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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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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.

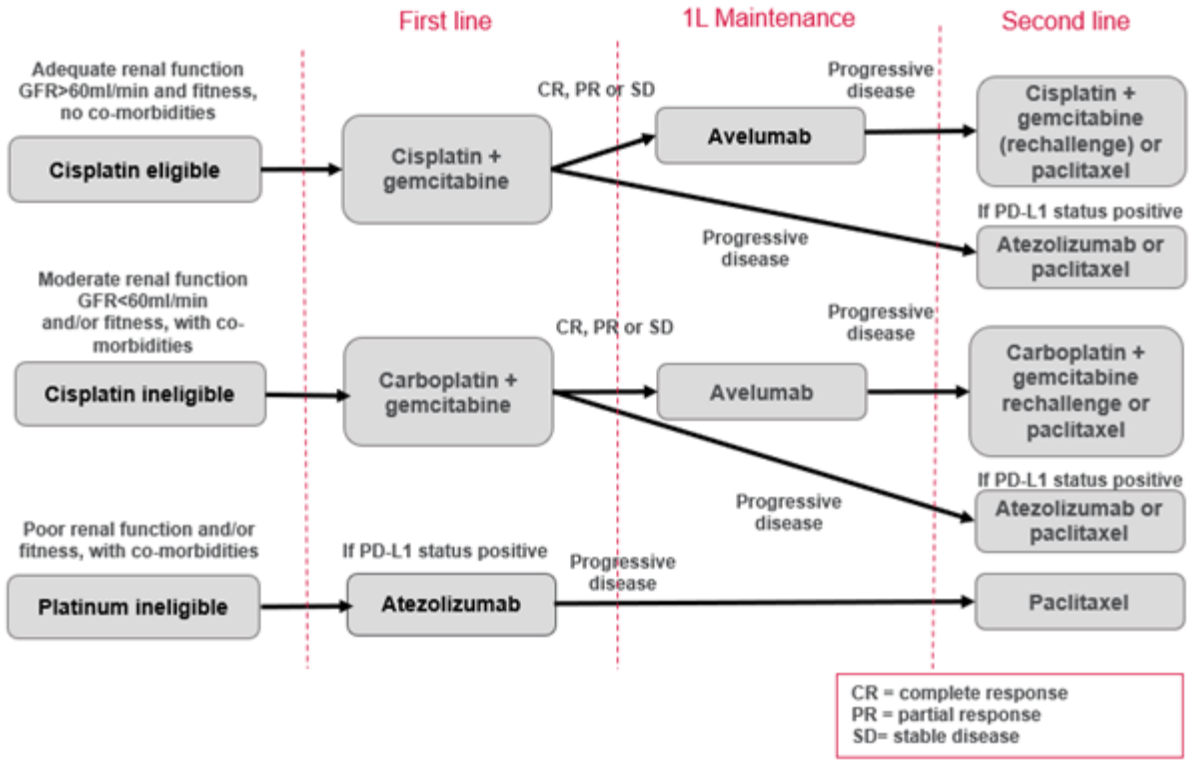

Figure 1 Current treatment of unresectable or metastatic urothelial cancer in NHS practice in England

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).

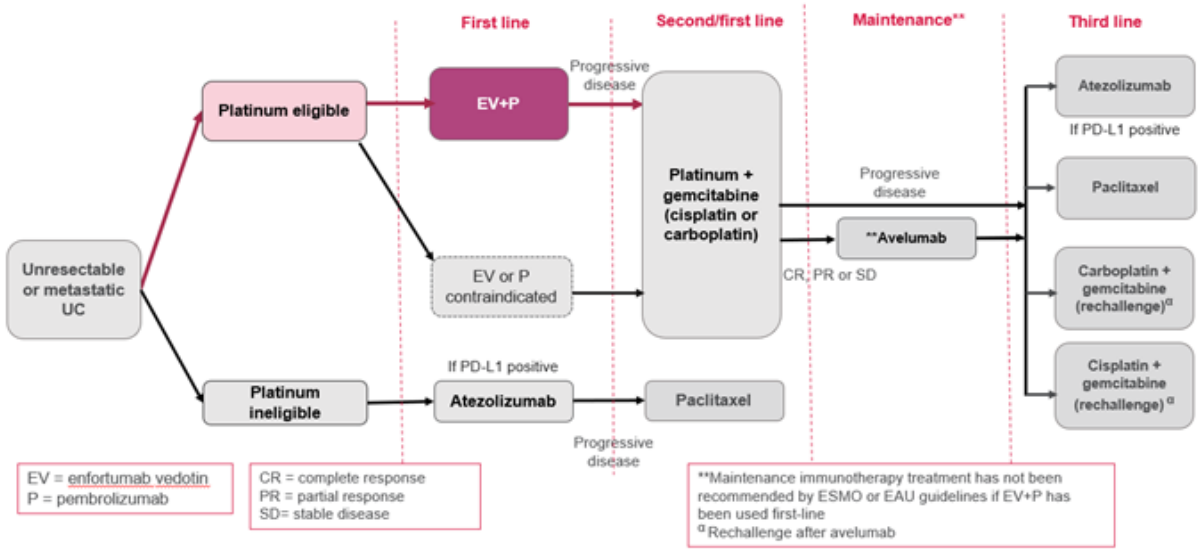

Figure 2 Proposed position of enfortumab vedotin combined with pembrolizumab in the treatment pathway

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.

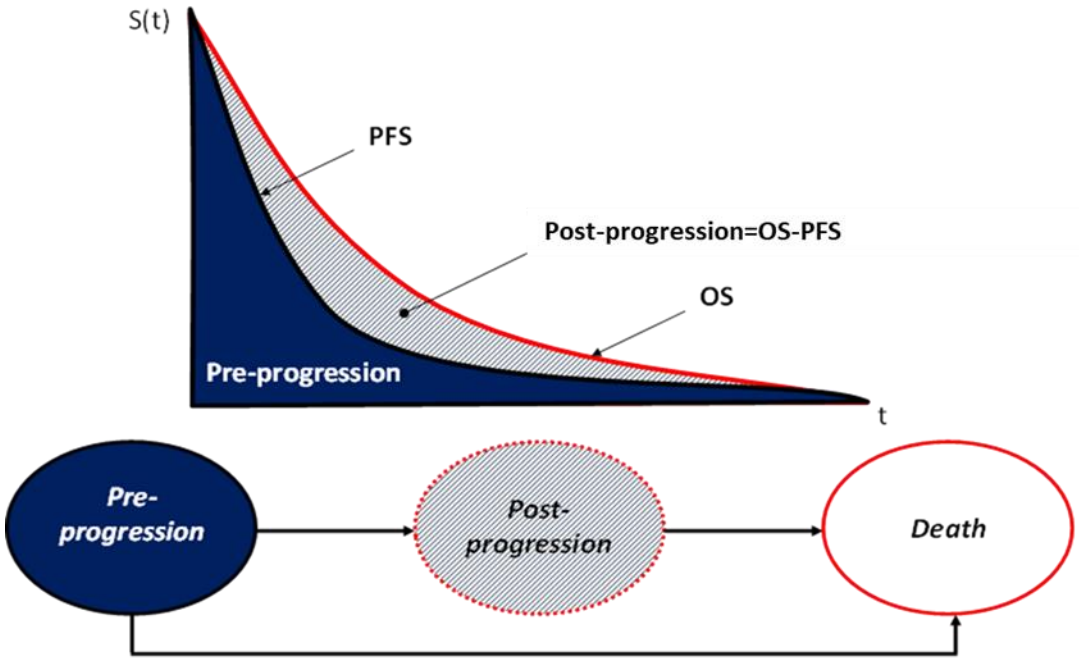

Figure 3 Partitioned survival model structure, company model

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