin, P pembrolizumab, PBC platinum-based chemotherapy, gem gemcitabine, QALY quality adjusted life year, ICER incremental cost effectiveness ratio.

EAG conclusion

We consider the cost-effectiveness search strategy and review to be reasonable, however, there are three recent studies that evaluated the cost-effectiveness of enfortumab vedotin with pembrolizumab in advanced urothelial cancer that the EAG has identified.[16-18]

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of the NICE reference case (Table 15).

Table 15 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Appropriate – OS and PFS
Perspective on costs	NHS and PSS	Appropriate – NHS and PSS used

Element of health technology assessment	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Appropriate – cost-utility analysis with fully incremental analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Appropriate – Lifetime (max 30 years; patients enter model aged 67.9 years)
Synthesis of evidence on health effects	Based on systematic review	Yes – company conducted appropriate systematic reviews
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes – company collected EQ-5D-5L data from the EV-302 trial, which were cross-walked to EQ-5D-3L utilities appropriately
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes – company collected EQ-5D-5L data from the EV-302 trial
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes – EQ-5D uses representative sample from UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – CS discusses equality considerations in CS 1.4; company appropriately applies severity modifier of x1.2 (discussed in CS 3.6)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes - NHS Reference Costs 2021/22; PSSRU 2023 costs used
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes – 3.5% discount rate for both costs and health benefits in the company

Element of health technology assessment	Reference case	EAG comment on company's submission
		case; company ran scenarios testing 6%, 5%, 1.5% and 0% discount rates

Source: Partly reproduced from CS Table 51
Abbreviations: EQ-5D, European Quality of Life Working Group Health Status Measure 5 Dimensions; EQ -5D-3L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 Levels; EQ -5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, Quality-adjusted life year

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company's model structure is described in CS section B.3.2.2 and illustrated in CS Figure 20 (reproduced in Figure 3). CS Table 21 summarises the features of the company's model.

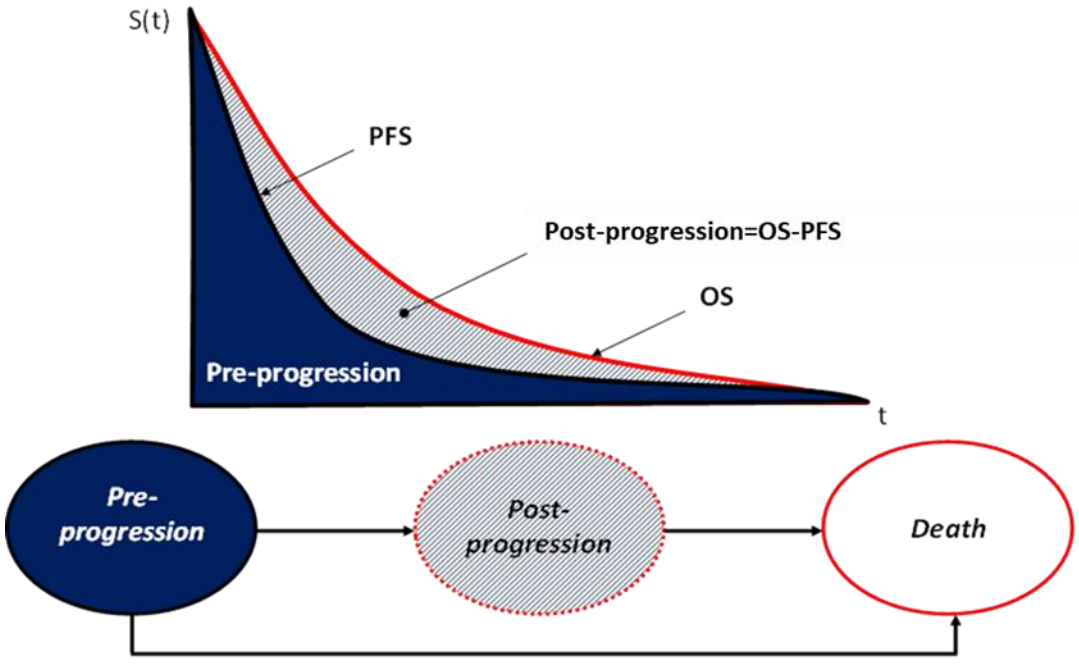

Figure 3 Partitioned survival model structure, company model

Reproduced from CS Figure 20.
OS, overall survival; PFS, progression-free survival; S(t), survival as a function of time; t, time.

The company use a partitioned survival model, which is in line with previous NICE appraisals for urothelial cancer: TA739[3] and TA788.[19] The model consists of three mutually exclusive health states:

- Alive without disease progression (pre-progression)
- Alive after the disease has progressed (post-progression)
- Death

The progression-free survival curve estimates the proportion of patients whose disease has not progressed and cannot exceed the overall survival curve at any time point.

Patients start in the pre-progression health state and receive either enfortumab vedotin with pembrolizumab, or platinum-based chemotherapy (cisplatin if eligible, or carboplatin) plus gemcitabine (hereafter referred to as 'chemotherapy') followed by avelumab maintenance therapy, and are either stable or responding to therapy. Over time, patients can transition directly to the death health state or to the post-progression health state where they may receive subsequent treatment before moving to the death health state.

EAG conclusion on model structure

The three-state partitioned survival model used in the company's economic evaluation is a standard modelling approach, which has been applied in previous NICE appraisals for urothelial cancer and is commonly used in oncology models. We consider that the model structure and partitioned survival approach is appropriate and reflects UK clinical practice.

4.2.3 Population

Patient characteristics for the modelled patient population align with the ITT population from the EV-302 trial (Table 16). The modelled population also matches the licensed indication for enfortumab vedotin with pembrolizumab (i.e. first-line adult patients with unresectable or metastatic urothelial cancer who are eligible for chemotherapy). The company's base case results use the ITT population, but the CS also presents results for the cisplatin-eligible and cisplatin-ineligible subgroups in the EV-302 trial. Age and gender inform general population background mortality and age-adjusted utility values; weight and body surface area govern drug dosing and costs in the economic model.

Both of our clinical experts considered that the modelled population adequately represents the patient population with unresectable or metastatic urothelial cancer who are eligible for platinum-based chemotherapy in the UK.

Table 16 Patient characteristics relevant for the economic model

Patient characteristic	ITT	Cisplatin-eligible	Cisplatin ineligible
Age at baseline (years, mean)	67.9	64.9	71.4
Gender (male %)	77%	79%	74%
Weight (kg)	75.89	78.34	73.01
Body surface area (m^2)	1.88	1.92	1.83

Source: Reproduced from CS Table 20
Abbreviations: ITT, intention to treat

EAG conclusion on the model population

We agree that the patient characteristics in the model match the patient population described in the NICE scope. Furthermore, the CS also includes subgroup analyses for patients who are eligible and ineligible for cisplatin-based chemotherapy, in line with the NICE scope. We note that the EV-302 trial was not powered statistically for the subgroup analyses and so consider there is uncertainty regarding the subgroup-based analyses.

We note that the model does not use data from the EV-103 study population. CS 2.2.1 states this is because the population (cisplatin-ineligible patients) only represents a subgroup of the submission (EV-302) population. We note that EV-103 was a multi-cohort, non-randomised study without a standard care control arm. We agree it is not appropriate to use data from EV-103 in the model, because it is unclear how these data can be included. Clinical advice to the EAG was that the population in the model is relevant to UK clinical practice. Overall, the EAG considers the modelled patient population to be appropriate.

4.2.4 Interventions and comparators

The economic model compares enfortumab vedotin with pembrolizumab to chemotherapy, using the dosing schedule based on the EV-302 trial (Table 17). CS section 3.2.3 states chemotherapy is the current standard of care in the patient population of interest. The company do not consider MVAC to be a relevant comparator, and the CS states it is only given to 1-2% of patients who receive chemotherapy (CS section 1.3.5.1).

Our experts consider it reasonable to exclude MVAC as a comparator. 'Dose dense' MVAC (i.e. MVAC given every 2 weeks) is used for some patients in the neoadjuvant setting, but is not used commonly in the metastatic setting, because it is more toxic than gemcitabine and consequently may be more difficult to tolerate for patients with metastatic disease.

The company also exclude atezolizumab as a comparator. CS Appendix T states that 3% of platinum-eligible patients (10% of all patients) received atezolizumab as first-line monotherapy, and that atezolizumab is mainly reserved for platinum-ineligible patients. The EAG notes that platinum-ineligible patients are outside of the scope of this appraisal.

Clinical advice to the EAG was that it is appropriate to exclude atezolizumab as a comparator. Atezolizumab is used infrequently in this setting, with clinicians preferring to use reduced dose gemcitabine plus carboplatin instead.

Table 17 Interventions and dosing used in the economic model

Treatment	Index treatment	Avelumab maintenance therapy
EV+P	EV: 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity, and Pembrolizumab: 400 mg IV on Day 1 of each 6-week cycle, as above to a maximum of 35 cycles	Not appropriate
PBC+gem (Cisplatin eligible)	Gemcitabine: IV 1000 mg/m^2 body-surface area) on Days 1 and 8 of a 3-week cycle, and Cisplatin: IV 70 mg/m^2 on Day 1	800mg on Day 1 of a 2-week cycle; for a maximum of 60 months ([redacted] of patients)
PBC+gem (Cisplatin ineligible)	Gemcitabine: IV 1000 mg/m^2 body-surface area) on Days 1 and 8 of a 3-week cycle, and Carboplatin: IV target area under the concentration versus time curve (AUC) equivalent to 4.5-5 mg/ml/min (Calvert formula) on Day 1	800mg on Day 1 of a 2-week cycle; for a maximum of 60 months ([redacted] of patients)

Source: EAG created table
Abbreviations: AUC, area under the curve; EV+P; enfortumab vedotin with pembrolizumab ; PBC+gem, platinum-based chemotherapy (cisplatin, or carboplatin) with gemcitabine; IV, intravenous

EAG conclusion on intervention and comparators

We consider that the intervention and comparators in the economic model are different to the NICE scope, because the company have excluded MVAC and atezolizumab as comparators. Based on the clinical advice we received, we consider it appropriate to exclude these treatments from the analyses (as discussed in section 2.3). We agree that the comparators included by the company are appropriate and reflective of UK clinical practice for this patient population.

4.2.5 Perspective, time horizon and discounting

The analysis takes the perspective of the NHS and Personal Social Services (PSS). In the company's base case, costs and QALYs are discounted at 3.5% per year. The model has a

lifetime horizon of 30 years, which the CS explains is sufficient to capture the plausible maximum life expectancy for the EV-302 ITT population (mean age 67.9 years). We note that discounting begins in year two of the company's base case.

EAG conclusion on perspective, time horizon and discounting

The company adopted the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines[1] and previous NICE appraisals for urothelial cancer. The EAG consider the perspective and time horizon used in the company's economic model to be appropriate, but prefer to use a more standard approach where discounting starts from the start of the model time horizon rather than after year 1 in our base case. We change this in the EAG base analyses in section 6.1.

4.2.6 Treatment effectiveness and extrapolation

CS section B.3.3.1 summarises the company's methodology for modelling time to event data. The company reviewed external study data, and consulted clinical experts from Italy, Sweden, the US, and Australia; and conducted a separate series of interviews involving three clinical experts from the UK for their survival estimates. This CS section consists of an explanation of the company's assessment of proportional hazards, extrapolation for progression-free survival, overall survival and time on treatment, and is based on the EV-302 trial data.

4.2.6.1 Assessment of proportional hazards

The company's method for assessing proportional hazards for overall survival and progression-free survival is described in CS section B.3.3.1.3 and the results are summarised in CS Table 25. The company assessed whether the proportional hazards assumption is supported using:

- Schoenfeld residuals plots
- The Grambsch and Therneau test
- Log-cumulative hazard plot versus log(time)
- Plots of smoothed empirical hazard versus time and log(time)
- Quantile-quantile (Q-Q) plot of times of survival percentiles

4.2.6.1.1 Overall survival

The original CS Appendix M Figures 4, 5 and 6 show the results of the proportional hazards assumption assessment for overall survival in the EV-302 ITT population, cisplatin-eligible, and cisplatin-ineligible patients, respectively. CS section B.3.3.2.1 states that overall survival data for the EV-302 ITT population would likely violate the assumption of proportional

hazards when the trial data were more mature, so the company fitted independent models to the enfortumab vedotin with pembrolizumab and chemotherapy arms in their base case.

The EAG agree with the company and consider that the assumption of proportional hazards does not hold for overall survival in the ITT group or cisplatin-ineligible subgroup; proportional hazards may hold for overall survival in the cisplatin-eligible subgroup. Consequently, we consider it appropriate that the company have fitted parametric curves independently when modelling overall survival.

4.2.6.1.2 Progression-free survival

The original CS Appendix M Figure 1, Figure 2 and Figure 3 show the results of the proportional hazards assumption assessment for progression-free survival in the EV-302 ITT population, cisplatin-eligible and cisplatin-ineligible patients, respectively. We consider that proportional hazards do not hold for the progression-free survival analyses. Consequently, we consider it appropriate that the company have also fitted parametric curves independently to the two trial arms for the ITT population and both subgroups for progression-free survival.

We note that the assumption of proportional hazards assessment was not repeated and presented in the CS addendum (29 November 2024), which uses results from the company's new data cut from 8 August 2024.

4.2.6.2 Overall survival extrapolation

In the CS addendum (29 November 2024), the company provide results of an exploratory ad hoc analysis with a data cut-off date of 8 August 2024 that has a median follow-up of 29.1 months. The company extrapolated time-to-event outcomes using parametric curves over the time horizon of the cost-effectiveness analysis. CS section B.3.3.1.7 explains that the parametric curves were ranked based on the lowest Akaike's information criterion (AIC) and Bayesian information criterion (BIC), and that the extrapolated curves would predict clinically plausible long-term estimates. The company also used the shape of the observed hazards over time in the EV-302 trial to inform the most appropriate survival distribution (i.e. those predicting initially increasing then decreasing hazards in the long-term).

CS addendum (29 November 2024) section 2.2.1 describes the company's extrapolations of standard parametric fits to the EV-302 ITT population Kaplan-Meier data. Results are shown in CS addendum (29 November 2024) Figure 5 and CS addendum (29 November 2024) Figure 6. CS addendum (29 November 2024) section 2.2.2 and CS addendum (29 November 2024) section 2.2.3 describe the company's approach to fitting curves to the

cisplatin-eligible and cisplatin-ineligible subgroups, respectively. The company's chosen curves for the three populations in their base case is shown in Table 18.

Table 18 Curves selected to model overall survival in the company's base case

Treatment	ITT population	Cisplatin-eligible	Cisplatin-ineligible
EV+P	Log-logistic	Lognormal	Log-logistic
PBC+gem	Log-logistic	Lognormal	Log-logistic

Source: EAG created table
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ITT, intention-to-treat; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine

The company selected log-logistic curves for both treatment arms for enfortumab vedotin with pembrolizumab and chemotherapy in their base case for the ITT population, and tested the lognormal and exponential curves in scenario analyses. Estimates of long-term survival using these different curves are shown in Table 19, along with estimates from the company's clinical experts.

Clinical advice to the EAG was that the survival predictions used in the company's base case were reasonable and generalisable to UK clinical practice. Our experts expected that a third of patients receiving usual care (chemotherapy) would be alive at three years, and considered it reasonable for 4% of patients receiving usual care to be alive at 10 years. One of our clinical experts commented that 16% of patients receiving enfortumab vedotin with pembrolizumab being alive at 10 years seems high.

CS section B.3.3.1.2 states that UK clinicians advised the company that patients who have not progressed at five years are expected to enter a durable remission. Our clinical experts thought that this was a reasonable assumption, because if patients survive to five years the probability of dying plateaus. In our experts' experience, about 20% of patients have a complete (i.e. durable) remission and have stable disease for a prolonged period of time. Our experts are uncertain whether EV will improve this durable remission over that seen with the checkpoint inhibitor (pembrolizumab).

CS section B.3.3.1.6 states that enfortumab vedotin with pembrolizumab efficacy is independent of cisplatin-eligibility. However, the CS comments that patients who are cisplatin-ineligible are usually older with more comorbidities, compared with cisplatin-eligible patients. Clinical advice to the EAG supported this assumption by the company. CS Figure 30 shows overall survival in the EV-302 ITT population and cisplatin eligibility subgroups (this Figure was not reproduced in the CS addendum (29 November 2024)). We note that

the cisplatin-eligible patient subgroup shows higher survival proportions at every timepoint compared with the cisplatin-ineligible subgroup and ITT population, in both trial arms.

Table 19 Estimates of overall survival in the long-term (ITT population)

Alive on PBC+gem	**Timepoint**		
	2 years	5 years	10 years
Average (range) of company expert estimates	35% (30-45%)	11% (5-20%)	6% (0-10%)
EV-302 modelled OS (independent fit, both arms log-logistic; company base case)	36%	13%	5%
Alive on EV+P			
Average (range) of company expert estimates	58% (50-60%)	32% (20-45%)	16% (5-35%)
EV-302 modelled OS (independent fit, both arms log-logistic; company base case)	60%	31%	16%
EV-103 Cohort K, EV+P (cisplatin-ineligible)	53.5%	-	-
EV-103 Cohort A (dose escalation), EV+P (cisplatin-ineligible)	56.4%	41.5%	-

Source: Partly reproduced from CS addendum (29 November 2024) Table 1 and Table 2
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; OS, overall survival; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine;

4.2.6.3 Progression-free survival extrapolation

CS section B.3.3.3.1 states that progression-free survival, as assessed by blinded independent central review, from the EV-302 trial was used to inform progression-free survival estimates in the model. We agree with the company that the proportional hazards assumption was violated for progression-free survival and agree with them fitting independent curves to the enfortumab vedotin with pembrolizumab and chemotherapy arms in their base case.

The company ranked the parametric curves based on the lowest AIC and BIC, selected those with credible long-term predictions, and used the shape of the observed hazards over time in the EV-302 trial (initially increasing then decreasing hazards in the long-term) to select the most appropriate survival distribution. However, the company do not consider that standard parametric curves appropriately capture the change in hazards over time in either treatment arm (CS addendum (29 November 2024) section 2.3.1). Figure 4 and Figure 5 show the observed progression-free survival hazards for the EV-302 ITT population for the enfortumab vedotin with pembrolizumab arm and chemotherapy arm, respectively.

The EAG agrees that observed hazards initially increase up to about 6 months and then gradually fall thereafter. We note that the lognormal, log-logistic and generalised gamma parametric curves all have increasing initial hazards that fall over time (Figure 4).

Figure 4 Progression-free survival hazards, EV+P ITT population

Source: Reproduced from CS addendum (29 November 2024) Figure 1
Abbreviations: AIC, Akaike's information criterion; EV+P, enfortumab vedotin with pembrolizumab; ITT, intention-to-treat

Figure 5 Progression-free survival hazards, PBC+gem ITT population

Source: Reproduced from CS addendum (29 November 2024) Figure 2
Abbreviations: AIC, Akaike's information criterion; EV+P, enfortumab vedotin with pembrolizumab; ITT, intention-to-treat; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine

The company use independent spline fitting (piecewise polynomial functions) to model progression-free survival. Splines are used to fit curves that have different shapes over time; knot points distinguish the different regions.[20] CS Appendix N describes the company's methods for fitting splines to the EV-302 progression-free survival data and CS addendum (29 November 2024) Appendix N shows the results of the spline fits using the most recent data cut.

Briefly, the company modelled transformed versions of the survival function S(t): the log cumulative hazard function and the log cumulative odds of survival, which allow cubic splines to capture non-linear relationships over time. As recommended by Royston and Palmer,[20] knots were placed at equal distances on the scale of the log event survival time, i.e. one knot is placed at the median of log time, two knots are placed at the 33% and 66% quantiles of log time, and three knots are placed at the 25%, 50% and 75% quantiles of log time (CS addendum (29 November 2024) Appendix N Table N.1). The company tested multiple scenarios using one, two and three knots. The model spline fits were assessed via the AIC and BIC (CS addendum (29 November 2024) Table N.2 and Table N.3 for the ITT population; Table N.4 and Table N.5 for the cisplatin-eligible subgroup; and Table N.5 and Table N.6 for the cisplatin-ineligible populations), and predicted survival curves were compared with the EV-302 Kaplan-Meier curves for progression-free survival (CS addendum (29 November 2024) Figure N.2 and Figure N.4 for the EV-302 ITT population).

The company's chosen curves (based on the lowest AIC and BIC and with what the company consider to be credible long-term predictions) for the three populations in their base case are shown in Table 20. We note that the company's choice results in a complicated hazard for the chemotherapy arm (Figure 6) and that the company use a different spline fit for each arm (Table 20).

Table 20 Curves selected to model progression-free survival in the company's base case

Treatment	ITT population	Cisplatin-eligible	Cisplatin-ineligible
EV+P	Spline fit to hazard with 2 knots	Spline fit to hazard with 1 knot	Spline fit to hazard with 2 knots
PBC+gem	Spline fit to odds with 3 knots	Spline fit to normal with 3 knots	Spline fit to odds with 1 knot

Source: EAG created table
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ITT, intention-to-treat; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine

Figure 6 Progression-free survival, hazards over 5 years (ITT population)

Source: Reproduced from the company model
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ITT, intention-to-treat; PBC, platinum-based chemotherapy; SOC, standard of care

CS addendum (29 November 2024) 2.3.1 states that long-term predicted hazards using the standard curves overestimate the observed hazards i.e. virtually no patients remain alive and progression-free at 10 years using standard parametric models (Table 21). Clinical expert advice to the company was that around 5% of patients receiving chemotherapy would still be alive and progression-free at 5 years, and a few patients to still be alive and progression-free at 10 years (Table 21).

The company performed scenarios for the next best spline fits and standard parametric curves with the lowest AIC/BIC, which met the company clinical experts' progression-free survival expectations (Table 21). Both of our EAG clinical experts considered that the company's modelled progression-free survival estimates in their base case were reasonable. One EAG expert commented that a 30% difference in progression-free survival at 2 years seems high, and that 16% of patients alive and progression-free at 10 years seems optimistic. We tested less optimistic progression-free expectations using standard parametric curves in scenario analyses (section 6.1.1).

Table 21 Estimates of progression-free survival in the long-term

Progression-free on PBC+gem				
Timepoint	2 years	3 years	5 years	10 years
Average (range) of company expert estimates	9.5% (6-10%)	-	5% (3-7%)	3.5% (2-7%)

EV-302 modelled PFS (spline fit, odds 3 knots; company base case)	11.5%	-	9.3%	5.0%
EV-302 modelled PFS (standard fit; log-logistic)	8.2%	-	1.6%	0.5%
Progression-free on EV+P				
Timepoint	2 years	3 years	5 years	10 years
Average (range) of company expert estimates	39% (36-50%)	-	25% (15-30%)	18% (7-25%)
EV-302 modelled PFS (spline fit, hazard 2 knots; company base case)	37.7%	-	25.6%	15.8%
EV-302 modelled PFS (standard fit; log-logistic)	35.2%	-	15.8%	7.7%
EV-103 Cohort K, EV+P (cisplatin-ineligible)	-	46.0%	-	-
EV-103 Cohort A (dose escalation), EV+P (cisplatin-ineligible)	-	38.2%	-	-

Source: Reproduced from the company's model
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; PFS, progression-free survival

4.2.6.3.1 Crossover of modelled overall survival and progression-free survival extrapolations

We note that, in the company base case, the progression-free survival curve would cross the overall survival extrapolation at about eight years for enfortumab vedotin with pembrolizumab (Figure 7, blue dotted line). But, the company have coded the model to prevent this (Figure 7, green dashed line).

We tested alternative extrapolations to find a situation where the two curves do not cross. We prefer to use the log-logistic curve for enfortumab vedotin with pembrolizumab overall survival (company's base case), and the log-logistic curve for enfortumab vedotin with pembrolizumab progression-free survival (Table 21) in our base case (Figure 7; section 6.1). Where parametric models are fitted separately to individual treatment arms, the NICE Decision Support Unit (DSU) recommends that the same parametric curve should be used for both arms.[21] Consequently, we also use the log-logistic curve for chemotherapy progression-free survival in our base case (Table 21).

Figure 7 Relationship between overall survival, progression-free survival and time on treatment (EV+P arm). (A) Company base case; (B) EAG base case.

Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; OS, overall survival; PFS, progression-free survival; ToT, time-on-treatment

4.2.6.3.2 Cisplatin-eligible and cisplatin-ineligible subgroups

As with the ITT population, the company's choice of progression-free survival curve crosses the overall survival curve for the cisplatin-eligible and cisplatin-ineligible subgroups. We also note that the company use different extrapolations for each trial arm. The EAG agree with the company's choice of parametric curves for overall survival for the cisplatin-eligible and cisplatin-ineligible subgroups, but Table 22 shows our preferred choice of parametric curves for progression-free survival for the two subgroups.

CS addendum (29 November 2024) Appendix M Figure M.2 shows that the generalised gamma curve for enfortumab vedotin has the lowest AIC for progression-free survival for the cisplatin-eligible subgroup. However, the generalised gamma curve crosses the overall survival curve. We prefer to use the lognormal curve for progression-free survival for the cisplatin-eligible subgroup, because it is the next best fit and does not cross the overall survival curve.

CS addendum (29 November 2024) Appendix M Figure M.12 shows that the lognormal (AIC = 967.1), generalised gamma (AIC = 967.8) and log-logistic (AIC = 969.3) extrapolations all provide curves that best fit the enfortumab vedotin progression-free survival Kaplan-Meier data and do not cross the overall survival curve. We prefer to use the log-logistic curve, because it offers an intermediate prediction of long-term progression-free survival; the generalised gamma curve is more optimistic, and the lognormal curve is more pessimistic.

Table 22 Progression-free survival curves for the cisplatin-eligible and cisplatin-ineligible subgroups

Treatment	Cisplatin-eligible		Cisplatin-ineligible	
	Company	EAG	Company	EAG
EV+P	Spline fit to hazard with 1 knot	Lognormal	Spline fit to hazard with 2 knots	Log-logistic
PBC+gem	Spline fit to normal with 3 knots	Lognormal	Spline fit to odds with 1 knot	Log-logistic

Source: EAG created table
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine

4.2.6.4 Time on treatment

CS section B.3.3.4.1 states there was a difference between progression-free survival (median of 12.5 months) and time on treatment (median of 9.4 months) for the enfortumab vedotin with pembrolizumab arm in the EV-302 trial. Consequently, the company model time on treatment separately from PFS. The EAG agree with this approach.

The company's method for modelling time on treatment for the ITT population is described in CS addendum (29 November 2024) section 2.4.1 for enfortumab vedotin with pembrolizumab, and CS addendum (29 November 2024) section 2.4.2 for chemotherapy. CS addendum (29 November 2024) section 2.4.3 and CS addendum (29 November 2024) section 2.4.4 summarise the time on treatment modelling for the cisplatin-eligible and cisplatin-ineligible subgroups, respectively, with detailed information in CS addendum (29 November 2024) Appendix M. Standard parametric curves were plotted to estimate time on treatment for enfortumab vedotin. Goodness of fit was assessed using the AIC/BIC criteria (CS addendum (29 November 2024) Table 7).

The time on treatment Kaplan-Meier data for pembrolizumab from the EV-302 trial are complete in the 8 August 2024 data cut. Therefore, the company's base case now uses the Kaplan-Meier curve to estimate pembrolizumab time on treatment. The Kaplan-Meier data for chemotherapy from the EV-302 trial are also complete, and so the company use the Kaplan-Meier curve to directly estimate the proportion of patients receiving chemotherapy each week.

CS addendum (29 November 2024) section 2.4.2 explains that a washout period of [redacted] weeks, based on a post-hoc analysis of the EV-302 trial, was applied after the end of

chemotherapy until the start of avelumab treatment. Avelumab maintenance time on treatment is extrapolated from the start of maintenance therapy using standard parametric distributions, which were assessed for goodness of fit using the AIC/BIC criteria (CS addendum (29 November 2024) Table 8). In the model, 30% of patients receive avelumab maintenance therapy and the company apply a stopping rule at 60 months, which is consistent with TA788.[19] The company's choice of time on treatment curves is shown in Table 23.

Table 23 Curves to model time on treatment, company base case

Treatment	ITT	Cisplatin-eligible	Cisplatin-ineligible
EV	Log-logistic	Lognormal	Lognormal
Pembrolizumab[a]	K-M curve	K-M curve	K-M curve
PBC+gem[b]	K-M curve	K-M curve	K-M curve
Avelumab[c]	Weibull	Weibull	Weibull

Source: EAG created table
Abbreviations: EV, enfortumab vedotin; ITT, intention-to-treat; K-M, Kaplan-Meier; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine
[a] K-M curve was complete, treatment stopping rule at 2 years
[b] K-M curve was complete; treatment stopping rule at 4.14 months (i.e. maximum of six three-week cycles of therapy)
[c] Treatment stopping rule at 60 months

Most of the company's time on treatment extrapolations for enfortumab vedotin in the ITT population (CS addendum (29 November 2024) Figure 13) predict that some patients will still be on treatment at five years. However, all patients had discontinued treatment by year 3 in Cohort A + dose escalation of the EV-103 trial (CS Figure 21). Clinical advice to the company was that the number of patients receiving enfortumab vedotin treatment would halve each year, and that no patients would be on treatment by Year 5 (CS Appendix P).

Table 24 shows the modelled time on treatment for enfortumab vedotin in the EV-302 ITT population. A proportion of patients are still on enfortumab vedotin treatment in Year 3 and Year 5, in contrast to data for Cohort A in the EV-103 study and experts' expectations. We note that if patients receive enfortumab vedotin therapy in Year 3 to Year 5, the costs in the enfortumab vedotin with pembrolizumab arm are increased and thus so is the ICER. We conducted a scenario analysis to test the effect of very few patients remaining on enfortumab vedotin treatment by 5 years (section 6.1.1)

Clinical advice to the EAG was that the company's estimates for time on treatment for pembrolizumab were reasonable. However, one of our experts thought than the mean avelumab treatment duration, and the proportion of patients on avelumab at one year and

two years, was high. Our expert commented that avelumab is usually given for less than a year (about 9 months) and suggested that the number of patients receiving avelumab in the EV-302 trial may have been higher than is usual in UK clinical practice. We prefer to use the exponential parametric curve for avelumab time on treatment in our base case, resulting in a mean time on treatment of 13.94 months, because this extrapolation produces the shortest time on treatment for avelumab therapy. We raise this as a key issue: EAG cost-effectiveness Issue 2.

Table 24 Modelled time on treatment for the different regimens, company base case (undiscounted, not half-cycle corrected)

Regimen	Mean (months)	1 year	2 years	3 years	5 years
Enfortumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC: PBC+gem[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC: Avelumab maintenance (from end of washout)[c]	[redacted]	41%	26%	18%	10%

Source: Reproduced from the company's model
Abbreviations: PB +gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; SOC, standard of care
[a] Company assume a maximum treatment duration of 2 years for pembrolizumab
[b] Company assume a maximum of 6 cycles (4.14 months) of treatment with Gemcitabine + PBC
[c] Company assume a maximum of 5 years (60 months) of maintenance treatment with avelumab

4.2.6.4.1 Cisplatin-eligible and cisplatin-ineligible subgroups

We prefer to use the log-logistic parametric curve for estimating time on treatment for enfortumab vedotin for both subgroups, because this curve has the lowest AIC/BIC (CS addendum (29 November 2024) Appendix M Tables M.2 and M.3). As in the case of the ITT population, we also prefer to use the exponential parametric curve for avelumab time on treatment for both subgroups, because this curve results in the shortest time on treatment for avelumab therapy, which is more in line with our experts' expectations.

4.2.6.4.2 Treatment effect waning

CS Table 21 states that the company consider trends in hazards should incorporate any treatment effect waning. Taylor et al. (2024) reviewed treatment effect waning in immuno-oncology Health Technology Assessments.[22] The authors noted that the implied treatment effect over time depends upon the ratio of the hazards of the survival models fitted to each treatment arm. If independently fitted curves result in hazards that gradually converge, it implies that any treatment effect waning is already accounted for in the model, without explicit treatment effect waning being added. The EAG note that the hazards for overall survival over the lifetime horizon of the model (30 years) do gradually converge (Figure 8).

Figure 8 Overall survival, hazards over 30 years

Source: Company model
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; PBC, platinum-based chemotherapy; SOC, standard of care

Patients stop pembrolizumab after a maximum of two years and it is unknown if this leads to treatment effect waning. Past NICE appraisals that have assessed pembrolizumab as part of a dual therapy, see Table 25, include:

- Pembrolizumab with axitinib for untreated advanced renal cell carcinoma (TA650)[23]
- Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858)[24]
- Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer (TA904)[25]
- Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma (TA983)[26]

Table 25 Committee waning assumptions from past NICE appraisals assessing pembrolizumab as part of a dual therapy

Appraisal	Waning assumption accepted by the NICE committee
TA650	Not enough evidence to assume a life-time effect of pembrolizumab; treatment benefit waning should be applied. Waning effect applied to all patients 5 years after starting pembrolizumab.
TA858	Committee considered a waning effect was plausible, but uncertain. The TA858 EAG noted that pembrolizumab treatment is limited to 2 years, but lenvatinib treatment could continue after this time point. The EAG acknowledged that there was uncertainty in the long-term treatment effect of pembrolizumab, but that it was not possible to plausibly separate out any potential waning of treatment effect.

Appraisal	Waning assumption accepted by the NICE committee
TA904	Committee concluded treatment waning was plausible, but uncertain. Committee preferred the TA904 EAG scenarios where treatment waning occurred 5-7 years after starting pembrolizumab treatment.
TA983	Treatment waning was not discussed.

Source: EAG created table

We test explicit treatment waning in scenario analyses (section 6.1.1), where:

- Waning starts when pembrolizumab treatment stops (at two years), and ends after five years
- Waning starts when pembrolizumab treatment stops (at two years), and ends after seven years
- Waning starts two years after pembrolizumab treatment stops (at four years), and ends after seven years

We note that these scenarios may over-estimate the effect of treatment waning, because patients are receiving a dual therapy i.e. the effect of pembrolizumab treatment may wane, but patients are still receiving enfortumab vedotin. So, we have not included explicit treatment waning in the EAG base case.

EAG conclusion on treatment effectiveness and extrapolation

We consider that the company's method for fitting parametric curves to the EV-302 trial data for overall survival, progression-free survival and time on treatment to be appropriate and consistent with NICE's recommended methodology.

We consider the company's selection of curves used for overall survival, progression-free survival and time on treatment to be broadly reasonable. We note that the company's choice of curves for overall survival generally fit well against clinical experts' expectations. Our clinical experts generally agreed with the modelled survival predictions for overall survival and progression-free survival. However, due to crossover of modelled overall survival and progression-free survival extrapolations we prefer to use the log-logistic to model progression-free survival for enfortumab vedotin with pembrolizumab and chemotherapy in our base case. We test alternative curves with less optimistic survival predictions in scenario analyses (section 6.1). For the same reason, we prefer to use the lognormal for the cisplatin-eligible subgroup, and the log-logistic for the cisplatin-ineligible subgroup, for progression-free survival.

Clinical advice to the EAG was that the duration of avelumab maintenance therapy was too long and did not reflect UK clinical practice. We prefer to use the exponential curve to model avelumab therapy in our base case (and for both cisplatin subgroups), because this reduces the proportions of patients receiving avelumab and the mean time on treatment. We prefer to use the log-logistic curve for estimating time on treatment for enfortumab vedotin for both cisplatin subgroups, because this curve has the lowest AIC/BIC (CS addendum (29 November 2024) Appendix M Tables M.2 and M.3).

We consider that treatment effect waning has been adequately accounted for within the model, but test immediate treatment effect waning via scenario analyses (section 6.1).

4.2.6.5 Adverse events

The model includes all adverse events that were Common Terminology Criteria for Adverse Events (CTCAE) grade 3+ that occurred in at least 3% of patients in either treatment arm of study EV-302. CS addendum (29 November 2024) section 3.1 explains that, in the new data cut, diarrhoea met the inclusion criteria for adverse events and is now included in both arms of the model. The company also included the incidence of grade 2 peripheral neuropathy, following clinical feedback. Clinical advice to the EAG was that peripheral neuropathy grading varies widely, and that peripheral neuropathy is more likely to be caused by pembrolizumab than enfortumab vedotin. However, the risk of pembrolizumab causing peripheral neuropathy is low. Enfortumab vedotin with pembrolizumab induced peripheral neuropathy would be treated in the same manner as cisplatin induced neuropathy i.e. by reducing or stopping the drug and treating with an anti-neuropathic. The EV-302 trial did not provide adverse event information for patients receiving avelumab maintenance therapy; the company use data from the JAVELIN Bladder 100 study.[27 28] The frequency of treatment-emergent adverse events included in the model (ITT population) are shown in CS addendum (29 November 2024) Table 9.

Our clinical experts commented that the proportion of patients experiencing peripheral neuropathy was slightly lower than expected in the chemotherapy arm of the EV-302 trial, but otherwise considered the adverse events included in the economic model to be appropriate. They also noted that 30% of patients in the chemotherapy arm had experienced neutropenia, but that the company had not distinguished patients who had experienced febrile neutropenia, which can lead to sepsis if untreated.

In their response to clarification question B5, the company explained that the neutropenia events reported refer to any neutropenia, and not febrile neutropenia specifically. Consequently, we are unable to use a corresponding disutility and cost for treating febrile neutropenia in our base case. Clinical expert advice to the company was that neutropenia is a severe complication of chemotherapy, requiring 2-5 days in hospital with IV antibiotics, and is associated with high fatality (about 5-10%). The model uses cost code 'WJ11Z: Other Disorders of Immunity', to represent the cost of neutropenia. All other codes within the WJ category are associated with higher unit costs. Given the difference in the incidence of febrile neutropenia events between the treatment arms, the company's approach is conservative because it reduces costs in the chemotherapy arm.

EAG conclusion on adverse events

We consider the company's approach to including adverse events in the model to be appropriate. We are uncertain what effect applying costs and benefits specifically for febrile neutropenia would have, but consider that the effect on the ICER would be minimal.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review for health-related quality of life studies, using the methodology described in CS Appendix H. Database searches were carried out in:

- MEDLINE, Embase, Cochrane CENTRAL, and EconLit with a start date limit of 2012 (the searches were completed on February 2023 and updated on 24 June 2024)
- The Northern Light database to search ISPOR and five other relevant oncology and urology conferences, as well as hand searching the EAU conference (from 2021 to 24 June 2024)
- The WHO ICTRP (from 2012 to 8 July 2024)
- HTA agency websites (searched from 2012 and bibliographies of relevant systematic literature reviews published since 2020)

Eligibility criteria are given in CS Appendix H 3.1. We consider that the systematic literature review would likely have found all relevant studies at the time.

CS Appendix H 4.3.1 reports that the combined economic and health-related quality of life searches identified 18 studies reporting utility values or disutilities. Of these studies, five

were HTA documents, 11 were full-text publications, and two were conference posters. Pre- and post-progression utility values are reported in CS Appendix H Table 19. The EAG notes only the utilities provided in the previous NICE submissions, for avelumab (TA788)[19] and atezolizumab (TA739),[3] are relevant to England and Wales. These values, along with utilities from the Scottish Medicines Consortium submission for pembrolizumab,[29] are presented below in Table 26. The company has tested all three of these sets of utilities in scenario analyses (section 5.2.2).

The EAG are aware of three recent economic evaluations of the EV-302 trial that were published after the company's searches (see section 4.1). However, none of the economic evaluations is from the perspective of the NHS in England and Wales. In addition, utilities were obtained from the literature in all cases, because the authors of the three new economic evaluations did not have access to the EV-302 utility data (Table 26).

Table 26 Utility values used in previous publications in adults with locally advanced or metastatic urothelial cancer who have not received prior systemic therapy in the locally advanced or metastatic setting

Publication	Utility for pre-progression	Utility for post-progression	Source of utility data
NICE TA739[3]	Atezolizumab: 0.642 PBC+gem: 0.527	0.567	IMvigor130
NICE TA788[19]	0.772	0.698	JAVELIN Bladder 100
SMC appraisal of pembrolizumab[29]	0.680	0.610	SMC appraisal of pembrolizumab
Li et al. (2024)[16]	0.800	0.750	Obtained from the literature
You et al. (2024)[17]	0.840	0.800	Obtained from the literature
Rieger et al. (2024)[18]	0.60	Range: 0.6 – 0.4	Obtained from the literature

Source: Partly reproduced from CS Table 35
Abbreviations: NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium

4.2.7.2 Study-based health related quality of life

CS section B.3.4.1 states that health-related quality of life data were collected from patients in the EV-302 trial using the EQ-5D-5L questionnaire. Patients completed the EQ-5D-5L

questionnaire at baseline (up to 24 hours prior to their first dose of study treatment), weekly from Week 1 to Week 12, then every three weeks from Week 17 onwards, including collection through disease progression and survival follow-up. The company's response to clarification question B2 explained that the EV-302 trial protocol did not mandate a time-point when EQ-5D-5L data collection had to stop. The completion and compliance rates for the EQ-5D-5L are presented in Appendix O (Figure O.1 and Figure O.2), updated data are presented in CSR Figure 12.3.9.1 and CSR Figure 12.3.9.2 of the 8th August 2024 data cut. The EQ-5D-5L compliance rate figures are not reproduced in the CS addendum (29 November 2024). The follow-up period for post-progression HRQoL was [redacted] days (median [redacted] days, range [redacted] days; as of the 8th August 2024 data cut).

The EQ-5D-5L data collected in the EV-302 trial were cross-walked to EQ-5D-3L using the method of Hernández Alava et al.[30]and Dolan et al.[31] applying the UK value set. The company analysed data from all randomised patients who received any amount of study treatment and completed at least one EQ-5D-5L assessment at baseline.

4.2.7.3 Utility values applied in the model

The model uses health state utilities from the EV-302 trial (Table 28). Patient-reported health utility was calculated via a longitudinal analysis of utility index scores. The pre-progression period health utility was estimated as the average EQ-5D index scores from when treatment started to the first documentation of disease progression. The post-progression health state utility was calculated from patient EQ-5D questionnaires completed after the disease had progressed.

CS Appendix O.2 describes the mixed effects model the company use to estimate the mean EQ-5D-3L scores for each health state, which included the following covariates: treatment arm, randomisation stratification factors, and baseline scores. CS Appendix O.2 does not explain why these specific covariates were chosen. The results of the mixed effects model are shown in Table 27.

Table 27 EV-302 trial mixed effects model for health state utilities

Covariate	ITT (Coefficient (S.E.)
Intercept	[redacted]
Health state, pre-progression vs. post-progression	[redacted]
Time since randomisation, weeks	[redacted]
Treatment, EV+P vs. PBC+gem	[redacted]
Cisplatin eligibility, eligible vs. ineligible	[redacted]
PD-L1 expression, high vs. low	[redacted]

Covariate	ITT (Coefficient (S.E.)
Liver metastases, present vs. absent	[redacted]
Baseline utility	[redacted]

Source: Reproduced from CS addendum (29 November 2024) Appendix O Table O.1
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ITT, intention to treat; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; PD-L1, programmed cell death ligand 1

CS addendum (29 November 2024) section 3.2 states that using treatment-specific pre-progression utility values in the company's base case is appropriate, because the treatment coefficient (i.e. treatment with enfortumab vedotin with pembrolizumab versus chemotherapy) was significant (p <0.001). The company notes that this is line with the approach taken in both TA739 (atezolizumab) and TA788 (avelumab).[3 19] The company tested using health state-specific utilities in a scenario analysis. The company's base case post-progression utility value is a combined value that uses data from patients in both treatment arms.

Clinical expert advice to the EAG was that there is toxicity associated with enfortumab vedotin with pembrolizumab, even though its mechanism of action is different to chemotherapy, so health-related quality of life in the two treatment groups would not necessarily be different. Our experts suggested that health-related quality of life would be lower in the chemotherapy patient group while they were on treatment (18 weeks). Patients would then start to improve over the next 2-3 months after stopping chemotherapy, and then health-related quality of life would be about the same for patients in both groups.

We note that the mean utility score of patients in the enfortumab vedotin with pembrolizumab arm in the EV-302 trial is [redacted] than the mean utility score of patients in the chemotherapy arm. However, standard error bars for the utility scores [redacted] suggesting that, by this time, the difference between the two estimates [redacted]. (Figure 9).

In their response to clarification question B1, the company highlight that the proportion of completed questionnaires is lower in the chemotherapy arm than in the enfortumab vedotin with pembrolizumab arm. The compliance rate in the enfortumab vedotin with pembrolizumab arm was below 50% only from week [redacted], whereas the compliance rate in the chemotherapy arm was below 50% from week [redacted]. This may bias the results if patients who did not fill in the questionnaire experienced worse health-related quality of life than patients who did. Consequently, the company also analysed the mean utility score data using a mixed effect model to account for missing data (Figure 10). We note that the utility score standard error bars for the two arms [redacted].

Figure 9 Mean utility over time in overall PRO FAS[a] population of the EV-302 trial, UK 3L tariff

Source: Company response to clarification question B1, Figure 1
Abbreviations: 3L, three level; EV, enfortumab vedotin; PRO FAS, patient-reported outcome full analysis set; SE, standard error
Notes: Values at the bottom of the figure represent number of patients at each time point.
[a] The PRO FAS population included all randomised patients who received any amount of study treatment and completed at least 1 PRO assessment at baseline.

Figure 10 Predicted mean utility over time by treatment in overall PRO FAS[a] population of the EV-302 trial, UK 3L tariff

Source: Company response to clarification question B1, Figure 4
Abbreviations: 3L, three level; EV, enfortumab vedotin; PRO FAS, patient-reported outcome full analysis set; SE, standard error
Notes: Figure generated based on predictions from mixed-effect model using DCO1
[a] The PRO FAS population included all randomised patients who received any amount of study treatment and completed at least 1 PRO assessment at baseline.

Given that health-related quality of life for both patient groups was not significantly different after 20 - 32 weeks (5 – 8 months) and based on advice from our clinical experts, we prefer to use the treatment-dependent pre-progression utility value for patients receiving chemotherapy for the first 6 months (18 weeks on treatment plus 8 weeks' recovery time), and then use the treatment-independent utility value for the remaining time before the disease progresses in our base case. For enfortumab vedotin with pembrolizumab, we prefer to use the treatment-independent utility value for pre-progression, so that both patient groups have the same utility scores in the pre-progression stage after the first 6 months (Table 28).

Table 28 Health state utility values used in the model

Health state	Treatment	EV-302			EAG base case values
		ITT	Cisplatin-eligible	Cisplatin-ineligible	
		Mean (SE)			
Pre-progression	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted] for the first 6 months; [redacted] for the remaining time in PFS
	Treatment-independent	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	Treatment-independent	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from CS addendum (29 November 2024) Table 11
Abbreviations: EV+P, enfortumab vedotin plus pembrolizumab; ITT, intention-to-treat; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; SE, standard error

4.2.7.4 Disutilities for adverse events

The company assume that the effect of adverse events is not completely captured by the treatment-specific health state utility values, because the completion rate of the EQ-5D-5L questionnaire in the EV-302 trial fell over time (CS section B.3.4.4).

Utility decrements for adverse events were identified via previous NICE appraisals and literature searching, and are shown in CS Table 37. The company's approach assumes that adverse event disutilities are governed by the specific adverse event, rather than the specific disease area. The EAG notes that this is consistent with previous NICE appraisals. The disutility for each adverse event is multiplied by its expected duration to estimate the

average QALY loss per treatment. The company also performed a scenario analysis that excluded the impact of adverse events.

The model applies adverse event-specific QALY decrements as a lump sum in the first cycle of the pre-progression health state, because the company assume that most adverse events are associated with starting treatment (CS section B.3.4.4). We note that EQ-5D data were recorded weekly in the EV-302 trial up to week 12 (CS section B.3.4.1) and so consider that the majority of the effects of adverse events would be captured by patients' global EQ-5D scores. Furthermore, we consider that the disutility for peripheral neuropathy is overestimated, but note that excluding the impact of adverse events has very little effect on the ICER (CS Table 58) and so include adverse event disutilities in our base case.

EAG conclusion on health-related quality of life

We consider that the utility values from the EV-302 trial used in the company's model are in line with previous technology appraisals. However, we do not agree with using treatment-dependent utilities for the entire time patients receiving chemotherapy will have a detrimental impact on patients' health-related quality of life while they are on treatment, and for a couple of months afterwards as they recover. Then patients receiving chemotherapy would likely have a health-related quality of life similar to that of patients receiving enfortumab vedotin with pembrolizumab. We prefer to use the treatment-independent pre-progression utility value for enfortumab vedotin with pembrolizumab and the treatment-specific pre-progression utility value for chemotherapy for the first 6 months, and then use the treatment-independent utility value in both treatment groups until disease progression in our base case (Table 28).

We consider that the disutility for peripheral neuropathy is overestimated, and that patients' global EQ-5D scores would capture most of the effect of adverse events. However, reducing the disutility associated with peripheral neuropathy or excluding the impact of adverse events has a negligible effect on the ICER, so we do not make any changes for our base case.

4.2.8 Resources and costs

Costs in the model included drug costs (acquisition and administration), monitoring costs related to treatment, health care resource use, adverse event costs, subsequent treatment costs and terminal care costs. These are discussed in the following sections.

4.2.8.1 Drug acquisition

The dosing schedule and costs of the drugs used in the model are shown in Table 17 and Table 29 (CS addendum (29 November 2024)). The list price for enfortumab vedotin is £867 for a 30 mg powder for concentrate for infusion vials. The list price for pembrolizumab is

£2,630 for 100mg/4ml concentrate for solution for infusion vials. These treatments are supplied with a confidential Patient Access Scheme (PAS) discount. The dosing schedule is the same as used in the EV-302 trial. The weight and body surface area of patients was also based on the EV-302 trial.

Relative dose intensity (RDI) was also included for each treatment based on the RDI observed in the EV-302 trial. New information was available for enfortumab vedotin with pembrolizumab from the new data cut. The updated model used time based RDI for enfortumab vedotin (CS addendum (29 November 2024) Table 12). The EAG notes that enfortumab vedotin is associated with a relative dose intensity of [redacted]. The company stated that 59.8% of patients had a treatment-related adverse event leading to dose interruption of enfortumab vedotin. The most common adverse events leading to dose interruption or reduction of enfortumab vedotin are shown in Table 2 of the company's clarification response. Drug acquisition costs for the comparator treatments were taken from eMIT[32] or the British National Formulary (BNF).[33] Chemotherapy is given for a maximum of six cycles.

Table 29 Drug dosing and total acquisition costs

Intervention	Administrations per cycle	Cycle length (days)	Relative dose intensity (%)	Cost per treatment cycle (with wastage) (£)	Modelled cost per week (with wastage) (£)
EV	2	21	[redacted]	[redacted]	[redacted]
Pembrolizumab	1	42	[redacted]	[redacted]	[redacted]
Gemcitabine	2	21	[redacted]	[redacted]	[redacted]
Cisplatin	1		[redacted]	[redacted]	
Gemcitabine	2	21	[redacted]	[redacted]	[redacted]
Carboplatin	1		92.9%	[redacted]	
Avelumab[a]	1	14	95.1%	[redacted]	[redacted]

Source: CS addendum (29 November 2024) Table 13
Abbreviations: EV, enfortumab vedotin
[a] Used as a maintenance treatment for patients responding to treatment with gemcitabine + cisplatin or carboplatin.

Avelumab treatment is given to patients who achieve response or stable disease after receiving platinum-based chemotherapy. It was assumed that 30% of patients would receive avelumab, as observed in the EV-302 trial, following a wash-out period of [redacted] weeks. The CS states that this proportion is consistent with real-world evidence in the UK and Europe. Avelumab was given for a maximum of five years, based on the stopping rule in TA788.[19]

4.2.8.2 Drug administration

The CS reports the drug administration costs for intravenous chemotherapy. The unit costs of administration were taken from National reference costs 2021/22[34] and are shown in CS Table 41. The total administration per treatment cycle and per week are shown in CS Table 42. The EAG agrees with drug administration costs used in the economic model.

4.2.8.3 Monitoring costs

The drug monitoring costs were informed by the EMA and Electronic Medicines Compendium (EMC) prescribing information (Summaries of Product Characteristics). The monitoring tests frequencies are shown in CS Table 43. One of the EAG's clinical experts was unsure which test the 'neurologic function test' was referring to and why this was only relevant to treatment with carboplatin rather than cisplatin.

4.2.8.4 Health care costs

The health care costs are shown in CS Table 46 for the progression-free and progressed health states. The costs and frequencies were assumed to be the same for both treatment arms. Unit costs were taken from the National Reference costs 2021/22[34] and PSSRU 2023[35]. Clinical advice to the EAG was that these estimates for health care resource use were reasonable and reflective of UK clinical practice, although our experts considered that patients may see urologists more often and noted that stoma nurses have not been included.

4.2.8.5 Subsequent treatment costs

A proportion of patients in the progressed disease health state were assumed to receive subsequent treatments and the remainder received no further treatment. The proportion of patients and the distribution of treatments were sourced from the EV-302 trial, with the following exceptions: enfortumab vedotin monotherapy is not reimbursed as a subsequent therapy; those who received pembrolizumab monotherapy in the trial were assumed to receive atezolizumab instead, as pembrolizumab monotherapy is not a treatment option for subsequent treatment in the UK; and taxane use was grouped and costed assuming the use of paclitaxel. CS addendum (29 November 2024) Table 14 presents the updated subsequent treatment distributions implemented in the company's economic model; this has been reproduced in Table 30 below.

The dosing regimen and duration of therapy for each subsequent treatment was taken from the EV-302 trial or the EMA label for interventions not evaluated in the EV-302 trial and are shown in CS Table 44. The cost of subsequent treatment in the model is calculated as a weighted average of the proportions receiving each treatment and the treatment cost (drug acquisition and drug administration costs) per cycle and median treatment duration. This cost is applied in the model weighted by the proportion of patients in the progressed disease

state. This method means that the total cost of subsequent treatment is the cost of one course of subsequent treatment. We note that many patients will have died before whilst on progression-free disease so we consider this an overestimate of the cost of subsequent treatment. However, we note that this change only has a minor effect on the model results and so we do not change this in the EAG base case and address this in the EAG scenarios (section 6.1.1).

Clinical advice to the EAG confirmed that the proportions of patients receiving subsequent treatment in Table 30 are broadly what our experts would expect in clinical practice, although they commented that they would not expect any patients to receive atezolizumab after receiving pembrolizumab as a first-line treatment. Our experts also suggested that they would expect the proportion of patients who are rechallenged with cisplatin to be higher (10-15%), although the rechallenge would be a year after finishing first-line treatment for some of these patients.

Table 30 Subsequent treatment distribution and total costs

		Post-progression/subsequent treatment					
		Gemcitabine + cisplatin	Gemcitabine + carboplatin	Atezolizumab	Paclitaxel	Total cost per course (£)	Total admin cost per course (£)
1L treatment	EV+P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS addendum (29 November 2024) Table 14
Abbreviations: 1L, first line; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy

4.2.8.6 Adverse event costs

The company economic model includes costs for grade 3+ adverse event events (and grade 2 peripheral neuropathy). Unit costs per adverse event were taken from NHS reference costs 2021/22[34] and were based upon recent NICE technology appraisals for urothelial cancer and renal cell carcinoma.[19 36] The costs of treating adverse events are shown in CS Table 47. The costs of the adverse events were applied as lump sum costs in the first model cycle. The total adverse event costs were calculated to be [redacted] and [redacted] for the enfortumab vedotin with pembrolizumab and chemotherapy arms, respectively. Using results from the most recent data cut, the company add an additional adverse event for diarrhoea and the cost of this is £696.19 (CS addendum (29 November 2024) Table 15).

Clinical advice to the EAG was that some patients receiving chemotherapy would be likely to have febrile neutropenia, which is potentially more serious than neutropenia and these data are not included in the model. A drug may also be given to patients receiving chemotherapy to reduce the incidence of neutropenia, such as Granulocyte colony stimulating factor (G-CSF). In response to clarification question B5, the company clarified that the incidence of febrile neutropenia was [redacted] patients ([redacted]%) with enfortumab vedotin with pembrolizumab vs [redacted] patients ([redacted]%) with chemotherapy.

Our experts also commented that it would be rare to admit patients with peripheral neuropathy to hospital, unless it is life threatening. The EAG are unsure whether the costs of treating peripheral neuropathy grade 2 would be the same as for grade 3. For example, whether fewer patients would receive a full course of 10 physiotherapy sessions.

In response to clarification question B6 on the health care resources needed to treat fatigue, the company stated that, after consultation with their clinical experts, there is no real treatment for grade 3 fatigue which would not require hospitalisation and is managed by dose interruption. The company included a scenario where the cost of fatigue was zero and the results are shown in clarification response table 3. The scenario only had a minor effect on model results.

4.2.8.6.1 End of life costs

The company implemented an end-of-life cost of £5,137,[37] applied when a patient transitions to the death state.

EAG conclusion on resources and costs

The EAG considers that the resources and costs for drug use and administration are reasonable. The doses used in the model are consistent with those used in the EV-302 trial and UK clinical practice. Further, we consider that the health state and monitoring costs used in the model are appropriate.

We consider that the calculation for subsequent treatment overestimates the cost of subsequent treatment and we have amended this calculation in an EAG scenario.

The EAG considers that the cost of treating fatigue has been overestimated. We consider that this cost should not include costs for hospitalisation. We also consider that the model should differentiate between febrile neutropenia and neutropenia. However, making these changes only has a minor effect on model results and so we have not included them in the EAG base case analysis.

We note that the company are using 2021/22 NHS reference costs. 2022/23 data are now available, but may not have been at the time the company were completing their submission. We consider that using the updated version of the reference costs will only have a minimal effect on the model results so we have not updated the costs.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's new data cut includes changes to the survival curves (section 4.2.6), utility values (section 4.2.7), treatment interruption and reduction (relative dose intensity) (section 4.2.8.1), adverse event frequency (section 4.2.6.5), and subsequent treatment costs (section 4.2.8.5).

The company's base case results, updated after their new data cut, are shown in CS addendum (29 November 2024) Table 19, for enfortumab vedotin plus pembrolizumab versus platinum-based chemotherapy and gemcitabine for patients with untreated unresectable or metastatic urothelial cancer. This, and all other cost effectiveness results in this report, include a confidential PAS price discount for enfortumab vedotin of [redacted]. The results are also shown with a severity multiplier of 1.2 which is applied to the incremental QALYs. Other treatments in the model are costed at list price, although some of these have confidential price discounts for the NHS. We provide a separate EAG confidential cPAS addendum with all treatments costed with their confidential price discounts. For the analysis with the severity modifier, enfortumab vedotin with pembrolizumab is associated with an additional cost of [redacted] and yields 1.74 additional QALYs with an ICER of [redacted] per QALY (Table 31)

For the analysis without the severity modifier, enfortumab vedotin with pembrolizumab is associated with 1.45 additional QALYs with an ICER of [redacted] per QALY (Table 31) .

Table 31 Base-case results for the ITT population with and without including severity modifier of 1.2 QALY weights and a confidential PAS of [redacted]% for enfortumab vedotin

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Without severity modifier							
PBC+gem	[redacted]	[redacted]	[redacted]				
EV+P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.45	[redacted]
With severity modifier of 1.2 (applied to QALYs)							
PBC+gem	[redacted]	[redacted]	[redacted]				
EV+P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.74	[redacted]

Source: CS addendum (29 November 2024) Table 19
Abbreviations: EV+P enfortumab vedotin with pembrolizumab, ICER incremental cost effectiveness ratio, incr. incremental, LYG life years; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; QALY quality adjusted life year
Note: All other treatments were costed using list prices.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The CS reports deterministic sensitivity analyses in section B.3.10.2 using the company's model. Parameters were varied according to their confidence interval limits or by calculating the upper and lower bounds by assuming a standard error of 10% of the mean. More details on the parameters varied are shown in CS Appendix Q. The deterministic sensitivity analyses do not vary the survival outcomes, these are varied in the scenario analyses instead. The most influential variables were then plotted in a tornado diagram (CS addendum (29 November 2024) Figure 19). The most influential parameters are the proportion of patients receiving avelumab maintenance therapy, the health state utility values, administration costs and components of monitoring and health state costs.

The EAG notes that the results are shown without the severity multiplier and the DSA results vary between [redacted] and [redacted] per QALY. Most parameters have been included in the deterministic sensitivity analyses.

5.2.2 Scenario analysis

The company conducted scenario analyses to test the robustness of the model results considering the structural and methodological uncertainties and alternative input sources. The list of scenarios are shown in CS section B.3.10.3 and include:

- Structural assumptions: time horizon, discount rate, excluding adverse events,

- Survival extrapolation: overall survival, progression-free survival and time-on-treatment.
- Utilities: Health-based utilities, removing age-adjusted utilities, alternative sources
- Drug cost calculations: pembrolizumab dosing based on trial protocol.

The results of the scenario analyses are shown in CS addendum (29 November 2024) Table 24 with and without the severity modifier. The scenario ICERs ranged from [redacted] to [redacted] per QALY, when including the severity modifier.

5.2.3 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) with input parameters and distributions detailed in CS Appendix Q. The PSA was run for 1000 iterations. The standard errors for the parameters were taken, where possible, from the parameters' data source or else the standard error of the parameter was assumed to equal 10% of the mean value. Most parameters have been included in the PSA and the EAG considers that the distributions used are reasonable.

The cost-effectiveness scatterplot with no severity weighting is shown in CS addendum (29 November 2024) Figure 18. The probabilistic results, shown in CS addendum (29 November 2024) Table 21, were in line with the deterministic results. enfortumab vedotin with pembrolizumab was associated with 0% probability of being cost-effective versus chemotherapy assuming a willingness-to-pay of £30,000.

5.2.4 Subgroup analyses

The CS presents subgroup results for the cisplatin-eligible and cisplatin-ineligible patients. The ITT analyses presented in the company base case include both cisplatin-eligible and cisplatin-eligible patients together. The results are shown for cisplatin-eligible patients in CS addendum (29 November 2024) Table 25 and for cisplatin-ineligible patients in CS addendum (29 November 2024) Table 26.

5.3 Model validation and face validity check

5.3.1 Company validation

CS section B.3.13.1 reports the validation process undertaken. Conceptual validation was provided by an advisory board and in-depth interviews with seven global clinical experts (three from the UK) with experience in treating patients with advanced urothelial cancer. The interviews also covered resource utilisation and model assumptions (CS Appendix P).

The model was quality checked using the TECH-VAR checklist.[38] Technical verification was undertaken to ensure internal consistency, including checking formulas, calculations and

links between cells. The model outputs were compared with source data used for model development. Results of the developed model were compared with results from clinical trials reported in the literature for the interventions of interest. The model structure was validated in discussion with clinical and health economic experts (CS Appendix P).

5.3.2 EAG validation

We conducted a range of checks on the company's model using an EAG checklist:

- Input checks: comparison of all parameter values in the model against the values stated in the CS and cited sources.
- Output checks: replication of results reported in the CS using the company model.
- 'White box' checks: manual checking of formulae which includes reviewing the calculations across each cycle and working backwards to trace links to input parameters and forwards to the results.
- 'Black box' checks: working through a list of tests to assess whether changes to key model inputs or assumptions have the expected effects on the model results.

5.3.2.1 Comparison with other studies

We compared the model results against other published studies for enfortumab vedotin with pembrolizumab versus chemotherapy for metastatic urothelial cancer.[16-18] More details of the published studies are shown in section 4.1. The results are shown for life years and QALYs in Table 32. The results for the company model are similar to those from Li et al.,[16] You et al.[17] and Rieger et al.[18] for chemotherapy, but the results from Rieger et al. have lower QALYs and life years for enfortumab vedotin with pembrolizumab than the other studies. We note that the model developed by Rieger et al.[18] uses constant probabilities for death and progression (i.e. exponential distribution), which leads to a shorter extrapolated tail and hence lower estimates for life years and QALYs.

Table 32 Comparison between company model results and other published studies for EV+P versus PBC and gemcitabine

EV+P	Company model	Li et al. [16]	You et al. [17]	Rieger et al.[18]
Life years	[redacted]	4.221	NR	3.17
QALYs	[redacted]	3.254	3.22	2.31
PBC + gem				
Life years	[redacted]	2.121	NR	2.36
QALYs	[redacted]	1.533	1.70	1.71

Source: CS addendum (29 November 2024) Table 19
Abbreviations: EV+P enfortumab vedotin + pembrolizumab; PBC+gem platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; QALYs quality adjusted life years.

5.3.3 EAG corrections to the company model

We have checked the company model and not detected any technical errors.

5.3.4 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 33. We investigate uncertainties through additional scenario analysis in section 6.1.

Table 33 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case
Model structure			
Model structure	Section 4.2.2	We agree.	No change
Population	Section 4.2.3	We agree.	No change
Comparators	Section 4.2.4	We agree.	No change
Perspective	Section 4.2.5	We agree	No change
Time horizon	Section 4.2.5	We agree.	No change
Discounting	Section 4.2.5	We agree.	We prefer to start discounting from beginning of the model time horizon rather than after year 1.
Survival curves			
OS	Section 4.2.6.2	We agree.	No change. We tested alternative curves with

Parameter	Company base case	EAG comment	EAG base case
			less optimistic survival predictions in scenario analyses.
PFS	Section 4.2.6.3 and 4.2.6.3.1	We disagree with the curves chosen for EV PFS, because the PFS curve crosses the OS curve at about 8 years.	We prefer to use the log-logistic curve for both EV+P and PBC+gem PFS in our base case. We prefer to use the lognormal curve for both EV+P and PBC+gem PFS for the cisplatin-eligible subgroup. We prefer to use the log-logistic curve for both EV+P and PBC+gem PFS for the cisplatin-ineligible subgroup.
ToT	Section 4.2.6.4	We disagree with the curve chosen for avelumab. Clinical advice to the EAG was that too many patients receive avelumab for too long in the company's base case compared with UK clinical practice. We disagree with the company's choice of curve for EV for the cisplatin subgroups; the log-logistic is a better fit (lowest AIC/BIC).	We prefer to use the exponential parametric curve for avelumab time on treatment for the ITT population and both cisplatin subgroups. We prefer to use the log-logistic for EV ToT in both cisplatin subgroups.
Adverse events			

Parameter	Company base case	EAG comment	EAG base case
Frequency of adverse events	Section 4.2.6.5	We agree	No change
Utilities			
Patient utilities	Section 4.2.7.3	We disagree. Clinical advice to the EAG was that HRQoL would be lower in the PBC+gem patient group while on treatment (18 weeks). Patients would improve over the next 2-3 months after stopping PBC+gem. HRQoL would then be about the same for patients in both groups.	EV+P pre-progression: treatment-independent ([redacted]). PBC+gem pre-progression: treatment-dependent for the first 6 months ([redacted]); treatment-independent for the remaining time in PFS ([redacted]) Post-progression: treatment-independent ([redacted])
AEs disutilities	Section 4.2.7.4	We agree.	No change.
Severity modifier	Section 7	We agree	No change
Resource use and costs			
Drug acquisition and administration	Section 4.2.8.1 and 4.2.8.2	We agree	No change
Healthcare resource use	Section 4.2.8.4	We agree	No change
Adverse event costs	Section 4.2.8.6	We agree	No change
Subsequent treatment	Section 4.2.8.5	We agree.	No change. We amend the calculation used in the model in a scenario analysis.

Source: EAG table
AE, adverse event; AIC, Akaike's information criterion; BIC Bayesian information criterion; EV, enfortumab vedotin; EQ-5D, EuroQol five dimensions; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; K-M, Kaplan-Meier; OS, overall survival; P,

pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; PFS, progression-free survival; QALY, quality-adjusted life year; ToT, time-on-treatment

6 EAG'S ADDITIONAL ANALYSES

6.1 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in Table 33, we have identified several key aspects of the company base case with which we disagree. The results are shown with a PAS discount for enfortumab vedotin and list price for the other treatments. We provide a separate EAG confidential cPAS addendum with all treatments costed with their confidential price discounts.
Our preferred model assumptions are the following:

For the EAG base case

- Discounting: we use the standard form of discounting starting in the first cycle, rather than starting at end of first year (section 4.2.5).
- Pre-progression utilities: we use the treatment specific utility for chemotherapy for the first six months (u=[redacted]) and then the treatment independent utility thereafter (u=[redacted]). We use the treatment independent utility for enfortumab vedotin with pembrolizumab (u=[redacted]) (section 4.2.7).
- PFS for enfortumab vedotin with pembrolizumab and chemotherapy: we use the loglogistic distribution, rather than splines (section 4.2.6.3).
- Time on treatment for avelumab maintenance therapy: we use the exponential curve, rather than the Weibull distribution (section 4.2.6.4).

The EAG base case results are shown in Table 34 using the EAG's preferred assumptions. When using these assumptions, the ICER increases to [redacted] and [redacted] and per QALY for enfortumab vedotin with pembrolizumab versus chemotherapy with and without the severity modifier. The model results are most sensitive to using the exponential distribution for avelumab maintenance treatment.

Table 34 EAG's preferred model assumptions, cumulative results, PAS for enfortumab vedotin

				Cumulative ICER £/QALY.	
Preferred assumption	Treatment	Total costs	Total QALYs	No severity modifier	Severity modifier of 1.2.
Company base-case	EV+P	[redacted]	[redacted]	-	-
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
+ Discounting applied at start of model time horizon	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
+ Pre-progression utilities: EV+P [redacted]; PBC+gem [redacted] for the first 6 months, then [redacted].	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
+ PFS: Use the loglogistic for EV+P and PBC+gem	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
+ToT for avelumab maintenance: exponential curve	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	EV+P	[redacted]	[redacted]	[redacted]	[redacted]
	PBC+gem	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAG created table
EAG, evidence assessment group; EV+P, enfortumab vedotin with pembrolizumab; HRQoL, health-related quality of life; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Severity multiplier of 1.2 applied to incremental QALYs.

6.1.1 EAG scenario analyses

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some model assumptions on the final cost-effectiveness results. Table 35 below summarises the results of the scenario analyses on the EAG base case. The following scenarios were conducted:

Scenarios

- Repeat selected scenarios from CS for overall survival, progression-free survival and time-on-treatment, and utilities.
- Overall survival – use an independent fit of the generalised gamma to both arms
- Treatment waning – 1) waning starts when pembrolizumab treatment stops at two years and ends at five years; 2) waning starts when pembrolizumab treatment stops at two years, and ends at seven years, 3) waning starts at four years, and ends at seven years.
- Alternative calculation of subsequent treatment

The results were most sensitive to changes in the survival curves used for overall survival. The ICERs for the scenarios varied between [redacted] per QALY (overall survival: constant hazard ratio, log-logistic) and [redacted] per QALY (overall survival: independent fit, both arms generalised gamma).

Table 35 EAG's scenario analyses with PAS for enfortumab vedotin

			ICER (£/QALY)	
Scenario	**Incr. costs**	**Incr. QALYs**	**No severity modifier**	**Severity modifier of 1.2.**
EAG base case	[redacted]	1.34	[redacted]	[redacted]
Selected company scenarios				
OS: Independent fit, both arms exponential	[redacted]	1.06	[redacted]	[redacted]
OS: Independent fit, both arms log-normal	[redacted]	1.57	[redacted]	[redacted]
OS: Dependent fit: Common shape parameter, log-logistic	[redacted]	1.08	[redacted]	[redacted]
OS: Constant hazard ratio, log-logistic	[redacted]	1.72	[redacted]	[redacted]
PFS: Spline, EV+P hazard 2 knots, PBC+gem Odds 3 knots	[redacted]	1.35	[redacted]	[redacted]
PFS: Standard fits, both arms log-normal	[redacted]	1.33	[redacted]	[redacted]
PFS: Standard fits, both arms generalised gamma	[redacted]	1.37	[redacted]	[redacted]
ToT: EV: log-logistic, P: KM ToT Avelumab: Weibull	[redacted]	1.34	[redacted]	[redacted]
ToT: EV: log-logistic, P: log-logistic Avelumab: Weibull	[redacted]	1.34	[redacted]	[redacted]
ToT: EV: generalised gamma, P: generalised gamma, Avelumab: Weibull	[redacted]	1.34	[redacted]	[redacted]
Utilities: Health state specific. No disutility for PBC+gem	[redacted]	1.33	[redacted]	[redacted]
Utilities: Treatment-specific in PFS, No disutility for PBC+gem. No age-adjustment	[redacted]	1.42	[redacted]	[redacted]

			ICER (£/QALY)	
Scenario	**Incr. costs**	**Incr. QALYs**	**No severity modifier**	**Severity modifier of 1.2.**
Utilities: Health-state specific, No disutility for PBC+gem. Source: NICE TA788	[redacted]	1.43	[redacted]	[redacted]
Utilities: Health-state specific, No disutility for PBC+gem. Source: NICE TA739	[redacted]	1.09	[redacted]	[redacted]
Utilities: Health-state specific, No disutility for PBC+gem. Source: SMC pembrolizumab	[redacted]	1.26	[redacted]	[redacted]
EAG scenarios				
OS: independent fit, both arms generalised gamma	[redacted]	0.95	[redacted]	[redacted]
Treatment waning, starts at 2 years and stops at 5 years	[redacted]	1.01	[redacted]	[redacted]
Treatment waning, starts at 2 years and stops at 7 years	[redacted]	1.09	[redacted]	[redacted]
Treatment waning, starts at 4 years and stops at 7 years	[redacted]	1.16	[redacted]	[redacted]
Alternative calculation of subsequent treatment costs	[redacted]	1.34	[redacted]	[redacted]

Source EAG created table
Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; LYG, life years gained; QALYs, quality-adjusted life years; EV+P, enfortumab vedotin with pembrolizumab; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; OS, overall survival, PFS progression-free survival; ToT, time on treatment.

6.1.2 Probabilistic sensitivity analysis

The EAG conducted a PSA for the EAG base case analysis with 1000 simulations. The results are shown in Table 36. The ICER is [redacted] and [redacted] per QALY for enfortumab vedotin with pembrolizumab vs chemotherapy with and without the severity modifier. Enfortumab vedotin with pembrolizumab has a 0% probability of being cost-effective at a willingness threshold of £30,000 per QALY.

Table 36 Probabilistic results for the EAG base case results (probabilistic) with PAS for enfortumab vedotin

					ICER versus baseline (£/QALY)	
Technologies	**Total costs (£)**	**Total QALYs**	**Incr. costs (£)**	**Incr. QALYs**	**Without severity multiplier**	**With severity modifier of 1.2**
PBC + gem	[redacted]	[redacted]				
EV+P	[redacted]	[redacted]	[redacted]	1.32	[redacted]	[redacted]

Source: EAG created table
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ICER, incremental cost-effectiveness ratio; Incr., incremental; LYG, life years gained; PBC + gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; QALY quality adjusted life year

6.1.3 Subgroup analyses

The EAG ran subgroup analyses for the cisplatin-eligible and cisplatin-ineligible subgroups. The EAG choice of survival curves for overall survival, progression-free survival and time-on-treatment are shown below:

Cisplatin-eligible

- Overall survival (both arms): lognormal. This is the same choice of curve as the company, which has the lowest AIC/BIC)
- Progression-free survival (both arms): lognormal (discussed in section 4.2.6.3.2)
- Enfortumab vedotin time-on-treatment: log-logistic. This curve has the lowest AIC/BIC (CS addendum (29 November 2024) Appendix M Table M2)
- Avelumab time-on-treatment: exponential. This is the same curve we use in our base case.

Cisplatin-ineligible

- Overall survival (both arms): log-logistic. This is the same choice of curve as the company, which has the lowest AIC/BIC (apart from exponential, which has incorrect hazards)
- Progression-free survival (both arms): log-logistic (discussed in section 4.2.6.3.2)
- Enfortumab vedotin time-on-treatment: log-logistic. This curve has the lowest AIC/BIC (CS addendum (29 November 2024) Appendix M Table M2)

- Avelumab time-on-treatment: exponential. This is the same curve we use in our base case.

The other aspects of the EAG base case were unchanged. The company's choice of the survival curves for the subgroups are shown in the company's response to clarification question B3. The results for the subgroup analyses are shown in Table 37 for cisplatin-eligible patients. The ICER is [redacted] and [redacted] per QALY with and without the severity modifier for enfortumab vedotin with pembrolizumab vs chemotherapy.

Table 37 EAG subgroup analyses for cisplatin-eligible patients with PAS for enfortumab vedotin

					ICER versus baseline (£/QALY)	
Technologies	**Total costs (£)**	**Total QALYs**	**Incr. costs (£)**	**Incr. QALYs**	**Without severity multiplier**	**With severity modifier of 1.2**
PBC + gem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EV+P	[redacted]	[redacted]	[redacted]	1.45	[redacted]	[redacted]

Source: EAG created table
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ICER, incremental cost-effectiveness ratio; Incr., incremental; LYG, life years gained; PBC + gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; QALY quality adjusted life year

The results for the EAG subgroup analyses are shown in Table 38 for cisplatin-ineligible patients. The ICER is [redacted] and [redacted] per QALY with and without the severity modifier for enfortumab vedotin with pembrolizumab vs chemotherapy.

Table 38 EAG subgroup analyses for cisplatin-ineligible patients with PAS for enfortumab vedotin

					ICER versus baseline (£/QALY)	
Technologies	**Total costs (£)**	**Total QALYs**	**Incr. costs (£)**	**Incr. QALYs**	**Without severity multiplier**	**With severity modifier of 1.2**
PBC + gem	[redacted]	[redacted]				
EV+P	[redacted]	[redacted]	[redacted]	1.27	[redacted]	[redacted]

Source: EAG created table
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ICER, incremental cost-effectiveness ratio; Incr., incremental; LYG, life years gained; PBC + gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; QALY quality adjusted life year

6.2 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of enfortumab vedotin with pembrolizumab compared to gemcitabine with platinum-based chemotherapy ('chemotherapy') for patients with metastatic urothelial cancer. The EAG considers the structure of the model to be reasonable, appropriate and consistent with previous cost-effectiveness models for cancer. In general, the EAG considers that the model is well constructed and coded and the parameters have been selected according to best practice as described in the NICE methodology manual.[1]

The company submitted an updated model using data from a new data cut, details can be found in the CS addendum (29 November 2024). The company's base case shows an ICER of [redacted] and [redacted] per QALY with and without a severity multiplier of 1.2 for enfortumab vedotin with pembrolizumab versus chemotherapy, including a PAS discount for enfortumab vedotin of [redacted].

The EAG disagrees with several of the assumptions in the company's model. Our preferred assumptions are shown in section 6.1 and include changes to discounting, utilities, survival curves used for progression-free survival and time-on-treatment. In general, these changes only have a minor effect on model results. Incorporating the EAG preferred assumptions increases the ICER to [redacted] and [redacted] per QALY with and without a severity multiplier of 1.2 for enfortumab vedotin with pembrolizumab versus chemotherapy, including a PAS discount for enfortumab vedotin of [redacted]. The model results are most sensitive to changes in the choice of parametric curve used to extrapolate overall survival.

7 SEVERITY

The company calculated the QALY shortfall for patients with metastatic urothelial cancer by using mortality from the UK National life tables[39] and general population utilities from Hernandez Alava et al.[40] The company used the gender proportion (77% male) and starting age (67.9 years) from the EV-302 trial (CS Table 20). The QALYs for patients with metastatic urothelial cancer are taken from the chemotherapy arm. The proportional QALY shortfall is 83% (see Table 39 below). We also calculated the absolute and proportional QALY shortfall using the EAG base case (Table 34) and obtained similar results to the company's revised base case (Table 39). For both the company and EAG's base case, the proportionate QALY shortfall is slightly lower than 0.85 and therefore, on this basis, may not be eligible for applying a 1.2 severity multiplier for QALYs. However, the EAG agrees with the company that there is some uncertainty over the expected total QALYs for chemotherapy and therefore we have raised this as a key issue.

The company states in the CS addendum (29 November 2024) that the chemotherapy estimates may overestimate QALYs because some of the patients had enfortumab vedotin as a second-line treatment ([redacted]), which is not consistent with current practice in the NHS. They also note the variability in estimates due to the survival curve chosen (CS addendum (29 November 2024) Table 18).

Table 39 QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have current treatment	Absolute QALY shortfall	Proportionate QALY shortfall
Company's revised base case	9.8	PBC+gem: 1.62	8.18	0.83
EAG base case	9.49	PBC+gem: 1.55	7.94	0.84

Source: Schneider et al. 2021[41]
PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine; QALY, quality adjusted life-year.

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9 APPENDICES

Appendix 1

Table 40 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	CS D Appendix D section 3.1 and Tables 4 and 5 provide details of eligibility criteria for the clinical SLR. Criteria were broader for population and intervention.
Were appropriate sources of literature searched?	Yes	Data sources searched are reported in CS Appendix D section 3.2. Searches covered sufficient databases (Embase (Embase.com), MEDLINE (PubMed) Cochrane (CENTRAL). And relevant grey literature (WHO ICTRP, oncology and urology conference proceedings, HTA websites, bibliographies of relevant SLRs)
What time period did the searches span and was this appropriate?	Yes	Time periods for searches are reported in CS Appendix D section 3.2. Embase and MEDLINE searches were carried out from 2000, to 10 June 2024. "Cochrane" (unclear if company are referring to CENTRAL or whole Cochrane library) and WHO ICTRP were searched from June 2020 to June 2023

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		Conference proceedings and HTA websites were searched from January 2015 to June 2024 The EAG considers the searches up to date.
Were appropriate search terms used and combined correctly?	Unclear	The search terms for Embase and MEDLINE were all appropriate (CS Appendix D Tables 8 and 9). The EAG consider the Cochrane search unconventional (CS Appendix D Table 10) but do not believe this would have led to trial records being missed. The searches did not specifically search for single-arm studies such as cohort or other observational studies (Company clarification response A3)..
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	CS Appendix D section 3.1 and Table 4 and 5 specify the inclusion and exclusion criteria, which were broader for the population, interventions and comparators than that of the NICE final scope.

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Were study selection criteria applied by two or more reviewers independently?	Yes	Title/abstract and full-text screening was conducted by two independent reviewers with any disagreements resolved by discussion with a third (CS Appendix D section 3.1).
Was data extraction performed by two or more reviewers independently?	Yes	Data extraction was carried out by one reviewer and checked by a second (CS Appendix D section 3.5). The EAG considers this acceptable
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The company used the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for RCTs. Single arm trials were assessed based on ROBINS-I (CS Appendix D section 3.6)
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No	CS Appendix D section 3.6 states risk of bias assessments were conducted by one reviewer. EAG independently appraised study EV-302 and agreed with the company's judgements (see section 3.2)
Is sufficient detail on the individual studies presented?	Yes	CS 2.2 to 2.7, CS Appendix D section 4.2 and 4.3, and CS Appendices E and F provide methodological

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		details and results from EV-302 and/or EV-103. The trial CSRs were also provided.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not applicable	Direct evidence was available from study EV-302, which was the only study comparing EV+P with platinum-based chemotherapy in first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy (i.e. eligible for either cisplatin or carboplatin). No pairwise meta-analysis, ITC, NMA were therefore undertaken

Source: Table created by the EAG
CENTRAL, Cochrane Central Register of Controlled Trials; CS, company submission; CSR, clinical study report; EAG, External Assessment Group; ITC, indirect treatment comparison; NMA, network meta-analysis; PICOD, population, intervention, comparator, outcome, design; RCT, randomised controlled trial; WHO ICTRP World Health Organisation International Clinical Trials Registry Platform

Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 7 January 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Factual inaccuracies in Executive Summary (Section 1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 2-3: Issue 1 on the severity modifier is linked to Issue 2 on avelumab time on treatment. This connection should be clarified in the text.	Under "What alternative approach has the EAG suggested?", please add the sentence below: *One of the experts interviewed by the EAG commented that avelumab treatment is usually given for a shorter time period in NHS clinical practice than observed in the EV-302 trial (see also Issue 2 below); this contributes to the uncertainty about whether the severity modifier applies.*	The amendment clarifies the connection between Issue 1 and Issue 2, thereby highlighting the need for the committee to consider how Issue 2 will be resolved when deliberating Issue 1.	We do not consider this to be a factual inaccuracy. Changing the time on treatment for avelumab does not affect the life expectancy of patients in the chemotherapy arm in the economic model.
Page 5, Table 3: Results for EV+P and PBC+gem arms were switched when presenting the company base case	Switch numerical results for total costs and total QALYs to the correct row for the company base case in Table 3 (i.e. the results currently presented for EV+P are the predicted results for PBC+gem and vice versa)	Incorrect numerical results	We agree. The results have been corrected (page 5, Table 3).

Issue 2 Factual inaccuracies in Clinical Effectiveness section (Section 3)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 30, second line: the proportion of patients enrolled in the USA is incorrect – see CSR Table 12.1.1.3.	… while study EV-302 recruited only [redacted]% from the USA.	Incorrect number provided in the text.	We agree. The percentage has been corrected (page 30)
Page 37, second paragraph and Page 46, last paragraph: OS from the [redacted] data cut is described as 'final'. This is not accurate as there will be further data cuts in the future.	Please remove the wording describing the OS results as 'final'.	There will be further data cuts.	Not a factual inaccuracy – no change made. We based the term final from this quote from the company submission: "The study was designed to test OS twice, first at interim analysis (same time as the PFS final analysis) and second at ***final*** analysis, which was to be performed after approximately 489 events" (page 45)
Page 43, Table 11, row 21, column 2. Value for Acute kidney injury is given as '[redacted]	Replace with [redacted]	Incorrect result due to mistyping.	We agree. The value has been corrected (Page 43, Table 11, row 21, column 2)

Issue 3 Factual inaccuracies in Cost-Effectiveness section (Section 4)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 84: Section 4.2.8.6 Adverse event costs cites AE costs calculated from the original data cut, while all other results refer to the updated data cut	The total adverse event costs were calculated to be [redacted] and [redacted] for the enfortumab vedotin with pembrolizumab and chemotherapy arms, respectively.	Presenting AE costs based on the second data cut provides consistency with all other reported results.	We agree. The text has been corrected and CIC marking added (section 4.2.8.6, page 84).
Page 95, Table 34: Results for EV+P and PBC+gem arms were switched when presenting the company base case	Switch numerical results for total costs and total QALYs to the correct row for the company base case in Table 34 (i.e. the results currently presented for EV+P are the predicted results for PBC+gem and vice versa)	Incorrect numerical results	We agree. The results have been corrected (page 95, Table 34).

Confidentiality marking inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 22, last paragraph	The percentage of participants enrolled from the UK should be marked as confidential as it is unpublished, but is unmarked	Patients were enrolled from 25 countries, including the UK ([redacted]; EV-302 Clinical Study Report (CSR) Table 12.1.1.3)	We agree. CIC marking has been added (page 22, last paragraph).
Page 23, Table 5, Row on Randomisation	The number of patients randomised from the UK should be marked as confidential as it is unpublished, but is unmarked	N=886 patients randomised (including [redacted] from the UK).	We agree. CIC marking has been added (page 23, Table 5, row on Randomisation).
Page 23, Table 5, Row on Duration of treatment	The date of the data cut off should be marked as confidential as it is unpublished, but is unmarked	Duration of treatment (months) in data cut [redacted]	We agree. CIC marking has been added (page 23, Table 5, row on Duration of treatment).
Page 23, Table 5, Row on Duration of treatment	Median durations of treatments should be confidential as they are from the unpublished second data cut, but were unmarked.	**EV+P** (n=440): median [redacted] **PBC+gem** (n=433): median [redacted]	We agree. CIC marking has been added (page 23, Table 5, row on Duration of treatment).
Page 28, third paragraph	The percentage of participants enrolled from the UK should be marked as confidential as it is unpublished, but is unmarked	Specifically, [redacted] were from the UK	We agree. CIC marking has been added (page 28).

Page 29, last paragraph	Values pertaining to the baseline characteristics of cohort K should be marked as confidential as they are unpublished, but are unmarked. The proportion of patients enrolled by country in EV-302 (and here specifically the USA) should be marked confidential as it is unpublished (note that the number was incorrect; see factual inaccuracies table above).	Compared to study EV-302, as with cohort A + dose escalation, a greater proportion of patients in the enfortumab vedotin with pembrolizumab arm of cohort K were aged ≥ 75 years ([redacted] vs 23.7%), had ECOG PS2 ([redacted] vs 2.9%) and visceral metastases ([redacted] vs 71.8%). Unlike cohort A + dose escalation, the proportion of patients with ECOG 0 were similar between study EV-302 and the enfortumab vedotin with pembrolizumab arm of cohort K (49.4% vs [redacted]). Both cohort A + dose escalation and cohort K predominately recruited patients from the USA ([redacted]), while study EV-302 recruited only [redacted]% from the USA.	We agree. CIC marking has been added (page 29 and page 30).
Page 31, second paragraph	The completion rate description for the chemotherapy arm should be marked as confidential as it is unpublished, but it is unmarked.	Furthermore, post-hoc analysis showed that completion rates were [redacted] in the chemotherapy arm due to more participants having progressed.	We agree. CIC marking has been added (page 31).

Page 37, fifth paragraph	The CI values should be marked as confidential, but are unmarked.	(95% CI, [redacted])	We agree. CIC marking has been added (page 37).
Page 39, sixth paragraph	The upper 95% CI interval should be marked as confidential because it is from the unpublished second data cut, but it is unmarked.	For the subgroup analysis of region for OS, the upper 95% confidence interval for the North America subgroup was [redacted]	We agree. CIC marking has been added (page 39).
Page 41, Table 10, row 2, columns 4 and 5	The PY values should be marked as confidential because they are from the unpublished second data cut, but are unmarked.	EV+P (PY=[redacted]) Events (Events/PY) [a] PBC+gem (PY=[redacted]) Events (Events/PY [a])	We agree. CIC marking has been added (page 41, Table 10, row 2, columns 4 and 5).
Page 44, first paragraph	The AE rates should be marked as confidential as they are from the unpublished second data cut, but are unmarked.	… skin reactions ([redacted]) and peripheral neuropathy ([redacted]).	We agree. CIC marking has been added (page 44).
Page 45, first paragraph	The any-grade AE rate for severe skin reaction should be marked as confidential as it is unpublished, but is unmarked.	… except for severe skin reaction, which were reported at a higher incidence in this	We agree. CIC marking has been added (page 45).

		study ([redacted]% (any grade), 22.2% (grade ≥3).	
Page 81, second paragraph	EV RDI from the second data cut should be marked as confidential, but is unmarked.	The EAG notes that enfortumab vedotin is associated with a relative dose intensity of [redacted]	We agree. CIC marking has been added (page 81).
Page 81, Table 29	EV RDI from the second data cut should be marked as confidential, but is unmarked.	EV Relative dose intensity (%) [redacted]	We agree. CIC marking has been added (page 81, Table 29).
Page 102, first paragraph	Information on population characteristics in the EV-302 trial is not confidential, but were marked as confidential.	The company used the gender proportion (77% male) and starting age (67.9 years) from the EV-302 trial (CS Table 20).	We agree. CIC marking has been removed (page 103).

Abbreviations: CIC, Commercial in confidence

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Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with unresectable or metastatic urothelial cancer or caring for a patient with unresectable or metastatic urothelial cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 14 February.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Patient expert statement

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

Part 1: Living with this condition or caring for a patient with unresectable or metastatic urothelial cancer

Table 1 About you, unresectable or metastatic urothelial cancer, current treatments and equality

1. Your name	JEANNIE RIGBY
2. Are you (please tick all that apply)	☐ A patient with unresectable or metastatic urothelial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with unresectable or metastatic urothelial cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	ACTION BLADDER CANCER UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with unresectable or metastatic urothelial cancer? **If you are a carer (for someone with unresectable or metastatic urothelial cancer) please share your experience of caring for them**	I co-authored and agree with our submission. However, I have completed Part 2 to state our strongest views on this treatment.
7a. What do you think of the current treatments and care available for unresectable or metastatic urothelial cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for unresectable or metastatic urothelial cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of enfortumab vedotin with pembrolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does enfortumab vedotin with pembrolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of enfortumab vedotin with pembrolizumab over current treatments on the NHS please describe these. For example, are there any risks with enfortumab vedotin with pembrolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from enfortumab vedotin with pembrolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering unresectable or metastatic urothelial cancer and enfortumab vedotin with pembrolizumab? Please explain if you think any groups of people with this condition are particularly disadvantage	

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is an urgent need for treatments for this patient group, to improve current poor outcomes and lack of treatment options.
- Evidence from clinical trials is compelling both for clinical efficacy and patient quality of life and improvement in side effects - Enfortumab Vedotin plus Pembrolizumab should be considered and approved for first line treatment.
- Enfortumab Vedotin plus Pembrolizumab has clearly demonstrated in clinical trials significantly improved survival vs common current treatments.
- Enfortumab Vedotin plus Pembrolizumab has clearly demonstrated in clinical trials significantly improved quality of life and significant benefits in terms of treatment side effects when compared with current common treatments.
- New emerging therapies should be given proper consideration particularly where there is such an acute patient need. Enfortumab Vedotin plus Pembrolizumab is a significant advance in the treatment of bladder cancer, it is vital that this is acknowledged and this treatment be granted the wider access which these patients merit.

Thank you for your time.

Your privacy

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Patient expert statement

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Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

Patient expert statement

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Information on completing this form

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NICE National Institute for Health and Care Excellence

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Patient expert statement

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

Part 1: Living with this condition or caring for a patient with unresectable or metastatic urothelial cancer

Table 1 About you, unresectable or metastatic urothelial cancer, current treatments and equality

1. Your name	Melanie Costin
2. Are you (please tick all that apply)	☐ A patient with unresectable or metastatic urothelial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with unresectable or metastatic urothelial cancer? ☒ A patient organisation employee or volunteer? ☒ Other (please specify): Bladder cancer patient
3. Name of your nominating organisation	Fight Bladder Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with unresectable or metastatic urothelial cancer? **If you are a carer (for someone with unresectable or metastatic urothelial cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for unresectable or metastatic urothelial cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for unresectable or metastatic urothelial cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of enfortumab vedotin with pembrolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does enfortumab vedotin with pembrolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of enfortumab vedotin with pembrolizumab over current treatments on the NHS please describe these. For example, are there any risks with enfortumab vedotin with pembrolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from enfortumab vedotin with pembrolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering unresectable or metastatic urothelial cancer and enfortumab vedotin with pembrolizumab? Please explain if you think any groups of people with this condition are particularly disadvantage	

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13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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Single Technology Appraisal

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Clinical expert statement

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Part 1: Treating unresectable or metastatic urothelial cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Syed A Hussain MBBS, MSc, MD, FRCP
2. Name of organisation	Clinical expert nominated by Industry
3. Job title or position	Professor of Medical Oncology, University of Sheffield and Sheffield Teaching Hospitals
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with unresectable or metastatic urothelial cancer? ☐ A specialist in the clinical evidence base for unresectable or metastatic urothelial cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for unresectable or metastatic urothelial cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The intent of current treatment is palliative. The primary aim of treatment in unresectable /metastatic disease setting is to improve disease control and improve survival.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improved disease control with improved disease-free survival and above all improvement in overall survival without compromising quality of life are clinically significant treatment response.
10. In your view, is there an unmet need for patients and healthcare professionals in unresectable or metastatic urothelial cancer?	Even with improved outcome for these patients over the last decade, and with provision of treatments through NICE improving overall survival, there remains an unmet need to further improve further the outcome for our patients, with improved long term and durable disease control and to achieve cure for a higher subset of patients.
11. How is unresectable or metastatic urothelial cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Advanced metastatic bladder cancer remains a life limiting illness. Median survival in platinum eligible patients was previously reported between 14-15 months and for cisplatin ineligible group this was approximately 8-9 months. More recently with the use of immune check point inhibitors and its availability through NICE we are seeing improvements in survival for patients with metastatic bladder cancer. Recent trial (Javelin -100) had reported median survival of 21.4 months in the maintenance avelumab arm compared to 14.3 months for standard of care arm [1]. Survival is measured from the time of randomisation into maintenance Javelin -100 trial. More updated survival data shows survival of 23.8 months in maintenance avelumab arm versus 15 months in standard of care arm with a survival benefit of 8.8 months in the maintenance avelumab arm. Post hoc analysis from the start of chemotherapy treatment shows a median survival of 29.7 months in the maintenance avelumab group.

	At ESMO 2023, Professor Thomas Powles presented EV 302 study that compared EV plus pembrolizumab and reported a median survival of 31.5 months in the experimental arm, compared to 16.1 months for standard of care chemotherapy arm [Powles et al; Presented at ESMO annual meeting 2023]. These practice changing results have since been published in NEJM. EV-302 was a phase 3, global, open-label, randomized trial to compare the efficacy and safety of enfortumab vedotin and pembrolizumab with the efficacy and safety of platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma. Patients were randomly assigned in a 1:1 ratio to receive 3-week cycles of enfortumab vedotin (at a dose of 1.25 mg per kilogram of body weight intravenously on days 1 and 8) and pembrolizumab (at a dose of 200 mg intravenously on day 1) (enfortumab vedotin–pembrolizumab group) or gemcitabine and either cisplatin or carboplatin (determined on the basis of eligibility to receive cisplatin) (chemotherapy group). The primary end points were progression-free survival as assessed by blinded independent central review and overall survival. A total of 886 patients underwent randomization: 442 to the enfortumab vedotin–pembrolizumab group and 444 to the chemotherapy group. As of August 8, 2023, the median duration of follow-up for survival was 17.2 months. Progression-free survival was longer in the enfortumab vedotin–pembrolizumab group than in the chemotherapy group (median, 12.5 months vs. 6.3 months; hazard ratio for disease progression or death, 0.45; 95% confidence interval [CI], 0.38 to 0.54; P<0.001), as was overall survival (median, 31.5 months vs. 16.1 months; hazard ratio for death, 0.47; 95% CI, 0.38 to 0.58; P<0.001). The median number of cycles was 12 (range, 1 to 46) in the enfortumab vedotin–pembrolizumab group and 6 (range, 1 to 6) in the chemotherapy group. Treatment-related adverse events of grade 3 or higher

	occurred in 55.9% of the patients in the enfortumab vedotin–pembrolizumab group and in 69.5% of those in the chemotherapy group. The updated results were presented at the recent ASCO GU conference on February 14th, 2025, by Professor Thomas Powles. With 29.1 months (95% Cl: 28.5–29.9) of median follow-up: • 54 (12%) patients remained on EV+P treatment and no patients remained on chemotherapy • 218 (49%) patients in the EV+P arm and 131 (30%) patients in the chemotherapy arm remained on study The PFS benefit with EV+P was maintained with 1 additional year of follow-up (median: 12.5 versus 6.3 months; HR: 0.48, p<0.00001). The risk of death was reduced by almost 50% in the EV+P arm (median 33.8 versus 15.9 months; HR: 0.51, 95% CI: 0.43–0.61, p<0.00001). The frequency and grade of treatment-related AEs and AEs of special interest in the EV+P arm remained consistent with the previously reported primary analysis, with no new safety signals. With these improvements in the landscape post chemotherapy, NICE technology appraisal has previously recommended the use of maintenance Avelumab in patients who derive response from chemotherapy or at least achieve stable disease. In the event of disease progression 2nd line Atezolizumab is also available for our patients through previously positive NICE technology appraisal. We are seeing higher subset of patients now who are fit for 3rd line treatment post platinum-based chemotherapy and immune check point inhibitors and may

	benefit from the use of erdafitinib for FGFR positive urothelial cancers (Under NICE REVIEW). In view of the EV 302 results, once this technology appraisal has a favourable response, this will lead to the use of Enfortumab Vedotin plus Pembrolizumab as the first line standard of care treatment for patients with unresectable /metastatic urothelial cancer who meet the eligibility criteria for this combination as defined by the protocol. A subset of patients in this setting who are ineligible for EV plus pembrolizumab combination will continue to receive first line chemotherapy followed by maintenance avelumab.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	In NHS platinum-based chemotherapy is routinely used. Patients who achieve complete response, partial response or stable disease and have received at least 4 cycles of chemotherapy (60-80%), are eligible to receive maintenance avelumab (2 weekly) treatment for up to 5 years as per NICE guidance. Following that weekly paclitaxel is used in patients with disease progression post platinum-based chemotherapy and immune check point inhibitors. 4 weekly cycle with 3 weeks on and 1 week off regimen is used that requires visit to the hospital at weekly intervals. We routinely do scan every 3 months during first line treatment and during further lines of treatment based on patients' fitness and eligibility for future treatments and clinical trials.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, based on the published data, we anticipate clinical meaningful benefits compared with current care with improvement in overall survival. The quality of life is also likely to improve.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	We will need to carefully follow these patients in real world setting. Patients with pre-existing neuropathy and raised Hb A1Cwho were excluded as per trial protocol will need to be carefully monitored.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The toxicity profile of antibody drug conjugate (EV) with immune check -point inhibitors (Pembrolizumab) have their own set of side effects related to the class of these drugs. Over the years with the efforts of academic and industrial collaborations and educational activities, we have learned to better manage the toxicity profile of Immune check point inhibitors. There are several ongoing educational efforts to help better understand and deliver toxicity management for Enfortumab vedotin and for this new combination. With these continued ongoing efforts in early identification and management of toxicities, this new combination can be safely delivered in real world setting.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The inclusion criteria requirements based on EV 302 results provide a useful guide to select eligible patients and start treatment. Similarly, the trial protocol provided guidance in terms of treatment related toxicity that will require, at times break from the treatment and in some cases discontinuation of treatment.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes, it is anticipated that the technology will result in health-related benefits. This treatment regimen is more easily administered with less chair time than platinum-based chemotherapy.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology will be a step -change in the management of metastatic urothelial cancer. This is likely to further improve the overall survival in this group of patients based on EV-302 results compared to current standard of care treatment.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As discussed above ongoing and continued efforts in better understanding the side effects of this combination will be important in successful and safe delivery of this treatment to our patients in the real-world setting.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, the trial was conducted in UK as well including my site. The overall survival benefit (doubled), improvement in disease free survival (doubled) and impressive complete response rate compared to control arm were impressive and are likely to be the game changer in metastatic urothelial cancer disease setting. The above are key trial end points and were measured in EV-302 trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA788 and TA817?	As discussed above in my detailed reply to point 11

23. How do data on real-world experience compare with the trial data? • Specifically, is the overall survival data in the clinical trial expected to be different to NHS clinical practice? Please take into account any differences in treatments used in the clinical trial and treatments currently available in the NHS.	The combination is not yest available on NHS while we await the technology appraisal. It is being used in other parts of the world including north America and parts of Europe. Close monitoring of the data in real world setting will be key in safe delivery of this technology. Smaller percentage of patients received maintenance avelumab in the control arm (30%) than routinely observed in NHS.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	There are no equality issues with this trial. 20% of Asian patients were recruited in the trial and the data thus reflects the outcome in Asian patients, however, the percentage of black patients (0.7%) in experimental arm and (1.6%) in control arm was underrepresented. Real world data will provide more evidence in the underrepresented groups. Approximately quarter (24%) of the patients were above 75 years old and hence the data is applicable to elderly patient groups as well.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Improvement of overall survival seen in EV 302 is unprecedented with median survival of 31.5 months in the experimental arm.

Doubling of disease-free survival is very impressive.

Durability of responses is very exciting for clinicians and patients.

Complete response rate seen within this trial and the improvement in overall survival is consistent with a subset of patients achieving long term disease control and achieving “? CURE”

Toxicity profile was manageable.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Part 1: Treating unresectable or metastatic urothelial cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Robert A Huddart
2. Name of organisation	Institute of Cancer Research and Royal Marsden FT
3. Job title or position	Professor of Urological Cancer and Hon Consultant Clinicial Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with unresectable or metastatic urothelial cancer? ☐ A specialist in the clinical evidence base for unresectable or metastatic urothelial cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

8. What is the main aim of treatment for unresectable or metastatic urothelial cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim is to reduce symptoms and improve quality of life, prevent symptomatic progression and extend life expectancy
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improve overall survival by more than 3 months, Improve average quality of life (improvement depends of scale) Improve progression free survival by average of 3 months 5% improvement in 2 year survivors
10. In your view, is there an unmet need for patients and healthcare professionals in unresectable or metastatic urothelial cancer?	Yes absolutely. Current therapy with cisplatin and gemcitabine was developed in early 2000's with no change in background chemotherapy since. The chemotherapy has reasonable response rate of around 40% and median survival in metastatic disease of 12-18 months depending on underlying prognostic factors and case mix. This is intensive chemotherapy, with many side effects including extreme fatigue, sickness, and neuropathy. It is not curative and relapse is inevitable. Addition of Avelumab (approved for use in TA788) has improved survival but is only available for responders to chemotherapy so many patients do not receive this therapy. Data suggests is underutilised Combination of Cisplatin/gemcitabine/ Nivolumab may also improve survival versus cisplatin gemcitabine but is not yet approved. The situation is even worse for patients unfit for/unable to have cisplatin where treatment with carboplatin based treatment is used with even poorer outcomes

	There is therefore scope and need to significantly improve treatment with less toxic and more effective therapies
11. How is unresectable or metastatic urothelial cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	First line therapy is cisplatin or carboplatin gemcitabine for 4-6 cycles and is then recommended to receive maintenance avelumab (as per improving outcomes guidance and technology appraisal of avelumab) Immunotherapy with atezoluzimab is approved as first line therapy for patients unfit for cisplatin chemotherapy who are pDL1 positive but is not used commonly In patients who fail or progress on first line chemotherapy treatment with Atezoluzimab is recommended with limited success in this population. Following progression on immunotherapy then most commonly second line therapy is with taxane based chemotherapy unless there was good initial response to first line chemotherapy and significant disease free interval ~12 months when rechallenge chemotherapy can be tried I think this is consistent pathway but take up and use of Avelumab does vary and some date suggests is sub optimal. Practice/use of second line chemotherapy may also vary and many patients elect for best supportive care only. The technology would replace first line chemotherapy and maintenance immunotherapy. Adoption would allow consistency of exposure to immunotherapy and allow people to benefit from what can be transformative therapy. Data also suggests that the new technology is less renally dependant and has less acute toxicity so is applicable to most of the population except the frailest so would ensure greater consistency of care and improved QoL.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Would use similar resources to current care. It is given of d1 and D8 of a 3 week cycle so mirrors cisplatin/gemcitabine chemotherapy. The infusion is shorter and does not need pre and post hydration as would be used with cisplatin so would be shorter treatment time (~1hr versus

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	4-5 hours). Whereas Cis/gem is given for max 6 cycles the trial used treatment to progression or toxicity or withdrawal of patient consent. I believe in the trial the median number of cycles was 10- so more cycles may be given. However after chemotherapy most patients would have immunotherapy so would still be having treatment every 2 weeks if receiving avelumab and every 4 weeks if receiving atezoluzimab. Avelumab is approved for up to 5 years treatment (though average treatment time is around 6 months) whereas pembroluzimab (which is given 3 rather than 2 weekly for avelumab) was stopped after 2 years. The side effect profile is very different to SoC chemotherapy so training on its toxicities and their management will be needed. There is a risk of hyperglycaemia, skin toxicity and rarely ocular toxciity which might require specialist endocrine, opthlamology and dermatology input. No special equipment is required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Please see Fight bladder cancer submission In the pivotal EV302 trial • The median survival improved from 16.5 to 31.5 months • At 18 months 69.5% of patients were alive with EVP compared to 44% with standard chemotherapy. From figure 2 in their paper at 30 months over 50% of patients were still alive compared to ~30% with SoC treatment. • Response rates improved from 44% to 68% • HRQoL was consistently better for EVP • Time to worsening of pain was longer in EVP arm (14.2 v 10 months)

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The therapy may be particular suitable for those who can only receive carboplatin/gemcitabine especially when renal function is impaired It may not be suitable for people with poorly controlled diabetes, autoimmune disease or other contraindications to immune therapy eg chronic immunosuppressive treatment.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Probably little difference but will be learning curve as to how to manage specific toxicities. In my limited experience with technology some of toxicities eg skin, liver can be caused my either EV or pembroluzimab than can make deciding best approach a challenge. Clear toxicity management guidelines would be helpful. Patients need regular toxicity review (but this is done already on chemotherapy. Monitoring for hyperglycaemia need to be undertaken (use of serum glucose and HBA1C levels) Immunotherapy toxicity monitoring as per Soc
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Generally the technology would stop if: 1. Evidence of disease progression 2. EV would stop if patient develops grade 2/3 peripheral neuropathy 3. Pembroluzimab stop after 2 years or if significant toxicity
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The psychological benefit of the possibility of long term disease control (we are not sure if leads to cure yet but recent data suggests patients with CR have long lasting benefit) cannot be underestimated and give people 'hope' for the future

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, it is a major step forward in the treatment of this condition with real survival and quality of life benefits. The technology has been widely adopted in US and parts of Europe and recommended in European guidelines. It particularly meets an unmet need in patients not able to receive cisplatin
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The key toxicities are 1. Skin rash – occasionally serious 2. Peripheral neuropathy- may be treatment limiting and can affect QoL 3. Uncontrolled Hyperglycaemia. 4. Ocular toxicities However day to day tolerance seems better than standard chemotherapy with less myelosuppression, fatigues and sickness. In my limited experience the patients have treated on average manage symptoms better than with chemotherapy
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes I believe the trial reflects UK population – accepting the trial populations may have a younger age and better fitness levels than the average patient. The endpoints are relevant the most important one being overall survival but HRQoL and time to developing pain is also highly relevant. The trial also reports response, DFS and other intermediate endpoints that are less relevant to patients. Though response and especially complete response is of significant psychological benefit for people being told that the cancer is in remission

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA788 and TA817?	There is the Checkmate 901 study that showed improved outcome for cisplatin/gemcitabine/nivolumab versus cisplatin gemcitabine [Van der Heijden et al 2023 https://www.nejm.org/doi/full/10.1056/NEJMoa2309863]. The improvement in survival is not as large as this technology. There has been updated and more mature data on avelumab with longer follow up. [e.g. Powles et al 2022 https://ascopubs.org/doi/10.1200/JCO.22.01792]. This reports a 23.8 month survival from randomisation. The survival from start of treatment (date of survival in EV302] is not given. Given patients would have had a min of 4 cycles of chemotherapy which takes 12 weeks and minimum of 4 weeks to start is ana additional 16 weeks up to max of 28 weeks. This would add 4-6 months to this figure i.e. 28-30 months median survival- though this does exclude poor responders which would have a much poorer survival (no information available on this)
23. How do data on real-world experience compare with the trial data? • Specifically, is the overall survival data in the clinical trial expected to be different to NHS clinical practice? Please take into account any differences in treatments used in the clinical trial and treatments currently available in the NHS.	Would expect to be similar but experience does suggests 'real world data' can be a little worse as people with poorer prognosis disease and with more co-morbidities, that may not make it into a trial, may receive treatment. It is possible that outcomes achieved in smaller centres may achieve less good results than in specialist centres taking part in a trial and following a strict protocol.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	Not specifically though across trials there is tendency for ethnic minorities to be under-represented Patients consulted by FBC are worried about less access for people in remote/rural areas.

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

EV Pembro is more active with better response rates, improved overall survival

EV Pembro maintains HRQoL and delays symptomatic progression

EV Pembro allows a subgroup of patients to be long term > 3year survivors

Toxicity profile is different but compares favourable with current SoC chemotherapy

Click or tap here to enter text.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy: ID6332

Redaction adjusted in response to NICE request; content otherwise unchanged

Addendum to company evidence submission: response to NICE requests of 16 January (v2)

February 2025

File name	Version	Contains confidential information	Date
Responses to NICE request_Severity Modifier_v2_redacted_28Feb2025	**2**	**Yes**	**28 Feb 2025**

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1 Background to addendum

NICE contacted Astellas on 16th January requesting additional evidence to support the committee's decision about the application of severity modifier. It was noted that the EAG agrees with Astellas that there may be uncertainty around the QALY estimates for the comparator treatment due to people in the trial having treatments not currently considered standard NHS practice. It was suggested that Astellas consider alternative data sources such as the systemic anti-cancer therapy (SACT) dataset to inform overall survival (OS) with the comparator platinum-based chemotherapy (PBC).

2 Summary of response

The Company's response is summarised as follows:

- In the Addendum to the Company submission, the Company considered that the 85% quality-adjusted life year (QALY) shortfall was likely to be met for the following reasons (see *3 Rationale in the Company submission)*:
    - Some subsequent post-progression therapies, which are likely to improve survival (namely enfortumab vedotin [EV] and erdafitinib), were used in the EV-302 trial but are not available on the NHS, therefore the OS of patients who receive PBC in the NHS is likely to be shorter than the patients in the EV-302 PBC arm; and
    - Due to five of the seven survival extrapolations meeting the 85% QALY shortfall criterion.
- Shorter treatment duration on avelumab maintenance in the NHS compared to the EV-302 PBC arm may also be associated with shorter OS: both the EAG clinical expert and clinical expert feedback sought by the Company indicated that the time on avelumab treatment is shorter in NHS clinical practice than in the EV-302 trial. If avelumab treatment duration is shorter in NHS clinical practice, OS rates are likely to be lower too – see *4.1 Subsequent therapies are likely to impact overall survival.*
- The clinical expert feedback indicated that taxanes are typically used in the NHS. The evidence of EV's efficacy from the EV-301 trial, and exploratory

analysis of EV-302 by subsequent therapy, support the hypothesis that OS rates of the EV-302 PBC arm are higher than in NHS clinical practice – see 4.1.2 *Impact of second subsequent therapies on OS*.

- Real-world data on long-term OS that reflects current NHS practice is not available. The use of SACT data to inform the QALY shortfall, as suggested by NICE, is not feasible because the follow-up period is currently too short to reflect the impact of avelumab availability, and such an analysis is not feasible within the timelines required to respond to NICE – see *4.2 Feasibility of using SACT data and relevance of other available real-world data*.
- The EAG's suggestion to adjust the OS extrapolation by removing the effect of unavailable treatments is not feasible as EV-302 did not collect the data needed to implement adjustment methods – see *4.3 EAG suggestion and feasibility of implementation*.
- Threshold analysis shows that, to reach the 85% QALY shortfall, the mean life expectancy of patients who receive PBC needs to be 9% lower (approximately 3 months) that what is currently predicted by both the Company's and the EAG's model – see *4.4.1 Threshold analysis on the magnitude of the reduction in predicted life expectancy to achieve 85% QALY shortfall.*
- Using alternative curves to extrapolate OS rates result in QALY shortfalls of at least 85%; for example, the generalised gamma curve results in a 85% QALY shortfall and estimates OS rates within the ranges predicted by clinical experts – see *4.4.2 Scenario analysis on OS extrapolation curves.*
- Given the likely impact of subsequent therapies and of shorter avelumab treatment duration on OS, and the small reduction in survival estimates needed to meet the 85% QALY shortfall criterion, the cost-effectiveness model is likely to overestimate OS with PBC compared to NHS clinical practice to the extent that the 85% QALY shortfall criterion would likely be met.

The responses are discussed in detail below.

3 Rationale in the Company submission

As discussed in the Company submission (see *Addendum to company evidence submission*, *5. Severity*, p31-34), there is uncertainty in the estimation of QALY shortfall and **OS rates observed in the chemotherapy arm of EV-302 are likely to overestimate OS in NHS clinical practice**, because:

- Some of subsequent therapies used in the EV-302 PBC arm are not available to patients in the NHS, namely [redacted]% of patients received EV monotherapy and [redacted]% received either sacituzumab govitecan or erdafitinib.
- Real-world evidence on long-term OS rates reflecting the current treatment pathway (where avelumab maintenance treatment is available) is currently not available, as avelumab was recommended in May 2022[1], and not enough time has passed yet to estimate long-term survival from real-world data post-avelumab recommendation.
- There is uncertainty due to the extrapolation of survival, given that, in five out of the seven parametric distributions, the relative QALY shortfall of 85% is reached.

The Company submission concluded that, for these reasons, **relative QALY shortfall of 85% was likely to be met, and the severity modifier of 1.2 should be applied.**

4 Detailed Company responses to NICE request

4.1 Subsequent therapies are likely to impact overall survival

4.1.1 Impact of avelumab time on treatment

A source of uncertainty in the QALY shortfall is related to the EAG's key issue 2, in that the time on treatment with avelumab maintenance may be shorter in clinical practice than in the EV-302 trial. As time on treatment is generally correlated with survival, **if avelumab's time on treatment is longer in EV-302 PBC arm than in clinical practice, it is likely that OS of the EV-302 PBC arm is longer too.**

The EAG reports that, according to one of their experts, avelumab is usually given for less than a year, and typically 9 months. A clinical expert consulted by the Company also noted that avelumab is usually given for less than a year, and that avelumab is discontinued due to (mainly) disease progression or (less frequently) toxicity (this clinical expert is a Professor and Consultant in Medical Oncology in a large cancer centre in England). The feedback from the EAG clinical expert and the clinical expert consulted by the Company is consistent with informal feedback from other clinical experts.

In the EV-302 trial, 30% of patients received avelumab, which is aligned to the real-world evidence available in the UK (see CS Appendix T).[2-4] Of these, [redacted]% of patients who received avelumab were on treatment at 12 months after avelumab initiation (N=[redacted] at risk) and [redacted]% were on treatment at 24 months ([redacted] patients at risk). If the avelumab time on treatment of these patients in NHS clinical practice is at most 12 months, and typically 9 months, their OS in clinical practice would likely be shorter than in EV-302 too.

The Company is not aware of a robust method to adjust survival after receiving a subsequent treatment to account for shorter time on treatment in clinical practice compared to in a clinical trial. Given the likely correlation between time on treatment and survival, it is not methodologically appropriate to only adjust treatment duration (or chose an extrapolation curve that predicts shorter treatment duration, as done in the EAG base-case) without adjusting survival too. Additionally, data on survival with avelumab outside of clinical trials is immature due to its recent NICE recommendation (see also point 4.2 below).

4.1.2 Impact of second subsequent therapies on overall survival

Almost a fifth of patients ([redacted]%, [redacted] patients) in EV-302 PBC arm received EV monotherapy as the second subsequent therapy; however, this is not available to patients in the NHS. EV-301 showed that EV monotherapy improved OS compared to chemotherapy in previously treated advanced UC: HR 0.704 (95% CI 0.581-0.852), with a median follow-up of 23.75 months. Median (95% CI) OS estimates were 12.91 months (11.01-14.92 months) and 8.94 months (8.25- 10.25 months) for

enfortumab vedotin and chemotherapy, respectively; therefore a median difference of 3.97 months (Rosenberg 2023).[5]

Erdafitinib was used by [redacted]% (N=[redacted]) of patients in EV-302 PBC arm, and it is also not available to patients in the NHS. In a Phase 3 trial, erdafitinib was shown to significantly improve median survival (12.1 months vs. 7.8 months; hazard ratio for death, 0.64; 95% confidence interval [CI], 0.47 to 0.88; P=0.005).[6] Sacituzumab govitecan was used by [redacted]% (N=[redacted]) of patients, however it did not meet its primary endpoint in a recent Phase 3 trial.[7] Therefore, its impact on OS rates of the PBC patients in the EV-302 trial is likely to be minor.

Two clinical experts were asked about the subsequent treatments in NHS clinical practice (both are Professors and Consultants in Medical Oncology in two different large cancer centres in England). Both clinical experts noted that taxanes are used in the NHS after PBC and after PD-1/L1 inhibitor (i.e., as second subsequent therapy), as EV monotherapy is not available in the NHS.

Figure 1 shows the Kaplan-Meier curves of OS by selected second subsequent therapies and for ITT. The median OS is [redacted] months (95% CI [redacted]) for patients receiving [redacted]; [redacted] months (95% CI [redacted]) for patients receiving [redacted]. However, this comparison should be interpreted with caution given that the treatment groups may not be comparable at the time of initiation of these therapies, and their treatment initiation time point may also have been different. Nevertheless, and alongside the EV-301 data, **it is supportive evidence to show that, if EV-302 patients only had taxanes available as second subsequent therapy as patients in the NHS typically do, their OS rates would likely be lower than observed in the PBC arm.**

Figure 1: EV-302 overall survival by second subsequent treatment

4.2 Feasibility of using SACT data and relevance of other available real-world data

As discussed in the Addendum to the Company Submission (see p32), to reflect the current OS rates in NHS practice, real-world data should include only patients who were treated after avelumab being recommended and followed for a minimum of 2-3 years to enable comparisons to the PBC arm in the EV-302 trial. Avelumab was recommended by NICE in May 2022.[1] Assuming 1 year for accrual of patient numbers (so up to June 2023), the earliest time point for 2 years of follow-up to have been accrued would be in mid-2025; for 5 years, it would be in mid-2028.

This does not consider time lag for data to be recorded and available for analysis. The Company has been advised that currently the data in the National Cancer Registration Dataset (on cancer diagnoses) and SACT includes cancer registrations up to the end of 2022, with follow-up up to July 2024.

Further, such an analysis would require access to patient-level data so that the relevant cohort is selected (i.e., patients with unresectable or metastatic UC who are eligible for platinum-based chemotherapy). However, the Company does not have direct access to the patient-level data in SACT, and is not aware of a method to access this data within the timeline needed by NICE.

For these reasons, **an analysis of SACT is not feasible within these timelines and, as discussed earlier, if conducted at this point in time, it would not provide the evidence to resolve this uncertainty until more follow-up is accrued.**

Furthermore, the Company is not aware of other available real-world evidence that can provide relevant evidence. To be relevant to resolve this uncertainty, real-world evidence should ideally pertain to the NHS in the UK, and after avelumab availability. Relevant to the patient population with locally advanced/metastatic UC, Cheeseman et al. included patients diagnosed between 2003-2017 and treated in the Leeds Cancer Centre, therefore before avelumab availability. This study reports 2-year survival of ~ 20% in platinum-treated locally advanced/metastatic UC patients overall, ~ 30% in the cisplatin sub-cohort, and ~ 5% in the carboplatin sub-cohort.[8] This is well below the OS rates estimated in EV-302 PBC arm at 36% (see Table 1).

4.3 EAG suggestion and feasibility of implementation

According to the EAG's preferred assumptions, the QALY shortfall is [redacted]%. The EAG suggested for the Company to explore adjusting the OS extrapolation by removing the effect of treatments unavailable in the NHS. The Company has now investigated this further, and concluded that this **is not feasible because EV-302 trial did not collect sufficient data to adjust for the effect of subsequent treatments.**

NICE TSD 24 on adjusting survival time estimates in the presence of treatment switching recommends inverse probability of censoring weights (IPCW) and two-stage estimation (TSE) to adjust for switching to subsequent treatments which do not reflect clinical practice (NICE TSD 24).[9]

Regarding the IPCW approach, and as explained by TSD 24, "*the method [IPCW] relies upon the no unmeasured confounding assumption, and therefore requires data for each patient on prognostic characteristics that influence the probability of switch and survival (or another outcome of interest). A positivity assumption is also required, which specifies that there are no confounding factors that perfectly predict switching.[3, 11]*" (page 34). This means that data needs to be available on the characteristics that predict censoring (i.e., the factors in the decision whether to use, e.g., EV as a treatment) and which are prognostic factors for survival. EV-302 collected a large range of characteristics at trial entry but only ECOG performance status was collected at the time of the second progression. However, some patient characteristics may change as patients progress. Therefore, the IPCW method is not feasible.

Regarding the TSE approach, "[it] *requires that switching only occurs at or after a disease-related "secondary baseline" time-point.[5] Often, disease progression fits the criteria of a suitable secondary baseline. The method also requires the no unmeasured confounding assumption to hold, whereby switching must be independent of potential outcomes, conditional on patient characteristics measured (and included in the model) at the secondary baseline.*" Given the limited data collected in the EV-302 trial after second progression, the TSE approach is also not feasible.

4.4 Scenario analyses

The Company has run a number of scenario analyses.

4.4.1 Threshold analysis on the magnitude of the reduction in predicted life expectancy to achieve 85% QALY shortfall

According to the Company base-case, the estimated lifetime discounted QALYs for the general population are 9.80, so the discounted QALYs with PBC should be no higher than 1.47 to reach an 85% proportional shortfall. According to the EAG base-case, the estimated lifetime discounted QALYs for the general population are 9.49 (as reported in the EAG's model), therefore the discounted QALYs with PBC should be no higher than 1.42 QALYs to reach an 85% proportional shortfall. This corresponds to a reduction in the discounted QALYs with PBC of [redacted]% in the

Company base-case (from [redacted] QALYs to 1.47 QALYs) and of [redacted]% with the EAG base-case.

From this, only the undiscounted life expectancy needed can be approximated, as the impact of discounting depends on the shape of the OS curve. Assuming that the pre-progression period and the impact of adverse events on quality of life remains unchanged, and under the Company assumptions, patients spend [redacted] months in the progression-free (PF) period, with the current discounted PF QALYs estimated to be [redacted]. Therefore, to reach 1.47 total discounted QALYs, the discounted progressive disease (PD) QALYs should be [redacted]. Knowing the current the ratio of discounted PD QALYs ([redacted]) to undiscounted PD time in months ([redacted] months), it can be approximated that patients should spend [redacted] months in PD, which makes the total required undiscounted survival equal to [redacted] months.

Therefore, **to reach the 85% QALY shortfall, the mean survival of patients who receive PBC needs to be 9% lower than predicted by the model. The results are consistent between the Company's and the EAG's base-case** (Company: [redacted] – [redacted] = [redacted] months; EAG: [redacted] – [redacted] = -[redacted] months; a mean difference of approximately 3 months).

This difference refers to mean survival, as the model calculates health outcomes in terms of the mean. Given that the distribution of survival is skewed, the mean difference is larger than the median difference, which is what is typically reported in clinical trials. For example, the difference in median OS observed in the EV-302 trial was 17.9 months (data cut-off date of 8 August 2024), while the estimated mean difference was [redacted] months according to both the Company's model and the EAG's model. Therefore, a mean difference of 3 months is likely to correspond to a much smaller median difference.

4.4.2 Scenario analysis on OS extrapolation curves

As noted in the Addendum to the Company submission (Section 5, Severity [Table 18, p34]), the criteria for the 1.2 severity modifier are met if the OS for the PBC arm is extrapolated with any other curve except for log-logistic (used by both the Company and the EAG as the base case) and lognormal. The closest extrapolation

to the base case that meets the criteria for the 1.2 severity modifier uses the generalised gamma curve. The difference in (undiscounted) OS compared to the original base-case is 3.8 months.

Figure 2 shows the Kaplan-Meier curve for OS of the PBC arm of EV-302, alongside with the log-logistic extrapolation and the generalised gamma, and the range predicted by clinical experts; and Table 1 shows the corresponding landmark OS rates. The generalised gamma curve predicts similar OS rates to the log-logistic curve at 2 and 5 years, but slightly smaller at 10 years; and the predicted OS rates are within the ranges elicited from seven clinical experts. Therefore, the generalised gamma curve could also be used to plausibly extrapolate OS, resulting in EV+P meeting the 85% QALY shortfall criterion.

Figure 2 Kaplan-Meier curve for OS of the PBC arm of EV-302, alongside with the loglogistic and generalised gamma extrapolations, and the range predicted by clinical experts

Table 1 Comparison of OS rates for PBC arm

Model	AIC	BIC	Time point		
			2 years	5 years	10 years
EV-302 PBC KM			36%	--	--
TA788, BSC, 8 UK oncologist			--	5-15%	2-7%
Astellas clinical validation, PBC, 7 clinicians (mean, range)			35% (30-45%)	11% (5-20%)	6% (0-10%)
Log-logistic	2484.83	2493.02	36%	13%	5%
Generalised gamma	2491.04	2503.33	37%	12%	3%

Notes: TA788 included a selected patient population (those not-progressing after PBC).
Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BSC, best supportive care; EV, enfortumab vedotin; KM, Kaplan-Meier; OS, overall survival; P, pembrolizumab; TA, technology appraisal; UK, United Kingdom. Table adapted from Table 2 (p10) of Addendum to Company Submission.

5 Conclusion

The cost-effectiveness model, based on the EV-302 trial, is likely to overestimate survival estimates with PBC compared to NHS clinical practice. This is because some patients in the EV-302 PBC arm used subsequent therapies which are effective, but which are not available to patients in the NHS; and because the patients who received avelumab maintenance treatment in the EV-302 trial are likely to have received it for longer than patients in the NHS. Therefore, the survival outcomes estimated based on the patients in the EV-302 PBC arm are likely to be better than those of patients in the NHS.

Real-world evidence is currently not available to inform the long-term survival of patients in the NHS, as the follow-up period post-avelumab recommendation is currently too short to be informative.

It is not feasible to reliably adjust survival of the patients in the EV-302 PBC arm to remove the effect of these subsequent therapies and of longer avelumab treatment duration, given the data collected in the EV-302 trial and the lack of real-world evidence.

Scenario analyses of the cost-effectiveness model suggest that small reductions in the projected life expectancy of patients on PBC are needed to meet the 85% QALY

shortfall (9% lower than the life expectancy currently predicted by the model; approximately 3 months). These projections can be achieved if an alternative extrapolation curve is chosen (e.g., generalised gamma). This alternative curve estimates OS rates within the ranges predicted by clinical experts, therefore it is a plausible alternative.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

External Assessment Group's critique of the company's addendum (response to NICE requests of 16 January 2025)

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1. INTRODUCTION

This document is the External Assessment Group (EAG)'s critique of the response by the company, Astellas, to the NICE requests of 16 January 2025 for the technology appraisal of enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy (ID6332). The EAG received the company's response documents on 31 January 2025.

NICE requested additional evidence to support the committee's decision about the application of the severity modifier.

In this document we summarise the company's response to each the requests made by NICE, and provide a critique of the company response to each item (Table 1).

Table 1 Summary of the company's response to the NICE requests

Number	Company comment	New data / new analyses
1	Impact of subsequent therapies on overall survival	Yes
2	The use of SACT data to inform QALY shortfall	No
3	Adjust overall survival extrapolation by removing treatments not available in the NHS	No
4	Alternative overall survival extrapolation	Yes

2. SUMMARY OF THE COMPANY'S RESPONSE AND EAG CRITIQUE

2.1 Impact of subsequent therapies on overall survival

Company summary response

1. Some subsequent post-progression therapies, which are likely to improve survival (namely enfortumab vedotin [EV] and erdafitinib), were used in the EV-302 trial but are not available on the NHS, therefore the overall survival of patients who receive platinum-based chemotherapy (PBC) in the NHS is likely to be shorter than the patients in the EV-302 PBC arm
2. Shorter treatment duration on avelumab maintenance in the NHS compared to the EV-302 PBC arm may also be associated with shorter overall survival: both the EAG clinical expert and clinical expert feedback sought by the company indicated that the time on avelumab treatment is shorter in NHS clinical practice than in the EV-302 trial. If avelumab treatment duration is shorter in NHS clinical practice, overall survival rates are likely to be lower too.
3. The clinical expert feedback indicated that taxanes are typically used in the NHS. The evidence of EV's efficacy from the EV-301 trial, and exploratory analysis of EV-302 by subsequent therapy, support the hypothesis that overall survival rates of the EV-302 PBC arm are higher than in NHS clinical practice.

EAG comment

We agree that overall survival of patients in the EV-302 PBC arm is likely to be longer than for patients receiving PBC in clinical practice in the NHS for the reasons the company stated.

1. Company Additional Evidence 31-Jan-2025, section 4.1.2 explains that in the EV-302 PBC arm:
    - [redacted] (n = [redacted]) of patients received enfortumab vedotin monotherapy as the second subsequent therapy
    - [redacted] (n = [redacted]) of patients received erdafitinib as the second subsequent therapy
    - [redacted] (n = [redacted]) of patients received sacituzumab govitecan as the second subsequent therapy

    The EAG agrees with the company's evidence that both EV monotherapy, and erdafitinib treatment, improved median overall survival time by about four months.

2. We note that the company consulted a further clinical expert (Professor and Consultant in Medical Oncology in a large cancer centre in England) who agreed with the EAG's clinical expert that avelumab therapy is typically given for less than a year in the NHS, which is shorter than in the EV-302 PBC arm.
3. We note that overall survival of patients receiving subsequent treatment with taxanes is shorter than the PBC + gemcitabine ITT population of EV-302, and shorter than for patients in the PBC + gemcitabine arm of EV-302 who received subsequent treatment with EV (Company Additional Evidence 31-Jan-2025, Figure 1). We agree that patients in the NHS, who only have taxanes available as second subsequent therapy, would likely have shorter overall survival than that observed in the PBC arm of EV-302.

Furthermore, trial participants are likely to be healthier than patients with unresectable or metastatic urothelial cancer receiving PBC in the NHS, therefore overall survival is likely to be shorter for these patients receiving PBC in the NHS. Consequently, the cost-effectiveness model is likely overestimating overall survival in the PBC arm, thus overestimating the QALYs accrued in the PBC arm, and underestimating the QALY shortfall. However, we are uncertain as to the size of the QALY gain overestimate in the PBC arm, and whether the severity modifier threshold would be reached if the overestimate was corrected.

2.2 The use of SACT data to inform QALY shortfall

Company summary response

Real-world data on long-term OS that reflects current NHS practice is not available. The use of SACT data to inform the QALY shortfall, as suggested by NICE, is not feasible because the follow-up period is currently too short to reflect the impact of avelumab availability, and such an analysis is not feasible within the timelines required to respond to NICE.

EAG comment

We acknowledge that time is needed for new treatments to be adopted into the NHS, and that as not enough time has passed for data to be available, the company cannot complete the requested analysis. We consider their response to be reasonable and have no further comments.

2.3 Adjust overall survival extrapolation by removing treatments not available in the NHS

Company summary response

The EAG's suggestion to adjust the OS extrapolation by removing the effect of unavailable treatments is not feasible as EV-302 did not collect the data needed to implement adjustment methods.

EAG comment

If these data are not available, the company cannot complete the requested analysis. We consider their response to be reasonable and have no further comments.

2.4 Alternative overall survival extrapolation

Company summary response

1. Threshold analysis shows that, to reach the 85% QALY shortfall, the mean life expectancy of patients who receive PBC needs to be 9% lower (approximately 3 months) than what is currently predicted by both the Company's and the EAG's model.
2. Using alternative curves to extrapolate OS rates result in QALY shortfalls of at least 85%; for example, the generalised gamma curve results in a 85% QALY shortfall and estimates OS rates within the ranges predicted by clinical experts.

EAG comment

We acknowledge that there is uncertainty around the estimates of 83% (company base case) and 84% (EAG base case) for the QALY shortfall. We agree that both the company and EAG base cases predict a survival difference of about three months, and that if other parametric curves are used to extrapolate overall survival (other than the lognormal and log-logistic), the severity modifier threshold is reached.

We do not object to the generalised gamma parametric curve being used to extrapolate overall survival, because the survival results fall within estimates from clinical experts (Company Additional Evidence 31-Jan-2025, Table 1). However, we note that using the generalised gamma curve to extrapolate overall survival in both model arms increases the ICER from [redacted] to [redacted] per QALY in the EAG base case scenarios (EAG report section 6.1.1, Table 35, scenario analysis). This is because survival estimates are less optimistic when using the generalised gamma extrapolation, which has a greater effect on the EV + P arm. In this case there is a 85% QALY shortfall.

3. EAG CONCLUSION

The use of subsequent therapies in the EV-302 trial, which are not used in NHS clinical practice, and the shorter duration of avelumab treatment in the NHS, means the cost-effectiveness model is likely overestimating overall survival of patients receiving PBC compared with NHS clinical practice. However, the size of this overestimate, and whether the severity modifier threshold would be reached if the overestimate was corrected, is unknown.

We consider using the generalised gamma to extrapolate overall survival in both model arms to be reasonable, but note that this increases the ICER for EV + P compared with PBC + gemcitabine.