Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende enfortumab vedotin til fremskreden urotelialkræft efter behandling med platinbaseret kemoterapi og en PD-1/L1-hæmmer

Vers. 2.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. enfortumab vedotin
2. Ansøgers endelige ansøgning vedr. enfortumab vedotin

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04.07.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	Revurdering august 2024
Leverandør	Astellas
Lægemiddel	Padcev (enfortumab vedotin)
Ansøgt indikation	Padcev (enfortumab vedotin) som monoterapi er indiceret til behandling af voksne patienter med lokalt fremskreden eller metastatisk urotelial cancer, der tidligere har modtaget en platinbaseret kemoterapi og en hæmmer mod programmeret celledød receptor-1 (PD-1) eller programmeret celledød ligand 1 (PD-L1)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Padcev (enfortumab vedotin):

Tabel 1: Forhandlingsresultat

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

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

Prisen kan være gældende hurtigst muligt efter mødet i Medicinrådet og vil løbe indtil 31.12.2024.

[redacted]

Information fra forhandlingen

[redacted]

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler, som indgår i Medicinrådets vurderingsrapport.

Tabel 2: Lægemiddeludgifter pr. patient på udvalgte sammenlignelige lægemidler (fra MR vurderingsrapport)

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift i perioden (SAIP, DKK)
Padcev	30 mg	1 stk.	1,25 mg/kg på dag 1,8 og 15 i 28-dages cyklusser, iv*	[redacted]	[redacted]
Javlor (vinflunin)	25 mg/ml	10 ml	320 mg/m^2 hver 3. uge/ iv***	8.891,80	209.761****

* Gennemsnitsvægt 73,9 kg (se Medicinrådets vurderingsrapport)
**Behandlingsperioden for Padcev (enfortumab vedotin) er 8,3 måneder (se Medicinrådets vurderingsrapport)
*** Gennemsnitligt overfladeareal på 1,9 m^2 (se Medicinrådets vurderingsrapport)
****Behandlingsperioden for Javlor (vinflunin) er 6,7 måneder (se Medicinrådets vurderingsrapport)

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Ikke anbefalet		Link til vurdering
England	Ikke vurderet	Citat NICE: *"Astellas did not provide an evidence submission. We will review this decision if the company decides to make a submission."*	Link til vurdering
Sverige	Anbefalet		Link til vurdering

Konklusion

[redacted]

Application for the assessment of enfortumab vedotin (EV)

– As monotherapy for treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1(PD-1/L1) inhibitor

Version 2.0

Contact information

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Tables and Figures

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Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse Events
AIC	Akaike information criterion
AIP	Apotekernes indkøbspris
ANC	Absolute neutrophil count
BC	Bladder cancer
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BSA	Body surface area
BSC	Best supportive care
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CPI	Checkpoint inhibitor
CR	Complete response
CT	Computed tomography
D	Docetaxel
DaBlaCa	Danish Bladder Cancer Group
DCR	Disease control rate
DKK	Danish Kroner
DMC	Danish Medicines Council
DoR	Duration of response
DoT	Duration of treatment
DP	Docetaxel and paclitaxel
DPV	Docetaxel, paclitaxel, or vinflunine
DSA	Deterministic sensitivity analysis
EAU	European Association of Urology
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ED	Emergency department
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life-Core 30
EPAR	European public assessment report
EQ-5D-5L	European Quality of life – 5 Dimensions- 5 levels
ESMO	European Society for Medical Oncology
EV	Enfortumab vedotin
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized estimating equation
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values

HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent data monitoring committee
IgG1	Immunoglobulin G1
IQR	Interquartile range
IRT	Interactive response technology
ITT	Intention-to-treat
KM	Kaplan-Meier
La/mUC	Locally advanced or metastatic urothelial carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	Muscle-invasive bladder cancer
MMAE	Monomethyl auristatin E
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
n	Sample size
NA	Not applicable
NA	Not available
NC	Not calculable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NICE	National Institute for Health and Care Excellence
NMIBC	Non-muscle invasive bladder cancer
OR	Overall response
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
P	Paclitaxel
PD	Progressive disease
PD-1	Programmed death receptor 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PFS1	PFS on study therapy
PH	Proportional hazard
PR	Partial response
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-years
QoL	Quality of life
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RES	Response evaluable set
RR	Relative risk
SAF	Safety analysis set
SE	Standard error

SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TNM	Tumor, Node & Metastasis
TRAE	Treatment-related adverse event
TURBT	Transurethral resection of a bladder tumor
UC	Urothelial carcinoma
UK	United Kingdom
US	United States
UTC	Urinary tract cancer
V	Vinflunine
VAS	Visual analog scale
WHO	World Health Organization

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	PADCEV™
Generic name	Enfortumab Vedotin (EV) [1]
Therapeutic indication as defined by EMA	PADCEV™ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1(PD-1/L1) inhibitor. [1]
Marketing authorization holder in Denmark	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden Holland
ATC code	ATC code L01FX13. [1]
Combination therapy and/or co-medication	Not applicable
Date of EC approval	13/04/2022
Orphan drug designation	Not applicable
Other therapeutic indications approved by EMA	Not applicable
Dispensing group	BEGR
Packaging – types, sizes/number of units, and concentrations	20 mg, powder for concentrate for solution for infusion, 1 vial, after reconstitution the concentration will be 10 mg/ml. [1] 30 mg, powder for concentrate for solution for infusion, 1 vial, after reconstitution the concentration will be 10 mg/ml. [1]

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	PADCEV™ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1(PD-1/L1) inhibitor. [1]
Dosage regiment and administration	The recommended dose is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle, until disease progression or unacceptable toxicity. [1]
Choice of comparator	Vinflunine (V)is, as the treatment recommended in the DMC treatment guideline, considered the most relevant comparator for this application. To reflect other national guidelines Docetaxel (D) and Paclitaxel (P) will also be presented as comparators but are of less interest due to the limited use in Danish clinical practice.
Prognosis with current treatment (comparator)	Median OS was 9.5 months for V and 9.0 months for DPV in the head-to-head study vs Enfortumab Vedotin (EV) [15]
Type of evidence for the clinical evaluation	Head-to-head study EV vs DPV, which also include subgroup analysis of EV vs preselected vinflunine patients
Most important efficacy endpoints (Difference/gain compared to comparator)	**OS**: 12.91 vs DPV 8.94 months for EV and DPV (XXXXXXXX months for EV vs V) **PFS**: 5.55 vs 3.71 months for EV and DPV (XXXXXXXX months for EV and V) **ORR:** 41.3% vs 18.69% for EV and DPV (XXXXXXX months for EV and V)
Most important serious adverse events for the intervention and comparator	Of special interest adverse events, treatment-related skin reactions occurred in 47.3% of patients receiving EV and 15.8% of patients receiving DPV; peripheral neuropathy occurred in 48.0% versus 31.6%, respectively, and hyperglycemia in 6.8% versus 0.3%. Adverse events were manageable.
Impact on health-related quality of life	The humanistic value of EV was assessed using the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 (EORTC QLQ-C30), and the European Quality of life – 5 Dimensions- 5 levels (EQ-5D-5L). EQ-5D-5L The assessment showed that patients treated with EV maintained quality of life (QoL) and had less variability in QoL compared with chemotherapy, with confirmed clinically meaningful.

Summary	
	Pre-progression - EV: Mean XXXXXXXXXXXXXX Pre-progression - V: Mean XXXXXXXXXXXXXX Post-progression - EV and V: Mean XXXXXXXXXXXXXX Health economic model: EQ-5D-5L result and comment above
Type of economic analysis that is submitted	The cost-effectiveness analysis (CEA) was conducted using a three-state partitioned survival model structure from a limited societal perspective in accordance with DMC's guidance.
Data sources used to model the clinical effects	Head-to-head data from EV-301 with 24 months FU data for EV vs preselected V patients (OS, PFS, DoT, AE)
Data sources used to model the health-related quality of life	EQ-5D-5L data from EV-301 trial and the Danish EQ-5D-5L value set
Life years gained	XXXX incremental LY XXXXXXXXX
QALYs gained	XXXX incremental QALY XXXXXXXXX
Incremental costs	XXXXXXXXX DKK
ICER (DKK/QALY)	XXXXXXXXX DKK/QALY
Uncertainty associated with the ICER estimate	[Describe the model assumptions with the largest overall impact on the incremental costs and QALY gain]
Number of eligible patients in Denmark	Incidence: 25-48 Prevalence: 25-48
Budget impact (in year 5)	XXXXXXXXXXXXXX (based on 48 patients with 100% uptake)

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

3.1 The medical condition

Urothelial carcinoma (UC) is the most common type of bladder cancer (BC), accounting for more than 90% of all cases of BC [24,25]. UCs originate in the transitional cells in the inner lining of the bladder, urethra, ureter, or renal pelvis. Even though UCs are not confined exclusively to the

bladder and can be found in other parts of the urinary tract, more than 90% of UCs originate in the bladder. [6,24–26]

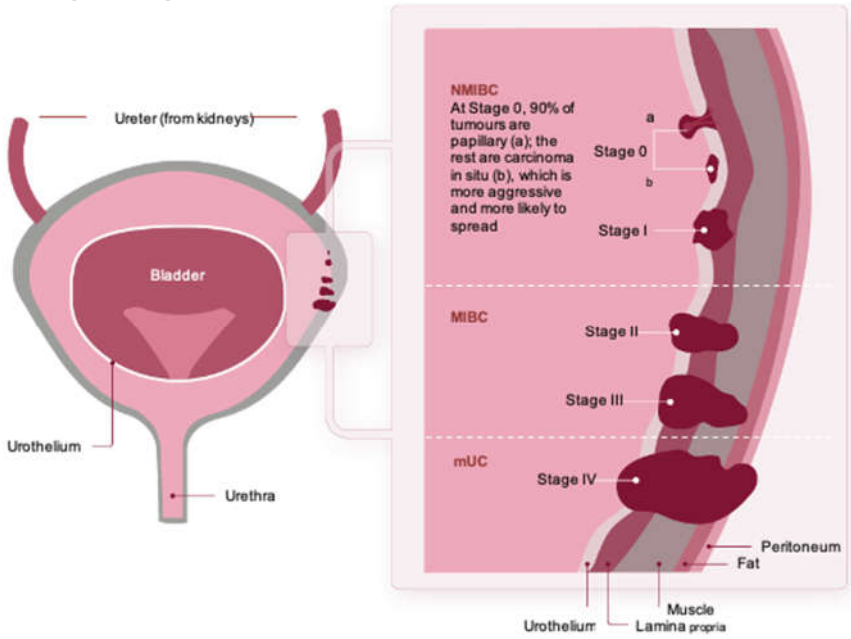


Figure 1. Staging of urothelial carcinoma*.
* Figure adapted from Bedirk, 2017
MIBC= Muscle-invasive bladder cancer; mUC= metastatic urothelial cancer; NMIBC= Non-muscular invasive bladder cancer.
Sources: [30]

UC is usually characterized clinically by the extent of invasion and can be non-muscle invasive (NMIBC), muscle-invasive (MIBC), or metastatic [27]. A disease that involves regional metastasis is referred to as locally advanced [7]. At presentation, approximately 70% of patients have NMIBC, with MIBC and metastatic UC representing approximately 20% and 10% of newly diagnosed BC cases, respectively [27,28]. Pathological staging is according to the Tumor, Node, Metastasis (TNM) classification based on the primary tumor size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M). Information on TNM is then combined to assign overall staging for the disease. [29] Figure 1 illustrates the staging of UC and is adapted from Bedirk, 2017 [30].

Risk factors

The most common risk factor for BC is smoking; tobacco smoking increases the risk, progression, and development of BC. Cigarette chemicals that are excreted in the urine can damage the lining of the bladder [30] . A United States (US) study with a 10-year follow-up period (N=466,000) found that the risk of BC was 2.22-fold higher in former smokers and 4.06-fold higher in current smokers compared with non-smokers [32]. A meta-analysis of 83 studies found that the pooled relative risk (RR) of BC in current smokers vs individuals who had never smoked was 3.47 (95% confidence interval (CI): 3.07, 3.91) and was 2.04 (95% CI: 1.85, 2.25) for ex-smokers compared with people who had never smoked [5].

Other common risk factors for BC include age and gender [8,33]. The incidence of BC increases with age, and age over 45 years is a risk factor for BC [33]. The median age at diagnosis in the US is

72 years, reflecting the fact that BC is most frequently diagnosed in individuals aged 65–84 years, according to data from the Surveillance, Epidemiology and End Results Program (2011–2015) [34]. Similarly, a Danish real-world study reported a median age of 69 years (63-75) in the baseline characteristics of a metastatic UC cohort initiating first-line chemotherapy [10]. Being male is also a risk factor for BC; the incidence of BC is almost three times higher in men than women [8]. This is supported by statistics reported in Denmark by NORDCAN (Cancer statistics for the Nordic countries) in 2018, where approximately 73% of patients with BC or other urinary tract cancers (UTC) were male [8].

Diagnosis and clinical presentation

Several tests and procedures are used to diagnose BC. It usually includes a general physical examination, urine cytology to look for abnormal cells, and cystoscopy. Cystoscopy is the gold standard for initial diagnosis and staging as it allows visual inspection of the bladder to determine the need for biopsy or surgery. [35,36] If abnormal cells are found, treatment might include transurethral resection of a bladder tumor (TURBT). Imaging tests may also be used to determine whether the tumor has metastasized; computed tomography (CT) is considered most appropriate to determine tumor size and identify large lymph nodes while magnetic resonance imaging (MRI) is useful for identifying MIBC and enlarged lymph nodes [36,37].

Bellmunt risk scores can be used to classify the patient's prognosis. These scores range from 0 to 3 according to the presence of the following risk factors: a hemoglobin level of less than 10 g per deciliter, an Eastern Cooperative Oncology Group Performance Status score (ECOG PS) greater than 0, and the presence of liver metastases. [15] Other prognostic risk factors include the presence of other visceral metastases, age, and stage of disease [34,38–41].

Patients with UC often present with urinary symptoms (polyuria, dysuria, urinary retention, and hematuria), and lower back or abdominal pain. In addition, patients with metastatic disease may also experience fatigue, weight loss, appetite loss, and/or pain specific to the site of metastasis. Patients are impacted by worsening physical function, role function, pain, and overall quality of life (QoL) as metastatic UC progresses. [4]

Prognosis and unmet need

A Danish study assessed the real-world treatment patterns and outcomes of patients with locally advanced, unresectable, and metastatic UTC initiating 1st line chemotherapy. The median overall survival (OS) for 1st line chemotherapy was 14 months for cisplatin-based chemotherapy and 9.8 months for carboplatin-based chemotherapy. [10] For 1st line treatment with atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, the median OS is assessed to be 15.9 months [42]. Pembrolizumab for 2nd line treatment demonstrates a median OS of 10.3 months, whereas vinflunine (V) for 2nd line therapy demonstrates a median OS of 6.9 months [43,44]. A study from 2020 reported that avelumab maintenance therapy after 1st line treatment demonstrated a median OS of 21.4 months [45]. Immunotherapy has changed the field of general oncology and further exploration of immunotherapeutics has, among other things, led to the development of a novel post-immunotherapy, enfortumab vedotin (EV) for the treatment of advanced UC. The need for further exploring the field of immunotherapy stands and is necessary to keep improving the QoL and survival for patients with cancer. As in other cancers, UC has a high frequency of mutations and despite the introduction of immunotherapy with checkpoint inhibitors

(programmed death receptor 1 (PD-1)/PD-L1 inhibitor), approximately 80% of patients do not achieve a response with treatment. [11]

There are currently no standard therapies indicated for patients who are progressing after platinum-containing chemotherapy and PD-1/L1 inhibitors. However V, and taxanes (docetaxel (D) and paclitaxel (P) are, despite a lack of strong evidence, widely used for treatment in 2nd line, according to clinical guidelines. [4,9,43,46] As these chemotherapies are not indicated for the treatment of UC in 2nd line after maintenance treatment with avelumab, the use is off-label [47–49]. There is an unmet need for treatment options in the post-platinum-containing chemotherapy and PD-1/L1 inhibitor treatment setting for patients with locally advanced or metastatic urothelial cancer (la/mUC) that can prolong life, offer pain palliation, and improve the overall QoL. Among the small proportion of patients who receive treatment in the post-platinum chemotherapy and post-PD-1/L1 inhibitor setting, the options are limited and the outcomes are poor. [11,23]

3.2 Patient population

There is limited published data on the epidemiology of la/mUC with few studies and databases containing data specific to this population. As such, data for BC are considered a good proxy, given that UC accounts for approximately 90% of BC cases. BC is the 9th most common cancer worldwide, with 614,000 newly diagnosed cases in 2022 [50]. In the years 2017-2021, an average of 2,300 new cases and 600 deaths related to BC were reported in Denmark [8]. Due to the limited amount of published epidemiology data for BC with few studies and databases containing data specific to this population, it has not been possible to identify an exact prevalence for the last 5 years in Denmark [51]. However, in 2021 it was estimated that 24,500 people in Denmark were living with a diagnosis of BC or UC (Table 1) [8]. Further, a Danish study in a real-world setting reported that approximately 1100 patients are diagnosed with UTC in Denmark every year, (of which 3 in 4 are men. The study further reported a median age of 69 (Interquartile range (IQR), 63-75) years at the initiation of 1st line chemotherapy. [10]

Table 1. Incidence, prevalence, death of bladder cancer in Denmark in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	2,340	2,340	2,340	2,340	2,340
Prevalence in Denmark	24,476	24,476	24,476	24,476	24,476
Death	552	552	552	552	552

Source: Nordcan average data 2017-2021 [8]

EV as monotherapy is indicated for the treatment of adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor [3]. The incident population, post-platinum, and post-PD1/L1 eligible for EV was estimated by Astellas to be within the range of 25-48 patients (Table 2). The range was set based on input from expert in the Danish Medicines Council (DMC) at the dialogue meeting held on August 24th, 2021, and a Danish population-based, medical chart review. The eligible pool of patients on EV has not changed in this application.

The DMC expert estimated that at least 25 patients per year would be eligible for EV. This estimate was based on the DMC assessment of Avelumab, published in June 2021, where the total patient population with la/mUC was reported to be approximately 150 patients a year in Denmark [9]. In addition, it was expected, that approximately 50% would progress to 2nd line and that at least 1/3 of these would be eligible for EV – equivalent to at least 25 patients per year.

The Danish population-based, medical chart review assessed the real-world treatment patterns and overall survival in la/mUC patients treated with chemotherapy in Denmark in the pre-immunotherapy era [10]. Based on a 952-patient cohort, 303 (31.8%) received 2nd line treatment, primarily V. Based on the incidence of 150 patients and the ~32% patients on 2nd line treatment approximately 48 patients would be eligible for treatment with EV per year in Denmark [9,10]. The calculation is based on a population evaluated prior to the approval of immune therapy for the cisplatin-ineligible patients [10]. Thus, the assumptions are that the eligible patient number is somewhere within the range of 25-48 [9,10].

Table 2. Estimated number of patients eligible to receive treatment with enfortumab vedotin*

Year	2024	2025	2026	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	25-48	25-48	25-48	25-48	25-48

* For patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor

3.2.1 Patient populations relevant for this assessment

In summary, the patient population relevant for this assessment is adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor [3]. In Denmark, the population indicated for the treatment with EV is estimated to include 25-48 patients per year. The estimate on EV is not taking into account future indications for EV.

3.3 Current treatment options

The European Association of Urology (EAU) guideline was updated 2023 and include the recommendation of avelumab as monotherapy for 1st line maintenance treatment of adult patients with la/mUC who are progression-free following platinum-based chemotherapy [4]. In Denmark, two treatment algorithms for the treatment of la/mUC exist. One guideline is defined by the Danish Bladder Cancer Group (DaBlaCa) and was updated in 2023. The other guideline was defined by the DMC in the assessment report of avelumab for maintenance treatment of UC and was published in June 2021 [9,12]. This application is primarily based on the treatment guideline defined by the DMC, but the guideline defined by the DaBlaCa has been consulted for the mapping of the current treatment options.

The Danish treatment guidelines are overall divided into three groups of patients. Cisplatin-eligible patients, cisplatin-ineligible patients with negative PD-L1 biomarker expression, and cisplatin-ineligible patients with positive PD-L1 biomarker [9]. Around 30–50% of patients with mUC are ineligible to receive cisplatin-based chemotherapy due to age or comorbidities [4,12].

The recommended 1st line treatment for cisplatin-eligible patients is cisplatin [4,9,12]. The cisplatin-ineligible patients with negative PD-L1 biomarker are treated with carboplatin in combination with gemcitabine or gemcitabine monotherapy [4,9,12]. Cisplatin-ineligible patients with positive PD-L1 biomarker expression can be treated with carboplatin in combination with gemcitabine, gemcitabine monotherapy, or immunotherapy with the checkpoint inhibitors pembrolizumab or atezolizumab [9]. The choice of 1st line treatment for cisplatin-ineligible patients with positive PD-L1 biomarker expression is based on an individual assessment, since not all patients are eligible for chemotherapy with carboplatin and/or gemcitabine [9].

Since June 2021 the checkpoint inhibitor avelumab is recommended in Denmark as maintenance treatment for patients who are progression-free following platinum-based chemotherapy. This includes the cisplatin-eligible patients, cisplatin-ineligible patients with negative PD-L1 biomarker expression, and the cisplatin-ineligible patients with positive PD-L1 biomarkers, who have been treated with chemotherapy. Cisplatin-ineligible patients with positive PD-L1 biomarkers, who have been treated with chemotherapy also have the option to switch to immunotherapy. [9]

The 2nd line treatment initiated at disease progression after 1st line treatment and maintenance treatment is individual and could be V or re-induction of platinum-based chemotherapy. [9]

Among the small proportion of patients who receive treatment in 2nd line, the options are limited and the outcomes are poor [10,11,15]. Until recently, there have been no specific clinical trials after 1st line treatment in UC [11,15,43]. Previously, the efficacy of immunotherapy after the failure of cisplatin-based treatment have been assessed in patients who have received several lines of prior treatments, however a phase 3 trial of vinflunine plus best supportive care compared with best supportive care exclusively examined patients who previously received 1st line treatment [4,43,52]. In Denmark, the therapies D and P are also recommended for 2nd line treatment by the DaBlaCa but are, according to experts, not widely used in Danish clinical practice [9,12]. The current treatment algorithm for UC was confirmed by the DMC at the dialogue meeting and an overview of the algorithm is provided in Figure 2 [9].

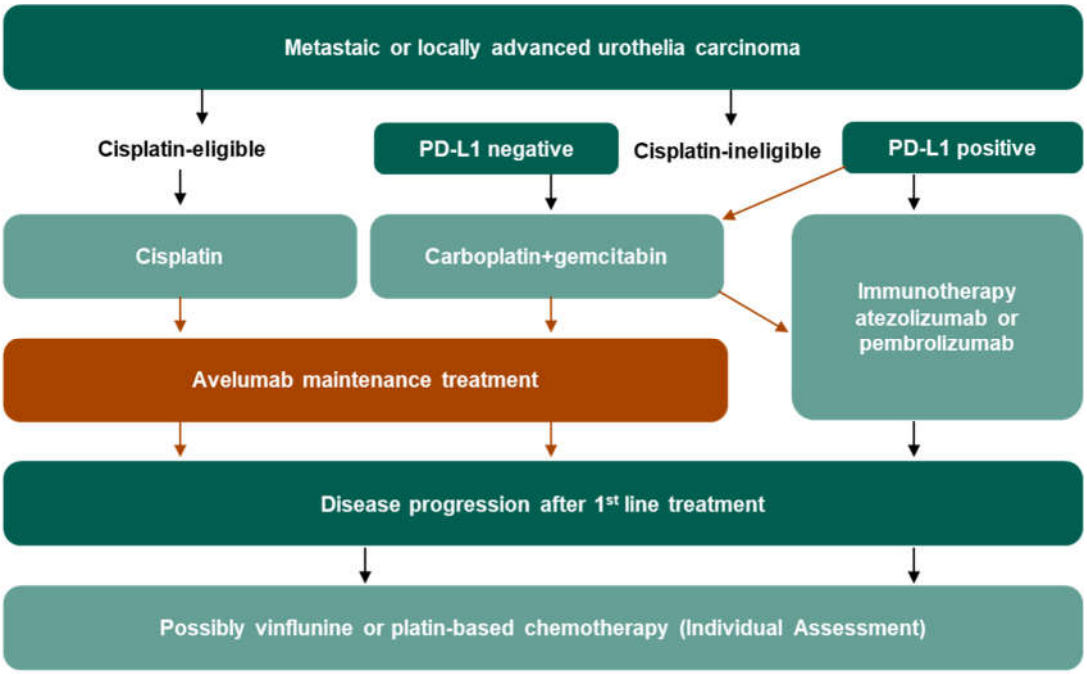


Figure 2. Current treatment algorithm for UC in Denmark, adapted from the appendix of the DMC assessment of avelumab as maintenance treatment for UC.

PD-L1= programmed death-ligand 1

Source: [9]

3.4 The intervention

PADCEV™ is the brand name of the intervention presented in this application, but the abbreviation of the substance "EV" (Enfortumab Vedotin) will be used throughout the application.

EV is the first antibody-drug conjugate (ADC) approved for use in locally advanced or metastatic urothelial cancer (la/mUC). EV is an ADC targeting Nectin-4, an adhesion protein located on the surface of the urothelial cancer cells. It is comprised of a fully human Immunoglobulin G1 (IgG1)-kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of EV is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. The release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death. MMAE released from EV targeted cells can diffuse into nearby Nectin-4 low-expressing cells resulting in cytotoxic cell death.

EMA approved EV the 13 April 2022 as a monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy. A type II indication extension variation was submitted to EMA 8 January 2024 to request a new indication to Padcev, supported by data from the EV302/KNA39 study. The proposed EU indication for Padcev is "Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy". A separate Type II variation was submitted in

parallel to the EMA by Merck Sharp & Dohme B.V. to extend the indication of Keytruda (pembrolizumab).

This is an application for reassessment of the approved monotherapy indication. The first assessment of EV was led to a negative recommendation by DMC the 28th of September 2022. The 5th of January 2024 DMC approved EV for a new assessment as a monotherapy treatment within 2-3 line for patients with La/mUC.

Table 3. Overview of PADCEV™ – Enfortumab Vedotin (EV)

Overview of intervention	
Therapeutic indication relevant for the assessment	PADCEV™ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1(PD-1/L1) inhibitor.
Method of administration	Intravenous infusion
Dosing	The recommended dose of EV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered on Days 1, 8, and 15 of a 28-day cycle.
Dosing in the health economic model (including relative dose intensity)	Patient level data from EV-301. Relative dose intensity: 78.33%
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Until disease progression or unacceptable toxicity
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored starting with the first cycle and throughout treatment for skin reactions, for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction, or discontinuation of EV, pneumonitis/Interstitial lung disease, hyperglycemia and for ocular disorders. There is no known antidote for overdosage with EV. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate taking into consideration the half-life of 3.3 days (antibody-drug conjugate (ADC)) and 2.5 days (monomethyl auristatin E (MMAE)).
Need for diagnostics or other tests	No
Package size(s)	20 mg, powder for concentrate for solution for infusion, 1 vial, after reconstitution the concentration will be 10 mg/ml. 30 mg, powder for concentrate for solution for infusion, 1 vial, after reconstitution the concentration will be 10 mg/ml.

ADC= antibody-drug conjugate; monomethyl auristatin E= MMAE;

Sources: [1]

3.4.1 The intervention in relation to Danish clinical practice

EV is, based on the discussion with the DMC at the dialogue meeting, expected to replace vinflunine (V) in the treatment algorithm for the treatment of UC. The treatment algorithm is still applicable for this application. Figure 3 provides an overview of the treatment algorithm in Denmark if EV replaces V in the guideline. The clinical expert advising the DMC suggested at the dialogue meeting that EV should replace V in 2nd line. The assumption from the expert was that V will not be used in 2nd line after the introduction of EV, as V is only indicated after failure of prior platinum-containing regimen and not after having received a PD-1/L1 inhibitor and platinum-containing chemotherapy. Thus, the current placement of V in the DMC guideline is considered off-label, whereas the placement of EV in 2nd line after PD-1/L1 inhibitor and platinum-containing chemotherapy agrees with the label of EV and this placement of EV as standard of care has been stated in the recent European Society for Medical Oncology (ESMO) guideline with evidence grade 1, A [1,9,13,14].

The patients who will be considered eligible for EV include cisplatin-eligible patients and cisplatin-ineligible patients with negative PD-1/L1 biomarker who have received a PD-1/L1 inhibitor and platinum-containing chemotherapy. It also includes cisplatin-ineligible patients with positive PD-1/L1 biomarker, who have been treated with chemotherapy followed by maintenance treatment with avelumab or immunotherapy with pembrolizumab or atezolizumab. Thus, the only patients who are ineligible for treatment with EV are cisplatin-ineligible patients with positive PD-1/L1 biomarkers who are unfit for chemotherapy or who only receive immunotherapy.

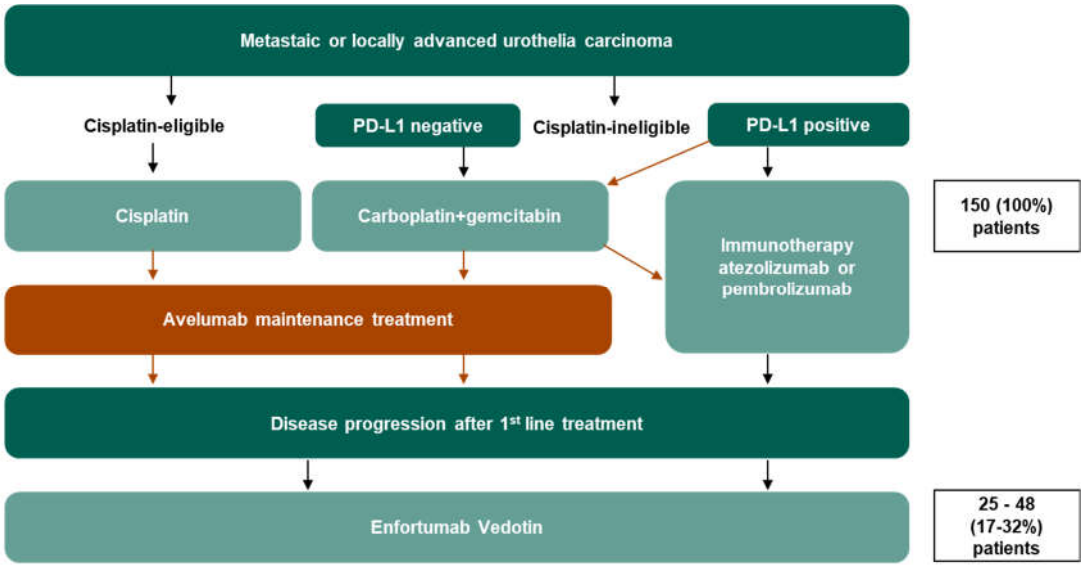


Figure 3. Treatment algorithm with possible placement of EV in guideline, including number of patients eligible for EV.

Adapted from the la/mUC treatment algorithm in Denmark from the Danish Medicines Council and updated based on expert opinion and Astellas' estimates for eligible EV patients.
* Cisplatin-ineligible patients with positive PD-1/L1 biomarker who are unfit for chemotherapy or who have only received immunotherapy are not eligible for treatment with EV.
PD-L1= programmed death-ligand 1

Source: [9]

3.5 Choice of comparator(s)

According to the current treatment algorithm defined by the DMC, V is the only pharmaceutical recommended for treatment of the indication similar to that of EV [9]. V is indicated for adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of prior platinum-containing regimen, where EV is indicated for adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor [1,3,13]. Another guideline, defined by the DaBlaCa, lists taxanes (D and P) as possible treatments [12]. However, taxanes are, according to experts not widely used in Danish clinical practice for this indication but are considered best supportive care by the DMC [9].

Thus, V is, as the treatment recommended in the DMC treatment guideline, considered the most relevant comparator for this application. Accordingly, the clinical expert advising the DMC at the dialogue meeting also designated V as the most relevant comparator. To reflect other national guidelines Docetaxel (D) and Paclitaxel (P) will also be presented as comparators but are of less interest due to the limited use in Danish clinical practice. There are no changes in international guidelines, treatment recommendations in Denmark or clinical practice between May 2022 and February 2024.

Table 4. Description of vinflunine.

Vinflunine	
Generic name (ATC-code)	Vinflunine (L01CA05)
Mode of action	Vinflunine binds to tubulin at or near the vinca binding sites inhibiting its polymerization into microtubules, which results in treadmilling suppression, disruption of microtubule dynamic, mitotic arrest, and apoptosis.
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate).
Dosing	The recommended dose is 320 mg/m² vinflunine as a 20-minute intravenous infusion every 3 weeks. In case of the World Health Organization (WHO) ECOG PS of 1 or PS of 0 and prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.
Dosing in the health economic model	Patient level data from EV-301. Relative dose intensity: 91.05%
Method of administration	Javlor must be diluted prior to administration. Javlor is for single use only and MUST ONLY be administered intravenously. It should be administered by a 20-minute intravenous infusion and NOT be given by rapid intravenous bolus. Either peripheral lines or a central catheter can be used for vinflunine administration. When infused through a peripheral vein, vinflunine can induce venous irritation. In case of small or sclerosed veins, lymphoedema or recent venipuncture of the same vein, the use of a central catheter may be preferred. To avoid extravasations it is important to be sure that the needle is correctly introduced before starting the infusion.
Should the pharmaceutical be administered with other medicines?	In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration
Treatment duration/ criteria for end of treatment	Not specified
Necessary monitoring, both during administration and during the treatment period	Before each cycle, adequate monitoring of complete blood counts should be conducted to verify the absolute neutrophil count (ANC), platelets, and hemoglobin as neutropenia, thrombocytopenia, and anemia are frequent adverse reactions of vinflunine.
Need for diagnostics or other tests	No need
Packaging	25 mg/ml x 2 ml or 25 mg/ml x 10 ml

ANC= absolute neutrophil count; ATC= Anatomical therapeutic classification; ECOG PS= Eastern Cooperative Oncology Group Performance Status score; WHO= World Health Organization

Sources: [13,49,54,55]

Table 5. Description of docetaxel.

Docetaxel	
Generic name (ATC-code)	Docetaxel (L01CD02) [47]
Mode of action	Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.
Pharmaceutical form	Concentrate for solution for infusion.
Dosing	Not specified for UC in the European Public Assessment Report (EPAR) or the Summary of Product Characteristics (SmPC)
Dosing in the health economic model	Patient level data from EV-301. Relative dose intensity: 91.73%
Method of administration	Infusion.
Dosing	Not specified for UC in EPAR or SmPC
Should the pharma-ceutical be administered with other medicines?	Due to the significant risk of hypersensitivity reactions and fluid retention, all patients should be premedicated with oral corticosteroids.[
Treatment duration/ criteria for end of treatment	Not specified for UC in EPAR or SmPC
Necessary monitoring, both during administration and during the treatment period	Frequent monitoring of complete blood counts should be conducted on all patients receiving docetaxel. Patients should be closely monitored for early manifestations of serious gastrointestinal toxicity. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop a hypersensitivity reaction to docetaxel, including a more severe hypersensitivity reaction. These patients should be closely monitored during the initiation of docetaxel therapy. Patients should be informed about the signs and symptoms of serious skin manifestations and be closely monitored. Patients with severe fluid retention such as pleural effusion, pericardial effusion, and ascites should be monitored closely. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Patients should be monitored for second primary malignancies. Patients at risk of tumor lysis syndrome (e.g., with renal impairment, hyperuricemia, bulky tumor, rapid progression) should be closely monitored. Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow-up period. In case of overdose, the patient should be kept in a specialized unit and vital functions closely monitored.[47]
Need for diagnostics	No
Packaging	20 mg/ml x 1 ml, x 4ml or 8 ml

ATC= Anatomical therapeutic classification; EPAR= European Public Assessment Report; UC= Urothelial cancer
Sources: [47,56,57]

Table 6. Description of paclitaxel.

Paclitaxel	
Generic name (ATC-code)	Paclitaxel (L01CD01)
Mode of action	Paclitaxel is an antimicrotubular agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.
Pharmaceutical form	Powder for dispersion for infusion.
Posology	Not specified for UC in EPAR or SmPC
Method of administration	Infusion
Dosing	Not specified for UC in EPAR or SmPC
Dosing in the health economic model	Patient level data from EV-301. Relative dose intensity: 92.08%
Should the pharmaceutical be administered with other medicines?	Due to the significant risk of hypersensitivity reactions, all patients must be premedicated with glucocorticoid, antihistamine, and H2-receptor antagonist.
Treatment duration/-criteria for end of treatment	Not specified for UC in EPAR or SmPC
Necessary monitoring, both during administration and during the treatment period	Frequent monitoring of blood cell counts should be performed during paclitaxel therapy. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to >1500 cells/mm3 and platelets recover to >100,000 cells/mm3. Closely monitor all patients for signs and symptoms of pneumonitis. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for the development of profound myelosuppression. Patients receiving paclitaxel should be vigilantly monitored by physicians for the occurrence of cardiac events. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during the administration of the medicinal product.
Need for diagnostics or other tests (i.e., companion diagnostics)	No need
Packaging	6 mg/ml x 16,7 ml, 15, ml or 50 ml

ATC= Anatomical therapeutic classification; EPAR= European Public Assessment Report; UC= Urothelial cancer

Sources: [48,58–60]

3.6 Cost-effectiveness of the comparator(s)

The cost-effectiveness of V has not previously been assessed by the DMC, and therefore a scenario will be added in the sensitivity analysis using the cost of taxanes instead of vinflunine in the comparator arm. Due to the low drug prices of D and P, these treatments are assumed to be cost-effective.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

As per agreement with the DMC, the primary endpoints, selected key secondary endpoints (PFS, ORR, DCR and HRQoL), and the safety profile are all presented based on data from the EV-301, ITT population, and the pre-selected vinflunine sub-population from the post hoc subgroup analysis.

The efficacy of EV was assessed by appropriate imaging (radiographic imaging) and bone scintigraphy was performed every 8 weeks throughout the trial. Brain imaging was only performed if it was clinically indicated. The follow-up continued until radiographic disease progression, until discontinuation criteria were met, or until completion of the trial. The efficacy endpoints were evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The safety profile was investigator-assessed and evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. [15]

The trial used a group-sequential design with two planned analyses (an interim and a final analysis) [15]. The primary endpoint, OS, and selected key secondary endpoints (PFS, overall response rate (ORR), and disease control rate (DCR)) were tested with the hierarchical gatekeeping procedure. To assess the QoL and patient-reported outcomes, the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 (EORTC QLQ-C30) and the European Quality of life – 5 Dimensions- 5 levels (EQ-5D-5L) were used. The interim efficacy analysis was planned to occur after approximately 285 OS events (65% of the total planned events). Based on results from the interim analysis at the data cut-off July 15th, 2020 the trial met the superiority threshold and the Independent Data Monitoring Committee (IDMC) recommended stopping the study for efficacy. The study database was subsequently locked for the primary efficacy analysis and the protocol was amended to allow for patients in the chemotherapy arm to crossover to receive EV therapy. [15]

The intention-to-treat (ITT) population consists of all patients who were randomized and was the full analysis set (FAS) for efficacy analyses, except for response-related endpoints. The safety analysis set (SAF) consists of all patients who received any amount of study drug and was used for some of the safety analyses. The response evaluable set (RES) consists of all patients in the ITT population who had measurable disease, per investigator at baseline, and was the primary analysis set for response-related endpoints. [15,31]

This assessment is mainly based on analysis with a median follow up period of 24 months (data cut July 2021). For example, patient report outcomes data is only available data from the 11 months data (data cut July 2020). In relevant sections, tables and figures it will be defined which data cut is used for the analysis.

The efficacy outcome measures relevant for this application is presented in Table 7 below.

Table 7. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) [15,18]	24 months FU (data cut 30 July 2021)	Time from the date of randomization until the documented date of death from any cause.	FAS was used for the analysis. Distribution of OS was estimated for each treatment arm using Kaplan-Meier methodology
Progression free survival 1 (PFS) [15,18]	24 months FU (data cut 30 July 2021)	Time from the date of randomization until the date of radiologic disease progression or until death from any cause.	FAS was used for the analysis. Distribution of PFS was estimated for each treatment arm using Kaplan-Meier methodology
Clinical response *Overall Response rate (ORR)* *Disease control rate (DCR)* *Duration of response (DoR)* [15]	24 months FU (data cut 30 July 2021)	*ORR*: proportion of participants with CR or PR based on to the date of radiologic progression or death (RECIST V1.1) *DCR*: proportion of participants with a CR, PR, or stable disease per RECIST V1.1 *DoR*: time from the date of the first response CR/PC per RECIST V1.1	RES was used for the analysis, which was defined as all subjects in FAS who had measurable disease (per RECIST v1.1) per investigator at baseline.
Health related Quality of life (HRQoL) [19,22]	11 months FU (data cut 15 July 2020)	Two validated HRQoL instruments were included in EV-301 to measure HRQoL; the EORTC QLQ-C30 and the EQ-5D-5L.	The QoL questionnaires were completed at baseline (Day 7- to -1 before baseline), on Day 1 of each week for the first 12 weeks, then every 12 weeks thereafter, as well as at the end of treatment and at follow-up visits.
Treatment emergent adverse events (TEAEs) [17,19,22]	11 and 24 months FU (data cut 15 July 2020 & 30 July 2021)	Overall TEAEs as well as serious TEAEs, TEAEs leading to withdrawal of treatment, grade>3 TEAE, drug related, TEAEs leading to dose reduction/interruption/death are presented in the dossier	TEAEs presented in the dossier is based on FAS. Note that the TEAEs presented in Rosenberg et al 2023 (15) is based on SAF.
Duration of Treatment (DoT) [17,18]	24 months FU (data cut 30 July 2021)	Time from start of treatment until either disease progression, a protocol-defined discontinuation criterion, study termination, or study completion was met	SAF was used for the analysis. Only data on file is available

* Time point for data collection used in analysis (follow up time for time-to-event measures)

FU=Follow up; CR=complete repsonse; PR=Partial repsone; RECIST= Response Evalution Criteria in Solid Tumors; TEAE=Treament emergent adverse events; FAS=Full Analysis Set; SAF=Safety Analysis Set; RES=Response evaluation set

4. Health economic analysis

4.1 Model structure

An economic model was developed in Microsoft Excel® 2016 to assess the cost-effectiveness (CE) of EV compared with chemotherapy for the management of adult patients with la/mUC previously treated with platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. The model was based on efficacy and safety data from the pivotal EV-301 trial. [15,18]

The EV CE model is a three-state partitioned survival model that predicts the long-term survival status of the target patient population. Partitioned survival analysis is the most commonly utilized decision modelling approach for appraisals of advanced and metastatic cancer interventions and is well-accepted by health technology assessment (HTA) bodies.[67] The partitioned survival model structure eliminates the need to generate assumptions for the transition of patients between health states and allows for the direct use of EV-301-derived KM or parametric fitted curves to estimate the proportion of patients in different health states. In particular, the strength of a partitioned survival model is the intuitive and transparent derivation of the proportion of patients occupying each health state directly from the trial-observed and parametric-curve-extrapolated cumulative survival probabilities for OS and PFS. Using the partitioned survival model approach, the proportion of patients in each health state is determined by the area under the curves fitted to the trial outcomes. In addition, partition survival model structure was also deemed appropriate in a prior submission of avelumab for maintenance treatment of la/mUC after platinum-based chemotherapy [9]. This model is based on a core de novo global EV cost-effectiveness analysis (CEA) developed in support of EV. No published CEA are available for EV.

At model start, all patients begin in the “pre-progression state” following treatment initiation. Over the modelled time horizon, patients flow between the following mutually exclusive health states (Figure 4):

1. **Pre-progression state:** The pre-progression state includes all patients without progression or with stable disease. All patients enter the model in the pre-progression state upon receipt of treatment with EV or comparators. The proportion of patients in the pre-progression health state of the model equals the PFS curve of each treatment as observed in the EV-301 study. Consistent with the EV-301 study, PFS was defined as the time from the date of randomization until the date of radiological disease progression per RECIST V1.1, or until death due to any cause.
2. **Post-progression state:** The post-progression state includes alive patients who progressed or relapsed. The proportion of patients in this health state equals the difference between the proportion of living patients and the proportion of progression-free patients (i.e., difference between OS and PFS curves). Consistent with the EV-301 study, OS was defined as the time from the date of randomization until the date of death from any cause.
3. **Death:** Deceased patients enter and stay in the death health state until the end of the model time horizon (i.e., an absorbing state). The proportion of patients in the death health state equals to 1 - the proportion of patients alive (i.e., 1-OS).

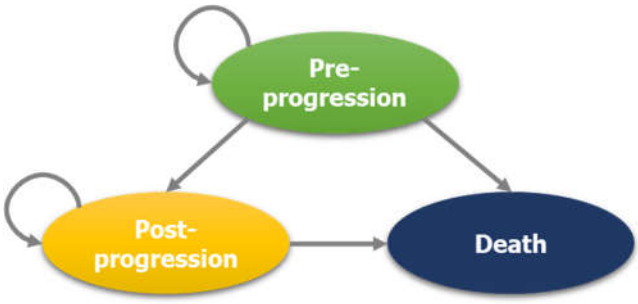


Figure 4. Partition survival structure of the EV model

Patients in the pre-progression state are expected to have better QoL and utilize less healthcare resources for disease management compared to those who are in post-progression state. By separating patients based on their progression and survival status, distinct utilities and medical costs can be applied to each health state. A monthly model cycle was used for estimating the proportion of patients in each heath state over time. During each monthly cycle, patients were redistributed among the three health states based on probabilities derived from the PFS and OS curves from EV-301. Half-cycle corrections were applied to both cost and effectiveness measures.

The global core EV model was subjected to rigorous internal verification as a quality assurance measure. This was done by having two separate researchers check the correctness of the model programming and mathematical calculations. The model's interface was thoroughly examined to ensure that equations and parameters were correctly cross-referenced against their sources and all modules of code were error-free and replicable. A replication audit was performed for key cost input calculations. A cell-by-cell check of all Excel sheets in the model was done to identify calculation errors. In addition to the calculation and code, the auditing team also validated inputs in the model against the original source. Furthermore, scenario analyses were performed during the deterministic sensitivity analysis (DSA) to check if the model behaved as expected when stress-tested using extreme input values.

A thorough quality assessment of the global core EV model was undertaken by two health economists from the University of Sheffield. The external review included error checking of the model structure, calculations, code implementation, along with an assessment of the plausibility of assumptions and inputs used in the model. The experts commented that the model was transparent with clear separation between raw inputs, intermediate calculations, and the values obtained from the model traces. There was also an extensive use of error trapping. No major implementation errors or bugs were identified. The survival models incorporated to extrapolate long-term efficacy were also deemed appropriate. Suggestions provided by the experts were carefully addressed and incorporated into the model as deemed appropriate. In summary, the core EV model was concluded to be well designed, appropriately implemented, and fit for the purpose of supporting the economic assessment of EV vs relevant alternative strategies, supporting country specific adaptations for reimbursement or health technology assessment needs.

4.2 Model features

In the base case, the CE of EV compared to V was assessed based on the subgroup of patients assigned to EV who had been pre-selected for V and the subgroup of chemotherapy patients who received V. In addition, a scenario analysis was conducted based on the EV-301 ITT population (rather than on subgroup data), which compared patients assigned to EV with those assigned to docetaxel, paclitaxel, or vinflunine (DPV). The economic analysis was conducted from a limited societal perspective in accordance with DMC guidance. A partitioned survival model with monthly cycle length (i.e., 30.4 days per cycle) and lifetime horizon was considered to comprehensively capture the expected costs and health outcomes of patients over their remaining lifetime from the initiation of EV or comparative chemotherapies. In the base-case, both costs and health effects were discounted at 3.5% annually in accordance with DMC guidance [61,65]. During the modelled time horizon, costs and health effects were estimated for each treatment arm included in the model. The following cost components were considered: drug acquisition and administration costs, disease management costs, AE costs, and patient costs (patient time and transportation costs). Effectiveness measures included LYs and quality-adjusted life-years (QALYs). The incremental cost-effectiveness ratios (ICERs) of EV vs each comparator was evaluated in terms of the incremental cost per QALY gained. Key features of the model are summarized in Table 8 below.

Table 8. Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with la/mUC who have been treated with a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor.	EMA approved indication
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (10 years)	To capture all health benefits and costs in line with DMC guidelines and DMC assessment report of EV 2022 [3]
Cycle length	30.4 days	Consistent with length of treatment cycle
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	EV	
Comparator(s)	V (base case), DPV (Scenario analysis)	According to national treatment guideline and DMC assessment of EV [3]
Outcomes	OS, PFS, DoT, and dosing inputs for all treatment arms were estimated using individual patient data from the EV-301 study (NCT03474107, data cut-off: July 30 2021). Grade ≥3 AEs input was based on data from data cut July 15 2020.	The base-case analysis used the EV (pre-selected for V) and V subgroups.

5. Overview of literature

5.1 Literature used for the clinical assessment

A head-to-head study comparing EV with the relevant comparators, vinflunine (V), docetaxel (D), and Paclitaxel (P) was identified and thus, a literature search was omitted, according to the DMC guideline [61]. The study is a global, open-label, Phase III randomized controlled trial (RCT) comparing the efficacy and safety of EV with chemotherapy in adult patients with la/mUC who have previously received platinum-based chemotherapy and a PD-1/L-1 inhibitor [15]. A post hoc analysis of Enfortumab Vedotin vs Chemotherapy based on the EV-301 trial is included to ensure transparency and to ensure that all evidence relevant for this application is presented and assessed. The studies relevant to this assessment are listed in Table 9 below.

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

No literature search since relevant HRQoL data (EORTC QÖC-C30 and EQ-5D-5L) was captured in EV-301 (see below). The utility score was estimated based on EQ-5D-5L and the Danish EQ-5D-5L value set [66].

5.3 Literature used for inputs for the health economic model

The model considered the following cost components: drug acquisition costs for EV and chemotherapies, associated drug administration costs, pre-progression and post-progression disease management costs, adverse event costs, and patient time and transportation costs. The pre-progression and post-progression disease management costs were estimated from Danish healthcare system unit costs. Resource use estimates were based on the literature and were aligned with advice from DMC clinical experts. The pre-progression and post-progression disease management costs are assumed to be the same across all the treatment arms. The cost for treatments and the cost for resource use are obtained from EV-301 trial, literature, and public databases to the extent feasible. All the costs are inflated to 2024 based on guidance from the Danish Medicines Council [75].

Table 9 Relevant literature included in the assessment of efficacy and safety

Reference	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
EV-301 long-term outcomes: 24-month findings from the phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. Rosenberg et al. Ann Oncol. 2023 Nov;34(11):1047-1054. [15]	A Study to Evaluate Enfortumab Vedotin Versus (vs) Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301)	NCT03474107	Start: 27/06/2018 Completion: 15/07/2020 Data cut-off 30/07/2021 Future data cut-offs NA	EV vs DPV
Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma, Powles T. et al. N Engl J Med, 2021;384:1125-1135 [20]	EV-301	NCT03474107	Start: 27/06/2018 Completion: 15/07/2020 Data cut-off 15/07/2020	EV vs DPV
Quality of Life, Functioning, and Symptoms in Patients With Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma From EV-301: A Randomized Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy. Mamtani R, Rosenberg JE, Powles T, Sonpavde GP, Loriot Y, Duran I, et al. ASCO 2021, Abstr No 4539. [22]	EV-301	NCT03474107	Start: 27/06/2018 Completion: 15/07/2020 Data cut-off 15/07/2020	EV vs DPV
A Post Hoc Analysis of Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer Enfortumab (EV-301). Astellas Pharma A/S. Data on File. 2022 [18]	EV-301	NCT03474107	Start: 27/06/2018 Completion: 15/07/2020 Data cut-off 30/07/2021 Future data cut-offs NA	EV vs V

Reference	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
A Post Hoc Analysis of Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer Enfortumab (EV-301). Astellas Pharma A/S. Data on File. 2021 [21]	EV-301	NCT03474107	Start: 27/06/2018 Completion: 15/07/2020 Data cut-off 15/07/2020 Future data cut-offs NA	EV vs V
Clincial Study Report addendum 1. EV-301. [17]	EV-301	NCT03474107	Start: 27/06/2018 Completion: 15/07/2020 Data cut-off 30/07/2021 Future data cut-offs NA	EV vs DPV
Astellas Pharma A/S. HRQoL. Data on file. [19]	EV-301	NCT03474107	Start: 27/06/2018 Completion: 15/07/2020 Data cut-off 15/07/2020	EV vs V and EV vs DPV

6. Efficacy

6.1 Efficacy of EV compared to chemotherapy in adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor

6.1.1 Relevant studies – EV-301

EV-301 is a multinational, randomized, open-label, phase III study comparing the efficacy and safety of EV with chemotherapy in adult patients with la/mUC who have previously received PD-1/L1 inhibitor, and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally, or metastatic setting. [15] An overview of study design for EV-301 is presented below.

The study consisted of three phases: screening, treatment, and follow-up. The screening took place up to 28 days prior to randomization. A total of 608 patients underwent randomization; 301 were assigned treatment with EV and 307 were assigned treatment with chemotherapy. The treatment phase started with cycle 1 and continued to subsequent 28-day or 21-day cycles (for Arm A and Arm B, respectively) until one of the discontinuation criteria were met or upon study termination, or study completion, whichever occurred first. [15]

Following discontinuation from the study drug, patients could enter the crossover extension. No further efficacy data were collected in the crossover extension period. Patients had a follow-up visit 30 days (+ 7 days) after their last dose of the drug for safety assessments. If a subject discontinued study drug prior to undocumented radiographic disease progression (i.e., progression-free survival (PFS)), the subject was to enter the post-treatment follow-up period and continue to undergo imaging assessments every 56 days (±7 days) until PFS on study therapy (PFS1) was documented, or the subject started another anticancer treatment, whichever occurred earlier. A study schematic is presented in Figure 5below. [15]

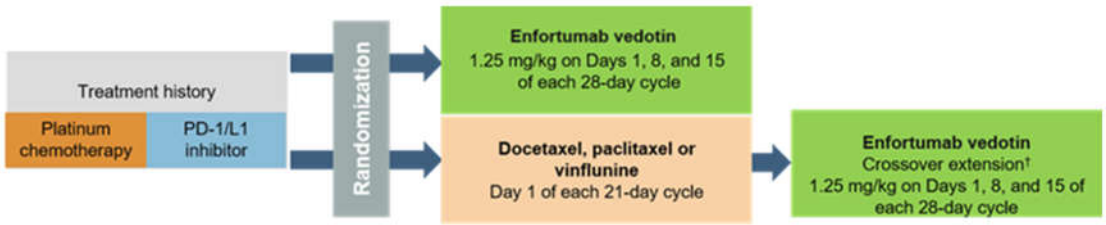


Figure 5. Study schematic of EV-301.

PD-1/L1= Programmed death receptor 1/ death-ligand 1

† Cross over extension. Treatment change to EV from the comparator arm (crossover) was not permitted at the start of the study. Protocol amendment Sept 2020 (post positive interim results): Change of treatment from the DPV arm was permitted to EV. 18 patients (5.9%) from the DPV arm received EV as subsequent treatment; 13 patients after protocol amendment and 5 patients before change of the study protocol (i.e included in interim OS analysis)

Sources: [15,31]

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

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
EV-301 NCT03474107 [15,17,18,20,21,22]	Multinational, randomized, open-label, phase III study comparing the efficacy and safety of EV with chemotherapy in	Patients received treatment until radiologic disease progression, other discontinuation criteria were met, or study completion, whichever occurred first.	Adult patients with la/mUC who have previously received PD-1/L1 inhibitor, and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally, or metastatic setting.	1.25 mg/kg (maximum weight, 100 kg) on days 1, 8, and 15 of each 28-day cycle	Chemotherapy: docetaxel 75 mg/m2 , paclitaxel 175 mg/m2 , or vinflunine 320 mg/m2 (capped at 35% of patients) on day 1 of each 21-day cycle; chemo-therapy was selected before randomization	The primary endpoint was overall survival evaluated according to RECIST, version 1.1. Secondary endpoints included; Progression-free Survival on study therapy (PFS1) per RECIST, version 1.1 and Overall Response Rate (ORR) (Complete Response (CR) and Partial Response (PR)) per RECIST V1.1, Duration of Response (DoR) per RECIST V1.1, Safety assessed by Adverse Events, number of participants with laboratory value abnormalities and/or adverse events, number of participants with vital signs abnormalities and/or adverse events and Disease Control Rate (DCR) (CR + PR + stable disease [SD]) per RECIST V1.1, , Safety assessed by 12- lead electrocardiogram, Safety assessed by 12- lead electrocardiogram (ECG). Patient-reported outcome assessed by quality of life: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and EuroQOL 5-dimensions (EQ-5D -5L) questionnaire. Patients had a follow-up visit 30 days (+ 7 days) after their last dose of drug for safety assessments. If a subject discontinued study drug prior to undocumented radiographic disease progression (i.e. PFS1), the subject was to enter the post-treatment follow-up period and continue to undergo imaging assessments every 56 days (± 7 days) until PFS1 was documented, or the subject started another anticancer treatment, whichever occurred earlier. Radiographic imaging was performed at baseline and every 8 weeks. Bone scintigraphy was performed in all patients at screening; repeat scanning

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						was performed at least every 8 weeks in patients with a positive scan. Imaging of the brain was performed, if clinically indicated, at baseline and throughout the trial. Patients were followed until radiographic disease progression, until discontinuation criteria were met, or until trial completion. Patients who discontinued treatment before disease progression underwent imaging assessments every 8 weeks until documented disease progression or initiation of a different anticancer treatment, whichever occurred earlier. After radiographic disease progression had occurred, patients entered the long-term follow-up phase and were followed at least every 3 months from the date of the follow-up visit for vital status until death, loss to follow-up, withdrawal of consent, or termination of the trial.

6.1.2 Comparability of studies

N.A.

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

Baseline characteristics of patients in EV-301 for the ITT population and the "preselected V" subgroup population is presented in Table 11 below, which shows that similar baseline characteristics were reported for the two populations. DMC concluded in their assessment report of EV that the population in EV-301 generally corresponds to the group of patients suitable for treatment in Danish practice [3]. Any further comparison of EV-301 population vs Danish population will therefore not be presented in this application.

Table 11 Baseline characteristics of patients in studies used for the comparative analysis of efficacy

	EV-301 - ITT		EV-301 – preselected V	
	EV (N = 301)	DPV (N = 307)	EV (N = 73)	Vinflunine (N = 78)
Median age (range)	68 (34–85)	68 (30–88)	[redacted]	[redacted]
Male, n (%)	238 (79.1)	232 (75.6)	[redacted]	[redacted]
Geographic region, n (%)				
Western Europe	126 (41.9)	129 (42.0)	[redacted]	[redacted]
The US	43 (14.3)	44 (14.3)	[redacted]	[redacted]
Rest of the World	132 (43.9)	134 (43.6)	[redacted]	[redacted]
Tobacco use, n (%)				
Former user	167 (55.5)	164 (53.4)	[redacted]	[redacted]
Current user	29 (9.6)	31 (10.1)	[redacted]	[redacted]
Never used	91 (30.2)	102 (33.2)	[redacted]	[redacted]
Unknown			[redacted]	[redacted]
NR	14 (4.7)	10 (3.3)	[redacted]	[redacted]
History of diabetes or hyperglycaemic, n (%)	56 (18.6)	58 (18.9)	[redacted]	[redacted]
ECOG PS, n (%)				
0	120 (39.9)	124 (40.4)	[redacted]	[redacted]
1	181 (60.1)	183 (59.6)	[redacted]	[redacted]
Bellmunt risk score, n (%)				
0–1	201 (66.8)	208 (67.8)	[redacted]	[redacted]
≥2	90 (29.9)	96 (1.3)	[redacted]	[redacted]
NR	10 (3.3)	3 (1.0)	[redacted]	[redacted]
Origin site of primary disease, n (%)				
Upper urinary tract	98 (32.6)	107 (34.9)	[redacted]	[redacted]

	EV-301 - ITT		EV-301 – preselected V	
	EV (N = 301)	DPV (N = 307)	EV (N = 73)	Vinflunine (N = 78)
Bladder or other site	203 (67.4)	200 (65.1)	[redacted]	[redacted]
Histologic type at initial diagnosis, n (%)				
Urothelial or transitional cell carcinoma	229 (76.1)	230/305 (75.4)	[redacted]	[redacted]
UC, mixed types	45 (15.0)	42/305 (13.8)	[redacted]	[redacted]
Other	27 (9.0)	33/305 (10.8)	[redacted]	[redacted]
Site of metastasis, n (%)				
Lymph node only	34 (11.3)	28/306 (9.2)	[redacted]	[redacted]
Visceral site	234 (77.7)	250/306 (81.7)	[redacted]	[redacted]
Liver	93 (30.9)	95/307 (30.9)	[redacted]	[redacted]
Bone	NR	NR	[redacted]	[redacted]
Lung	NR	NR	[redacted]	[redacted]
Previous systemic therapies, n (%)				
1–2	262 (87.0)	270 (87.9)	[redacted]	[redacted]
≥3	39 (13.0)	37 (12.1)	[redacted]	[redacted]
Best response among patients who previously received CPI treatment, n (%)				
Response	61 (20.3)	50 (16.3)	[redacted]	[redacted]
No response	207 (68.8)	215 (70.0)	[redacted]	[redacted]
Median time since diagnosis of metastatic or locally advanced disease (range)	14.8 (0.2–114.1)	13.2 (0.3–118.4)	[redacted]	[redacted]
Prior radiation therapy, n (%)	96 (31.9)	103 (33.6)	[redacted]	[redacted]
Prior PD-1/L-1, n (%)				
Nivolumab	21 (7.0)	13 (4.2)	[redacted]	[redacted]
Pembrolizumab	146 (48.5)	144 (46.9)	[redacted]	[redacted]
Atezolizumab	86 (28.6)	89 (29.0)	[redacted]	[redacted]
Avelumab	16 (5.3)	13 (4.2)	[redacted]	[redacted]
Durvalumab	35 (11.6)	56 (18.2)	[redacted]	[redacted]
Other	11 (3.7)	11 (3.6)	[redacted]	[redacted]
Type of prior platinum-based treatment, n (%)				
Cisplatin-based only	193 (64.1)	190 (61.9)	[redacted]	[redacted]
Carboplatin-based only	74 (24.6)	85 (27.7)	[redacted]	[redacted]
Both	34 (11.3)	31 (10.1)	[redacted]	[redacted]

6.1.4 Efficacy – EV-301

As per agreement with the DMC in 2022, the primary endpoints, selected key secondary endpoints (PFS, ORR, and DCR), and the safety profile are all presented based on data from the EV-301, ITT population, and the pre-selected vinflunine sub-population from the post hoc subgroup analysis. To support the consistency of the effect of EV in populations that are hard-to-treat and critically affect the unmet need, data on selected endpoints (OS and PFS), from hard-to-treat subgroups is provided in Appendix K.

6.1.4.1 Overall survival

The primary endpoint, OS, was defined as the time from the date of randomization until the documented date of death from any cause. All events of death on or prior to data cut-off date were included, regardless of whether the event occurred while the subject was still taking the study drug or after the subject discontinued the study drug. Subjects who were still alive at the time of data cut-off date were to be censored at the last known alive date or at the data cutoff date, whichever was earlier. All dates on or prior to the data cut-off date (e.g., laboratory testing date, drug administration date) that could support a subject's survival status were to be used to derive the last known alive date. Subjects with death or last known alive date after the data cutoff date were to be censored at the data cut-off date. [15]

OS ITT analysis (EV vs DPV) at 24 months FU

At data cut-off 30 July 2021 (median follow-up 23.75 months), 444 deaths had been reported; 207 deaths in the EV (ITT) arm and 237 deaths in the DPV arm. Consistent with the previous data cut-off, EV reduced the risk of death vs. DPV by 29.6% (HR=0.704 [95% CI; 0.58, 0.85], p=0.001), resulting in a significant and clinically meaningful improvement in OS. The median OS was higher in the EV (ITT) arm than in the DPV arm (12.91 months [95% CI; 11.01, 14.92] vs. 8.94 months [95% CI; 8.25, 10.25]), Figure 6. [15]

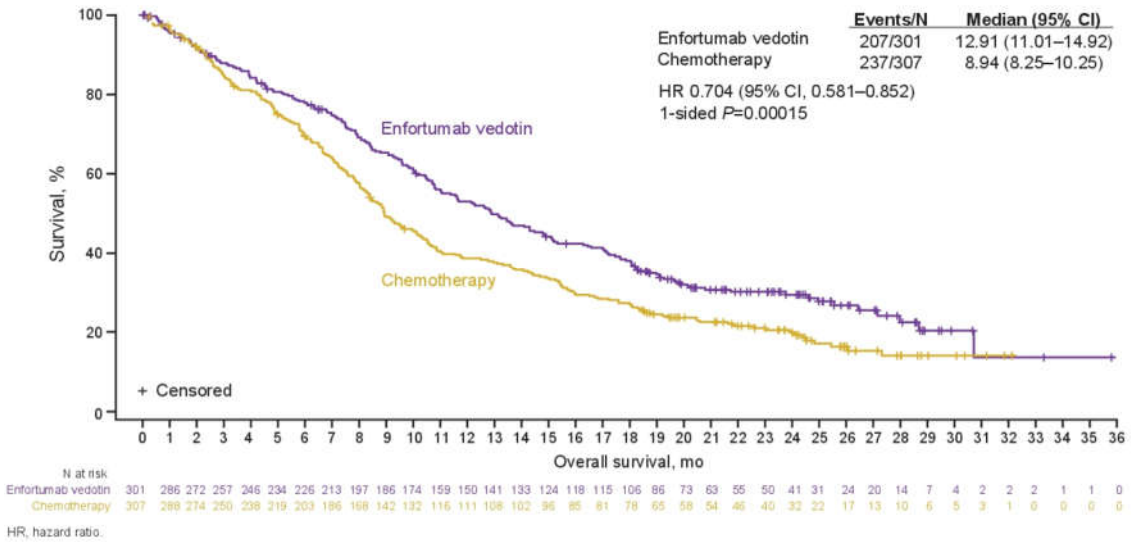


Figure 6. Kaplan-Meier estimates of OS, ITT population (Data cut-off 30 July 2021)

CI= Confidence interval; HR= Hazard ratio; OS= Overall survival
Source: [15]

OS EV vs Vinflunine subgroup at 24 months FU

In the post hoc vinflunine population, similar results to the ITT population were seen, with EV resulting in longer OS than vinflunine. A total of 48 deaths (66%) occurred in the EV (pre-selected V) arm compared with 60 deaths (77%) in the vinflunine (subgroup) arm; the corresponding median OS was 12.81 months XXXXXXXXXXXXX in the EV (pre-selected V) arm compared with 9.46 XXXXXXXXXXX in the vinflunine (subgroup) arm as presented in Figure 7. In pre-selected V subgroup EV demonstrated a 25.5% reduction in the risk of death with a HR = 0.745, [95% CI: 0.509;1.090], p=0.1289 compared with the vinflunine (subgroup) arm. [15,18]

Figure 7. Kaplan-Meier estimates of OS, vinflunine subgroup. (Data cut July 2021)

CI= Confidence interval; HR= Hazard ratio; OS= Overall survival

Note: "Enfortumab" in the figure reference the preselected Enfortumab vedotin patients and "Chemotherapy" reference vinflunine pre selected patients from the subgroup analysis.

Sources: [18]

Subgroup analyses of overall survival ITT analysis (EV vs DPV) at 24 month FU

The OS benefit of enfortumab vedotin was also observed in the majority of prespecified subgroups (Figure 8) and similar to the previous data cut. [15] For example was the HR 0.655 (0.475-0.902; 95% CI) for patients with liver metastases on EV (93 patients) vs ITT (95 patients), which was similar to the result from the interim analysis with a HR of 0.66 (0.46-0.96, 95% CI). The median OS was 15.11 months for EV patients with no liver metastases and 9.36 months for EV patients with liver metastases. The median OS was 10.55 months for the chemo patients with no liver metastases and 5.95 months for chemo patients with liver metastases.

Subgroup		Event, No./No.		HR (95% CI)
		Enfortumab vedotin	Chemotherapy	
All patients		207/301	237/307	0.704 (0.581-0.852)
Age group 1, y	< 65	76/108	84/111	0.776 (0.568-1.058)
	≥ 65	131/193	153/196	0.725 (0.573-0.916)
Age group 2, y	< 75	171/249	182/239	0.717 (0.582-0.884)
	≥ 75	36/52	55/68	0.888 (0.581-1.355)
Sex	Male	159/238	187/232	0.636 (0.514-0.786)
	Female	48/63	50/75	1.201 (0.806-1.789)
Region[b]	Western Europe	92/126	104/129	0.742 (0.560-0.983)
	United States	31/43	30/44	0.895 (0.540-1.484)
	Rest of the world	84/132	103/134	0.671 (0.503-0.896)
ECOG PS[b]	0	71/120	81/124	0.783 (0.569-1.077)
	1	136/181	156/183	0.695 (0.552-0.876)
Liver metastasis[b]	Yes	71/93	82/95	0.655 (0.475-0.902)
	No	136/208	155/212	0.765 (0.607-0.963)
Preselected control therapy	Paclitaxel	100/141	83/112	0.780 (0.582-1.044)
	Docetaxel	59/87	94/117	0.666 (0.480-0.924)
	Vinflunine	48/73	60/78	0.745 (0.509-1.090)
Primary site of tumor	Upper tract	62/98	76/107	0.803 (0.574-1.123)
	Bladder/other	145/203	161/200	0.696 (0.556-0.872)
Prior lines of systemic therapy	1–2	181/262	208/270	0.728 (0.596-0.889)
	≥ 3	26/39	29/37	0.778 (0.455-1.332)
Best response to prior checkpoint inhibitor	Responder	33/61	39/50	0.568 (0.357-0.904)
	Nonresponder	150/207	165/215	0.794 (0.636-0.991)

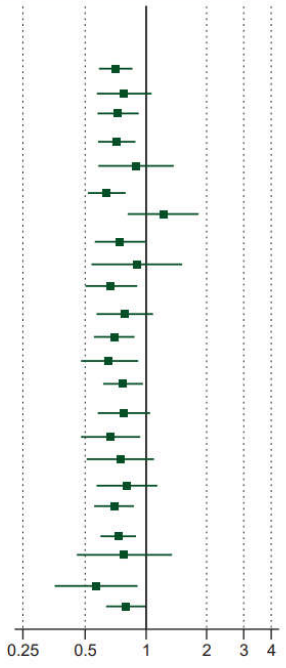


Figure 8. Subgroup analyses of overall survival (ITT, data cut July 2021).
Source: [15]

6.1.4.2 Progression-free survival 1

PFS 1 is defined as the time from the date of randomization until the date of radiological disease progression (per RECIST V1.1), or until death due to any cause. PFS1 was assessed by the Investigator on the FAS. Statistical comparison of the treatment arms was performed per the planned multiplicity adjustment rule. The distribution of PFS1 was estimated for each treatment arm using KM methodology and compared between Arm A and Arm B using log-rank test, stratified by ECOG PS (0 vs 1), region (US, EU, and the Rest of World) and liver metastasis status (Yes vs No) per IRT. In addition, the stratified Cox PH model was used to estimate the HR and the corresponding 95% CI. [15]

PFS ITT analysis (EV vs DPV) at 24 months FU

At data cut-off 30 July 2021 (median follow-up 23.75 months) 479 PSF1 events had been reported (231 and 248 events in the EV and chemotherapy arm, respectively). The median PFS was similar to the previous data cut-off for both EV and chemotherapy (5.55 months [95% CI; 5.32, 6.28] vs. 3.71 months [95% CI; 3.52, 3.94], respectively). Similar, EV significantly improved PFS1 compared to DPV, with a 37% reduction in the risk of disease progression (HR=0.63, [95% CI; 0.53, 0.76], p<0.001), Figure 9. [15]

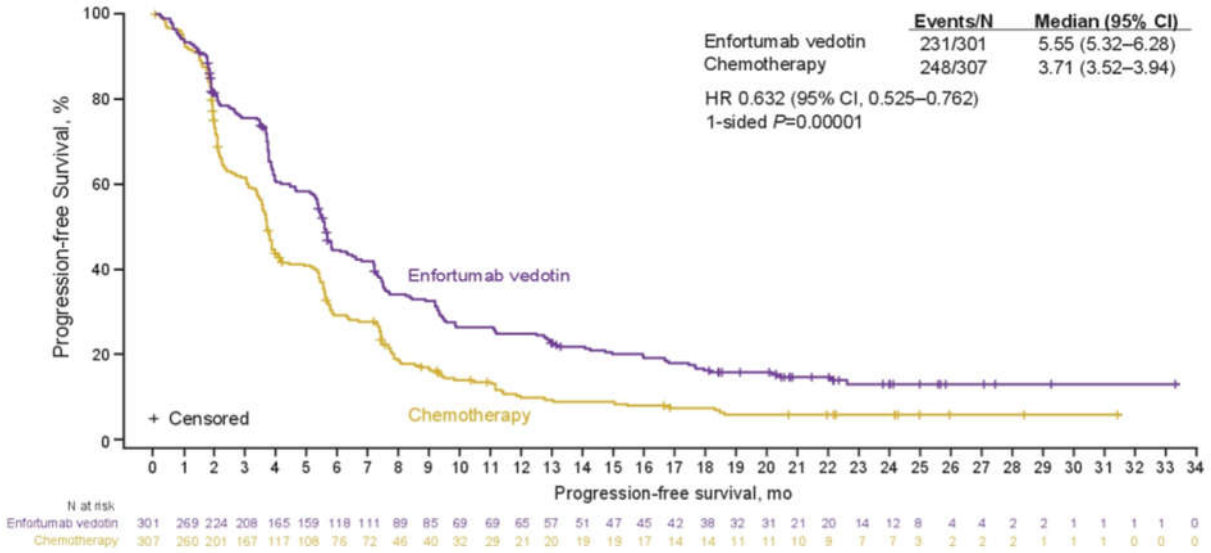


Figure 9. Kaplan-Meier estimates of PFS, ITT population (Data cut-off 30 July 2021).

CI= Confidence interval; HR= Hazard ratio
Source: [15]

PFS EV vs Vinflunine subgroup at 24 months FU

In the post hoc V (subgroup) population, similar results to the ITT population were seen, with EV resulting in longer PFS1 than vinflunine. A total of 55 deaths or progression events XXXXXX occurred in the EV (pre-selected V) arm compared with 59 events XXXXXX in the V (subgroup) arm; the corresponding median PFS was XXXXXXXXXXXXXXXX compared with XXXXXXXXXXXXXXXX in the EV (pre-selected V) and vinflunine (subgroup) arm respectively, as presented in Figure 10. In the pre-selected V population, EV demonstrated a XXXXX reduction in the risk of disease progression or death XXXXXXXXXXXX [18]

Figure 10. Kaplan-Meier estimates of PFS, vinflunine subgroup.

CI= Confidence interval; HR= Hazard ratio; PFS= Progression-free survival

Note: "Enfortumab" in the figure reference the preselected Enfortumab vedotin patients and "Chemotherapy" reference vinflunine pre selected patients from the subgroup analysis.

Sources: [18]

6.1.4.3 Clinical response at 11 months FU (15 July 2020)

The clinical response in this section includes ORR, DCR, and DoR. The ORR is defined as the proportion of participants with a CR or PR based on the RECIST V1.1. DCR is defined as the proportion of participants with a CR, PR, or stable disease based on RECIST V1.1. DoR is defined as the time from the date of the first response CR/PR per RECIST V1.1 (whichever is first recorded) that is subsequently confirmed as assessed by the investigator to the date of radiological progression or date of death for participants who achieved CR or PR. [20]

Clinical response - ITT population (11 and 24 months FU)

An overview of the clinical response; ORR, DCR, and DoR in the ITT population based on the two data cuts are presented in Table 12.The confirmed ORR was was two times higher in the EV (ITT) arm than in the DPV, 41.3% (119 of 288 subjects; 95% CI: 35.57, 47.25) for the enfortumab vedotin arm and 18.6% (55 of 296 subjects; 95% CI: 14.32, 23.49) for the chemotherapy arm, with a 1-sided P value < 0.001 [Table 12]. This ORR was consistent with the ORR for both arms in the primary analysis. DCR was unchanged between the two data cuts and it was significantly higher in the EV (ITT) arm compared with the DPV arm (71.9% [207 of 288 subjects; 95% CI: 66.30, 76.99] for the enfortumab vedotin arm vs 53.4% [158 of 296 subjects; 95% CI: 47.52, 59.17] for the chemotherapy arm, with 1-sided P value < 0.001). [15, 20]

Table 12. Clinical response, response-evaluable set (data cut 2020 and 2021)

	30 Jul 2021			15 Jul 2020		
	EV (N = 288)	DPV (N = 296)	RR **	EV (N = 288)	DPV (N = 296)	RR **
Best overall response, n (%)						
Complete response	20 (6.9)	10 (3.4)	2.06	14 (4.9)	8 (2.7)	1.80
Partial response	99 (34.4)	45 (15.2)	2.26	103 (35.8)	45 (15.2)	2.35
Stable disease	88 (30.6)	103 (34.8)	0.88	90 (31.3)	105 (35.5)	0.88
Progressive disease	44 (15.3)	84 (28.4)	0.54	44 (15.3)	83 (28.0)	0.54
Not evaluable	37 (12.8)	54 (18.2)	0.70	37 (12.8)	55 (18.6)	0.69
ORR, n (%) [95% CI]	119 (41.3) [35.57, 47.25]	55 (18.6) [14.32, 23.49]		117 (40.6) [34.90, 46.54]	53 (17.9) [13.71, 22.76]	
p-value	<0.001			<0.001*		
Disease control rate, n (%) [95% CI]	207 (71.9) [66.30, 76.99]	158 (53.4) [47.52, 59.17]		207 (71.9) [66.30, 76.99]	158 (53.4) [47.52, 59.17]	
p-value	<0.001			<0.001*		
Duration of response, median months [95% CI]	7.62 [5.68, 11.17]	8.21 [5.68, 9.56]		7.39 [5.59, 9.46]	8.11 [5.65, 9.56]	
Time to response, median months	Not available			1.87	1.91	

CI= Confidence interval; EV= Enfortumab vedotin; n= sample size; ORR=Overall response rate; RR=Relative Risk

*Stratified 1-sided P-value

**Calculated as described in Appendix D.

Sources: [15, 20]

Clinical response – Vinflunine subgroup (11 months FU)

This section presents ORR, DCR and DoR in the vinflunine subgroup based on the interim analysis with 11 months FU (July 2020 data cut) since all requested data is not available with the later data cut and the data it's not included in the cost-effectiveness analysis.

The confirmed ORR was more than two times higher in the EV (pre-selected V) arm than in the V (subgroup) arm, 40.0%, [redacted] vs. 16.0%, [redacted] respectively. In the EV (pre-selected V) arm, [redacted] achieved CR compared with [redacted] in the V (subgroup) arm [redacted], while partial response was achieved in 38.6% vs. 12% of patients respectively (RR=3.21).[15] A median DoR of [redacted] was reported in the EV (pre-selected V) arm and [redacted] in the V (subgroup) arm. DCR was higher in the EV (pre-selected V) arm than in the V (subgroup) arm [redacted]. [15,18]. See Table 13 below.

Table 13. Clinical response, response-evaluable set, vinflunine subgroup. (data cut July 2020)

	EV (N = 70)	Vinflunine (N = 75)	RR **
Best overall response, n (%)			
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
ORR, n (%) [95% CI]	28 (40.0) [redacted]	12 (16.0) [redacted]	
p-value	[redacted]		
Disease control rate, n (%) [95% CI]	[redacted] [redacted]	[redacted] [redacted]	
p-value	[redacted]		
Duration of response, median months [95% CI]	[redacted] [redacted]	[redacted] [redacted]	

CI= Confidence interval; EV= Enfortumab vedotin; ORR= Overall response rate

*Stratified 1-sided P-value

Calculated as described in Appendix D.

Sources: [15,18]

7. Comparative analyses of efficacy

This section is not applicable since a head-to-head study was used for comparing the intervention and comparator.

8. Modelling of efficacy in the health economic analysis

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

Efficacy inputs for the EV model include OS, PFS, and Duration of treatment (DoT), which were assumed to differ across treatment arms. Parametric curves of OS, PFS and DoT for EV (pre-selected for V) and V subgroups were estimated and extrapolated using individual patient data from the EV-301 study (NCT03474107, data cut-off: July 30 2021). [15,18]

The EV-301 study was powered to demonstrate differences in survival between EV and chemotherapies (D, P, or V) in the ITT population [15]. However, V is the most relevant comparator in Denmark, so the base case scenario compared EV vs V in the subgroup of patients pre-selected to receive V [15, 18].

8.1.1 Extrapolation of efficacy data

Efficacy (OS and PFS) and treatment duration beyond the follow-up of the EV-301 data were extrapolated in order to assess the CE of EV vs comparators over a 10-year time horizon. Parametric functions considered for OS, PFS, and DoT extrapolation included exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions. The suitability of parametric survival models was evaluated based on the following criteria suggested by the systematic survival model selection process by National Institute for Health and Care Excellence(NICE) DSU TSD14:[69]

8.1.1.1 Extrapolation of Overall survival (OS)

The selected base-case OS extrapolation approach for the EV (pre-selected V subgroup) and V arm was a parametric extrapolation with independently fitted log-logistic distribution. The approach was selected based on AIC/BIC statistics and visual fit inspection. See further details in Appendix D

Table 14 Summary of assumptions associated with extrapolation of Overall survival (OS)

Method/approach	Description/assumption
Data input	A Study to Evaluate Enfortumab Vedotin Versus (vs) Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301) (NCT03474107)
Model	Parametric extrapolation (one-piece)
Assumption of proportional hazards between intervention and comparator	See Appendix D
Function with best AIC fit	EV: Exponential, log-normal and log-logistic V: Log-logistic, exponential and Weibull
Function with best BIC fit	EV: Exponential, log-normal and log-logistic

Method/approach	Description/assumption
	V: Exponential, log-logistic and Weibull
Function with best visual fit	See Appendix D
Function with best fit according to evaluation of smoothed hazard assumptions	See Appendix D
Validation of selected extrapolated curves (external evidence)	N.A.
Function with the best fit according to external evidence	N.A.
Selected parametric function in base case analysis	EV: Log-logistic V: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

8.1.1.2 Extrapolation of Progression Free survival (PFS)

The selected base-case OS extrapolation approach for the EV (pre-selected V subgroup) and V arm was a parametric extrapolation with the Log-logistic distribution. This approach was selected based on AIC/BIC statistics, visual fit inspection.

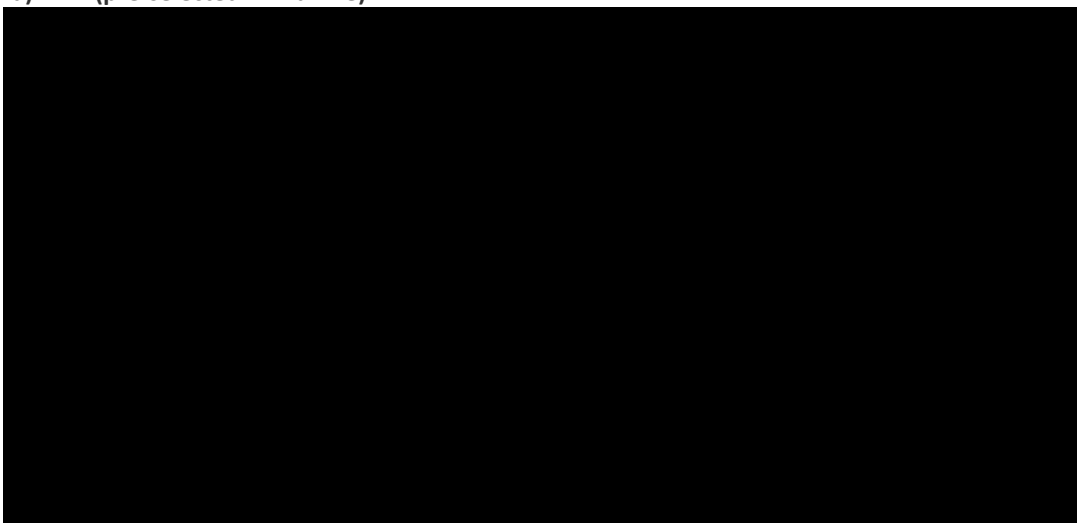
Table 15 Summary of assumptions associated with extrapolation of Progression Free survival (PFS)

Method/approach	Description/assumption
Data input	A Study to Evaluate Enfortumab Vedotin Versus (vs) Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301) (NCT03474107)
Model	Parametric extrapolation (one-piece)
Assumption of proportional hazards between intervention and comparator	See Appendix D
Function with best AIC fit	EV: Log-logistic V: Log-logistic
Function with best BIC fit	EV: Log-logistic V: Log-logistic
Function with best visual fit	See Appendix D
Function with best fit according to evaluation of smoothed hazard assumptions	N.A.
Validation of selected extrapolated curves (external evidence)	N.A.
Function with the best fit according to external evidence	N.A.
Selected parametric function in base case analysis	EV: Log-logistic V: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

8.1.1.3 Extrapolation of Duration of treatment (DoT)

Patients in the EV-301 study were allowed to receive the study treatment until the earlier of disease progression, a protocol-defined discontinuation criterion was met, study termination, or study completion. DoT for the model was derived using data from the EV-301 study to calculate the drug costs, see Figure 11 . For all treatment arms, DoT was capped by the estimated PFS. In the base-case, DoT for the EV (V subgroup) and V arms were based on the KM curve were extrapolated using the log-normal function. These approaches were selected based on AIC/BIC statistics, visual fit inspection and based on the function deemed clinically relevant by the DMC in the previous assessment of Padcev [3]. In scenario analyses other approaches are explored based on the plots provided in Appendix D.

a) EV (pre-selected vinflunine)



b) Vinflunine

Figure 11. Duration of treatment for a) EV (pre-selected vinflunine) and b) vinflunine

Table 16. Summary of assumptions associated with extrapolation of DoT

Method/approach	Description/assumption
Data input	A Study to Evaluate Enfortumab Vedotin Versus (vs) Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301) (NCT03474107)
Model	Parametric extrapolation (one-piece)
Assumption of proportional hazards between intervention and comparator	See Appendix D
Function with best AIC fit	EV: Log-normal V: Log-normal
Function with best BIC fit	EV: Log-normal V: Log-normal
Function with best visual fit	See Appendix D
Function with best fit according to evaluation of smoothed hazard assumptions	N.A.
Validation of selected extrapolated curves (external evidence)	N.A.
Function with the best fit according to external evidence	N.A
Selected parametric function in base case analysis	EV: Log-normal V: Log-normal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

8.1.2 Calculation of transition probabilities

N.A.

8.2 Modelling effects of subsequent treatments

In the EV-301 study, 39.5% and 42,3% patients from the EV (ITT) arm and chemotherapy (DPV) arm, respectively, initiated subsequent systemic treatments after having discontinued the study treatments, and paclitaxel was the most common subsequent treatment used in both arms [31].

Since cross over was allowed after the interim analysis (11 month data cut, 15 July 2020) a Rank preserving structural failure time (RPSFT) analysis was conducted to assess the impact of Arm B subjects who took EV as a subsequent therapy (18 patients or 5.9%). Sensitivity analyses were consistent with the primary OS HRs.

Given the comparable prevalence of subsequent treatment and use between EV and comparators, costs of these treatments were not accounted for in the model.

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

The modelled mean and median estimates for OS, PFS and DoT are compared to the observed mean from the EV-301 study (Table 17). The modelled health state distributions are shown in Figure 12 and Figure 13.

Table 17. Estimates for OS, PFS and DoT in the model

Treatment arm	EV (pre-selected V subgroup)		V	
	Observed, months	Predicted*, months	Observed, months	Predicted*, months
Median OS	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS	[redacted]	[redacted]	[redacted]	[redacted]
Mean PFS	[redacted]	[redacted]	[redacted]	[redacted]
Median DoT	[redacted]	[redacted]	[redacted]	[redacted]
Mean DoT	[redacted]	[redacted]	[redacted]	[redacted]

Figure 12.Health state distributions – EV

Figure 13.Health state distributions – vinflunine

9. Safety

9.1 Safety data from the clinical documentation

Results from the EV-301 study demonstrate that treatment with EV was tolerable with a manageable safety profile. Overall, in the ITT population, the incidence of treatment-emergent adverse events (TEAEs) was similar in the two arms. Also, the incidences of Grade ≥3 TEAEs, serious TEAEs, and TEAEs leading to death were similar between arms. [15]

Treatment-emergent adverse events – ITT (11 and 24 months FU)
A summary of TEAEs in the two data cuts- (15 July 2020 and 30 July 2021) is presented in **Error! Reference source not found.**. Overall, the incidence of TEAEs, serious TEAEs, TEAEs ≥ Grade 3, and TEAEs leading to withdrawal of treatment was similar between the enfortumab vedotin and chemotherapy arms. Given the difference between the 2 treatment arms in terms of time on treatment (median duration of treatment was 4.99 months for the enfortumab vedotin arm and 3.45 months for the combined chemotherapy arm). The incidence and severity of AEs in the enfortumab vedotin treatment arm of EV-301 were consistent with the known safety profile of the drug, as observed in the primary analysis.

At the data cut-off 30 July 2021, the incidence of overall TEAEs was similar to the results from the data cut-off 15 July 2020 ([redacted] and [redacted] for the EV (ITT) arm and DPV arm, respectively). Serious TEAEs were reported in [redacted] of EV (ITT) patients and [redacted] in DPV patients, and [redacted] in the EV (ITT) arm and [redacted] in the DPV arm experienced TEAEs leading to withdrawal of treatment. TEAEs of Grade 3 or higher occurred in [redacted] of the EV (ITT) patients and [redacted] of the DPV patients, with [redacted] and [redacted] of the patients, respectively, experiencing drug-related Grade ≥3 TEAE. [15, 20, 31]

Table 18. Summary of TEAEs, ITT population, 24 months FU and 11.75 months FU.

	24 months FU (July 2021)			11.75 months FU (July 2020)		
	EV (N = 296)	DPV (N = 291)	RR	EV (N = 296)	DPV (N = 291)	RR
TEAE, n (%)	[redacted]	[redacted]	[redacted]	290 (98.0)	288 (99.0)	0.99
Serious TEAE	[redacted]	[redacted]	[redacted]	138 (46.6)	128 (44.0)	1.06
TEAE leading to withdrawal of treatment	[redacted]	[redacted]	[redacted]	51 (17.2)	51 (17.5)	0.98
Grade ≥3 TEAE	[redacted]	[redacted]	[redacted]	210 (70.9)	193 (66.3)	1.07
Drug-related	155 (52.4)	147 (50.5)	1.04	[redacted]	[redacted]	[redacted]
TEAE leading to dose reduction	[redacted]	[redacted]	[redacted]	101 (34.1)	81 (27.8)	1.23
TEAE leading to dose interruption	[redacted]	[redacted]	[redacted]	180 (60.8)	85 (29.2)	2.08
TEAE leading to death	[redacted]	[redacted]	[redacted]	21 (7.1)	16 (5.5)	1.29

EV= Enfortumab vedotin; ITT= Intention-to-treat; RR= relative risk; TEAE= Treatment-emergent adverse events

Sources: [15, 20, 31]

Note that the safety data presented in Rosenberg et al 2023 refers to Safety population, which is defined as all patients which received study treatment, while Table 3 and 4 in Powels et al 2021 refers to the ITT population [15, 20].

Treatment-emergent adverse events – Vinflunine subgroup (11.75 and 24 months FU)
A summary of TEAEs based on the preselected V subgroup from the two data cut is presented in **Error! Reference source not found.** but the text below only refers to the 11.75 months data cut. Since the statistical analysis for the two different data cuts have used different measures to calculate the HR and P value, these values are only presented in the table for the 11.75 months FU since those are used in the cost-effectiveness model.. Almost all patients in each arm had a TEAE of any type, with [redacted] of patients in the EV (pre-selected V) arm and [redacted] of patients in the V (subgroup) arm experiencing a TEAE of any type. Serious TEAEs were reported in [redacted] of the EV (pre-selected V) population and [redacted] of the V (subgroup) population. In the EV (pre-selected V) arm [redacted] experienced TEAEs leading to drug discontinuation vs [redacted] in the V (subgroup) arm. The TEAEs of Grade 3 or higher occurred in [redacted] of patients in the EV (pre-selected V) arm and [redacted] in the V (subgroup) arm, with [redacted] of the patients, respectively, experiencing drug-related Grade ≥3 TEAE. [18]. In summary, the safety profile for the preselected EV patients is similar to EV in ITT population.

Table 19. Summary of TEAEs, vinflunine subgroup from 24 months FU and 11.75 months FU.

	24 months FU				11.75 months FU			
	EV (N = 71)	V (N = 75)			EV (N = 71)	V (N = 75)	HR, (95% CI)	P-value
TEAE, n (%)	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Not Severe TEAE	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 TEAE	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Drug-related Grade ≥3 TEAE	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: [18]

Treatment-emergent adverse events - Comparison of EV (ITT) and vinflunine subgroup
Similar results were seen when comparing EV (ITT) arm with V (subgroup) arm as when compared with the DPV arm (both data cuts). 98.0% of the patients in the EV (ITT) arm (both data cuts) experienced a TEAE compared with 98.7% of the patients in the V (subgroup) arm, RR=0.99. Only

46.6.0% of the patients in the EV (ITT) arm (11.75 months FU) experienced serious TEAEs compared with 65.3% of the patients in the V (subgroup) arm, RR=0.77. An overview of the comparison is provided in **Error! Reference source not found.**. [15,18, 31]

Table 20. Comparison of TEAEs in EV (ITT) and vinflunine subgroup.

	EV (N = 296) (24 months FU))	EV (N = 296) (11.75 months FU)	Vinflunine (N = 75) (11.75 months FU)	RR*
TEAE, n (%)	[redacted]	290 (98.0)	[redacted]	[redacted]
Serious TEAE	[redacted]	138 (46.6)	[redacted]	[redacted]
Grade ≥3 TEAE	[redacted]	210 (70.9)	[redacted]	[redacted]
Drug-related Grade ≥3 TEAE	155 (52.4)	[redacted]	[redacted]	[redacted]

RR for EV vs V based on the 11.75 months FU

Sources: [15, 18, 31]

Adverse reaction outcomes in the clinical documentation and health economic analysis

The inputs of AE rates were obtained from the EV-301 study safety cohort data cut 15 July 2020 (Table 21). In the base case, AE rates for EV were derived from the EV (ITT) population (following the recommendation received during the dialogue meeting with the DMC) and those for V were derived from the V subgroup. TEAEs of grade ≥3 were included in the model if they affected ≥ 5% of patients receiving any treatment considered in the model. The later data cut is not used since the data was not available for V, the summary of TEAEs only shows a small increase in the late data cut and the AE cost only have a marginal impact on the ICER.

Table 21. Adverse reaction outcomes*

Grade 3 or 4 AEs	Clinical documentation		Used in the model (numerical value)	
	EV (ITT; n=296) (%)	V (n=75) (%)	EV (ITT; n=296) (%)	V (n=75) (%)
Anemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]

*EV AE rates are from the ITT population of the EV-301 trial.

White blood cells are cells of the immune system and include monocytes, eosinophils, basophils, lymphocytes and neutrophils. In cases where only the neutrophils are decreased, the diagnosis is neutrophil count decreased and in severe cases, neutropenia. The overall white blood cell count can be low, but not related to the neutrophils only and is diagnosed as white cell count decreased. White blood cell count and neutrophil count decreased were differentiated in the clinical study.

AE = adverse events; EV = enfortumab vedotin; ITT = intention-to treat; V = Vinflunine

Sources: Powles 2021, Astellas Pharma [20,31]

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

Table 22 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	EV-310 [22,19]	Utilities

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The health-related quality of life (HRQoL) of EV was assessed in EV-301 using two instruments, the EORTC QLQ-C30 and EQ-5D-5L. EORTC QLQ-C30 and the EQ-5D-5L were both validated in the la/mUC patient population. In this section only the result from EQ-5D-5L will be presented since that's the data DMC request for the assessment [22,19]

For EQ-5D-5L both the utility index and the visual analogue scale (VAS) was used to collect HRQoL.

10.1.2 Data collection

The QoL questionnaires were completed at baseline (Day 7- to -1 before baseline), on Day 1 of each week for the first 12 weeks, then every 12 weeks thereafter, as well as at the end of treatment and at follow-up visits. QoL questionnaires were completed by the patient at home on handheld devices before each clinic visit, except for baseline Day 1 of the first week and at the end of treatment and follow-up visits, at which timepoints the questionnaires were completed by the patient at the clinic. [22,19]

The week 12 timepoint was selected to minimize the impact of missing data given that median of PFS for the chemotherapy arm is 4 months, therefore approximately half of the patients were expected to have progressed around week 12 on the chemotherapy arm. Additionally, PROs were collected weekly for the first 12 weeks, which provides a timeframe with the most granular data on the patient experience. [22,19]

Descriptive statistics were used to analyze data derived using the two PRO instruments. Domain and overall scores were also summarized using descriptive statistics for the PRO scores and the change from baseline in PRO scores at each visit, by treatment group. [22,19]

Change from baseline in PRO scores were analyzed using a restricted maximum likelihood (REML) based repeated measures approach (Mixed Model Repeated Measures (MMRM)). The primary objective of this analysis is to compare EV versus chemotherapy at Week 12 accounting for the multiple measurements during that time. [22,19]

Baseline compliance rates were comparable for the EV and chemotherapy treatment arms in both EORTC QLQ-C30 ([redacted] respectively) and the EQ-5D-5L ([redacted] respectively). A similar number of patients in each arm completed QoL assessments at each visit, with a slight decrease post-Week 12. [22,19]

There was a commensurate drop off in the number of subjects available for each visit, with both completion (Figure 14; Table 23) and compliance (Figure 15) rates between treatment groups comparable throughout the study, with a decrease post Week 12. At Week 12, XXXXXXXXX in the enfortumab vedotin arm and XXXXXXXXX in the chemotherapy arm completed the EQ-5D-5L questionnaire, meeting the minimum requirements for scoring XXXXXXXXXXXXXXXXXXXXXXX.

Figure 14. EQ-5D-5L completion rate (11.75 months FU – Data cut 15 July 2020)

Source: Astellas Pharma a/s data on file, 2021 [19]

Figure 15. EQ-5D-5L compliance rate (11.75 months FU – Data cut 15 July 2020)

Source: Astellas Pharma a/s data on file, 2021 [19]

Table 23. Response rate for the EQ-5D VAS (mFAS) - 11.75 months FU (Data cut 15 July 2020)

Visit	EV, n/N (%)	V, n/N (%)
Study start	[redacted]	[redacted]
Week 1	[redacted]	[redacted]
Week 2	[redacted]	[redacted]
Week 3	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Week 5	[redacted]	[redacted]
Week 6	[redacted]	[redacted]
Week 7	[redacted]	[redacted]
Week 8	[redacted]	[redacted]
Week 9	[redacted]	[redacted]
Week 10	[redacted]	[redacted]
Week 11	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 36	[redacted]	[redacted]
Week 48	[redacted]	[redacted]
Week 60	[redacted]	[redacted]
Week 72	[redacted]	[redacted]
Visit at end of treatment	[redacted]	[redacted]
30-day follow-up visit	[redacted]	[redacted]

Source: Astellas Pharma a/s data on file, 2021 [19]

EQ-5D = EuroQol-5 dimension instrument ; EV = enfortumab vedotin; mFAS = modified full analysis set; V = vinflunine

10.1.3 HRQoL results

EQ-5D-5L

Change from baseline defined as post-baseline value minus baseline value is calculated for each assessment for the EQ.5D-5L VAS and utility index scores. EQ-5D-5L visual analog scale (VAS) scores were summarized by treatment arm at each visit using descriptive statistics (mean, SD, median, minimum, and maximum). [19]

EQ-5D-5L results

Descriptive results from the EQ-5D-5L were largely consistent with the EORTC QLQ-C30 finding. Mean (SD) VAS scores at baseline were [redacted] in the EV arm and [redacted] in the chemotherapy arm. At week 12 the descriptive EQ-5D-5L VAS, reported as mean (SD) change from

baseline were [redacted] in the EV arm and [redacted] in the chemotherapy arm. At the timepoint, *end of treatment visit,* a change from baseline of [redacted] were reported in the EV arm and chemotherapy arm, respectively, Table 24.[19]

Results from the MMRM analysis indicated that EQ-5D-5L VAS score was maintained from baseline to Week 12, with a smaller decrease in the EV arm [redacted] compared with patients in the chemotherapy arm [redacted] and no significant difference noted [redacted]

Table 24. EQ-5D-5L results.

Follow-up time	EV (n=301) Mean (SD)	Chemotherapy (n=307) Mean (SD)
Baseline*	[redacted]	[redacted]
12 week *	[redacted]	[redacted]
12 week**	[redacted]	[redacted]
End of treatment visit*	[redacted]	[redacted]

* Descriptive statistical analysis
**MMRM analysis
EV= Enfortumab vedotin; ITT= intention to treat; MMRM= mixed model repeated measures; n= sample size; SD: standard deviation; SE: standard error
Source: [19]

Overall, patients treated with EV maintained QoL over the study period and had better global health score, with significant improvement in pain compared with patients treated with chemotherapy. Patients in the chemotherapy arm generally showed more deterioration and higher variability of QoL through the first 12 weeks of treatment.

EQ-5D-5L results – Vinflunine subgroup

Mean (SD) VAS scores at baseline were [redacted] in the EV (pre-selected V) arm and [redacted] in the V (subgroup) arm. The MMRM analysis indicated that QoL was maintained from baseline to Week 12, with a smaller decrease in the EV (pre-selected V) arm [redacted] compared with patient in the V (subgroup) arm [redacted] Health state utility values (HSUVs) used in the health economic model

10.1.4 Error! Reference source not found.HSUV calculation and mapping

The EQ-5D-5L was used to measure patients' health related quality of life in the EV-301 study. Descriptive statistics on the EQ-5D values were generated using the EV-301 data according to the following categories, which correspond to health states considered in the core EV model:

- **EQ-5D measures for the pre-progression health state:** any EQ-5D assessments corresponding to patients in the PFS state were used. This included all data collected from randomization day up to the earlier of the date of progressive disease, death, or being censored following the rule for analysis of PFS defined in the clinical statistical analysis plan of EV-301.
- **EQ-5D measures for the post-progression health state:** any EQ-5D assessment corresponding to alive patients not in the pre-progression health state was included.

EQ-5D utility scores were estimated based on EQ-5D-5L data from the EV-301 trial and the Danish EQ-5D-5L value set [66]. EQ-5D-5L data were obtained from all randomized patients in the EV-301 trial. The QoL questionnaires were completed at baseline (Day 7- to -1 before baseline), on Day 1 of each week for the first 12 weeks, then every 12 weeks thereafter, as well as at the end of treatment and 30 days post last dose. QoL questionnaires were completed by the patient at home on handheld devices before each clinic visit, except for baseline Day 1 of the first week and at the end of treatment and follow-up visits, at which timepoints the questionnaires were completed by the patient at the clinic. The week 12 timepoint was selected to minimize the impact of missing data given that median of PFS for the chemotherapy arm is 4 months, therefore approximately half of the patients were expected to have progressed around week 12 on the chemotherapy arm. Additionally, PROs were collected weekly for the first 12 weeks, which provides a timeframe with the most granular data on the patient experience.[22,64] Health state utility values were calculated as follows:

- Pre-progression utility was estimated based on EQ-5D data collected from randomization day up to the earliest of progressive disease, death, or being censored following the rule of progression free survival defined in the clinical statistical analysis plan of EV-301.
- Post-progression utility was estimated based on EQ-5D data corresponding to alive patients not in the pre-progression health state

No imputation was performed for missing evaluations and thus a subject who did not have an evaluation on a scheduled visit would be excluded from the analysis for that visit. Utility was estimated using a generalized estimating equation (GEE) model with a robust variance estimator to account for correlation within patients' repeated assessments. Utility by health states was estimated in one model with health state (pre- vs. post-progression) as the independent variable, and utilities from all included patients were used. Treatment-specific pre-progression utility was estimated only using pre-progression utilities from respective treatment. Pre-progression utility was estimated based on EQ-5D data collected from randomization day up to the earliest of progressive disease, death, or being censored following the rule of progression free survival defined in the clinical statistical analysis plan of EV-301. Post-progression utility was estimated based on EQ-5D data corresponding to alive patients not in the pre-progression health state. Treatment-specific pre-progression utility was estimated based on EQ-5D data collected from each treatment group in pre-progression health state.

The estimated pre- and post-progression utility results are presented in Table 25.

Table 25. Overview of the HSUV measured during clinical trials forming the basis for the relative efficacy

Health State	Results, mean (SE) [95% CI]*	Instrument	Tariff (value set) used	Comments
Pre-progression (EV – pre-selected V subgroup; n=62)	[redacted]	EQ-5D-5L	Denmark [66]	
Pre-progression (V subgroup; n=65)	[redacted]	EQ-5D-5L	Denmark [66]	
Post-progression (Full ITT population; n=262)	[redacted]	EQ-5D-5L	Denmark [66]	
Pre-progression (Full ITT population; n=521)	[redacted]	EQ-5D-5L	Denmark [66]	
Treatment-specific pre-progression utility				

Health State	Results, mean (SE) [95% CI]*	Instrument	Tariff (value set) used	Comments
EV (ITT)	[redacted]	EQ-5D-5L	Denmark [66]	
EV (subgroup DP)	[redacted]	EQ-5D-5L	Denmark [66]	
EV (subgroup D)	[redacted]	EQ-5D-5L	Denmark [66]	
EV (subgroup P)	[redacted]	EQ-5D-5L	Denmark [66]	
EV (subgroup V)	[redacted]	EQ-5D-5L	Denmark [66]	
DPV	[redacted]	EQ-5D-5L	Denmark [66]	
DP	[redacted]	EQ-5D-5L	Denmark [66]	
D	[redacted]	EQ-5D-5L	Denmark [66]	
P	[redacted]	EQ-5D-5L	Denmark [66]	
V	[redacted]	EQ-5D-5L	Denmark [66]	

CI = 95% confidence interval; DPV = docetaxel, paclitaxel, or vinflunine; EQ-5D-5L = EuroQol-5 dimension-5 level Instrument; EV = enfortumab vedotin; HSUV = health state utility values; ITT = intention-to treat; NA = not available; SE = standard error; V = vinflunine

Pre-progression utility was estimated based on EQ-5D data collected from randomization day up to the earliest of progressive disease, death, or being censored following the rule of progression free survival defined in the clinical statistical analysis plan of EV-301. Post-progression utility was estimated based on EQ-5D data corresponding to alive patients not in the pre-progression health state.

Treatment-specific pre-progression utility was estimated based on EQ-5D data collected from each treatment group in pre-progression health state. EV denotes all EV-treated patients. EV (subgroup DP) denotes EV-treated patients whose pre-selected chemotherapy was D or P.

*95% CIs were not available from the trial. 95% CIs are calculated using SE and beta distribution of the utility parameter

Source: [19,66]

10.1.5 HSUV results

The utility values underpinning the CEA are based on HRQoL measured directly using the EQ-5D-5L questionnaire, valued using general population preferences as per the Danish EQ-5D-5L valuation set.[66] Both in line with the reference case and following previous oncology appraisals, the key EQ-5D data were collected within the pivotal RCT for this submission, EV-301.

The CE model assigns utility values to pre-progression and post-progression health states. Patients in the post-progression health state are expected to experience a relatively worse HRQoL, with more frequent problems in mobility, self-care, usual activities, pain, and anxiety/depression. Thus, they are assigned a lower utility.

In the base-case analysis, health state utility values are estimated by the GEE model using EV-301 data from the safety population, informed by progression status and treatment received. Clinical feedback by experts at the University of Sheffield suggested that utilities would be similar across treatment arms following disease progression. Therefore, the base-case analysis considers utility values by treatment arm in the progression-free health state and consistent utility values in the progressed disease health state.

Aging effect on utilities is expected to be minor given the short life expectancy for the target population and therefore was not considered in the EV model.

Utilities for adverse reactions are not included in the model. The impact of increased AEs is assumed to be captured within treatment-specific pre-progression health state utilities.

The estimated pre- and post-progression utility results for relevant treatment groups are presented in Table 26.

Table 26. Summary of the HSUV (EQ-5D-5L) used in the model

	HSUV (SE)	95% CI*	Tariff (value set) used	Source
Pre-progression, EV (pre-selected for V subgroup) vs. V subgroup				
Pre-progression (EV – pre-selected V subgroup; n=62), mean utility (SE)*	[redacted]	[redacted]	Denmark [66]	EV-301 trial [18]
Pre-progression (V subgroup; n=65), mean utility (SE)*	[redacted]	[redacted]		
Pre-progression, EV (ITT) vs. DPV				
Pre-progression (EV – ITT; n=270), mean utility (SE)*	[redacted]	[redacted]	Denmark [66]	EV-301 trial [18]
Pre-progression (DPV; n=251), mean utility (SE)*	[redacted]	[redacted]		
Pre-progression and post-progression (full ITT Population)				
Pre-progression (Full ITT population; n=521), mean utility (SE)*	[redacted]	[redacted]	Denmark [66]	EV-301 trial [18]
Post-progression (Full ITT population; n=262), mean utility (SE)*	[redacted]	[redacted]		

* Values presented in this table calculated using SE and beta distribution of the utility parameter for use in the sensitivity analysis.

CI = 95% confidence interval; DPV = docetaxel, paclitaxel, or vinflunine; EV = enfortumab vedotin; EQ-5D-5L = EuroQol-5 dimension-5 level Instrument; HSUV = health state utility values; ITT = intention-to treat; NA = not available; OWSA = one-way sensitivity analysis; SE = standard error; V = vinflunine

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

Drug acquisition costs were calculated as a function of unit drug cost per dose, dose frequency, relative dose intensity, and treatment duration. As EV and V are intravenous infusion drugs, both vial wastage and patients' weight (for EV) or body surface area (BSA) (for V) pose non-trivial influences on drug cost estimation. As such, two vial sizes (i.e., standard and alternative vial sizes) and the unit costs associated with each vial size were considered to minimize vial wastage. The distributions of the weight and BSA were also considered in calculating the drug cost per dose, specifically by using means and standard deviations of weight and BSA from the EV-301 ITT population, distribution of weight and BSA were estimated in percentile form with 5% as the bin width. Within each bin of the weight and BSA distribution, drug costs of EV and chemotherapies were calculated, respectively. The average drug costs across all bins were then used to simulate treatment costs for the full cohort over the modelled time horizon.

Unit drug costs and sources of the cost inputs for EV and comparators are summarized in Table 27. The list price for a 20 mg and a 30 mg vial of EV are 4,643 DKK and 6,964 DKK which was retrieved from Medicinpriser.dk (February 2024). This translates to a monthly drug cost of 59,483 DKK for EV [three 30-min infusions considering wastage, dose intensity of [redacted] and average number of vials calculated assuming a normal distribution for mean (SD) body weight of 73.9kg (0.7)]. The unit drug cost for vinflunine for a 250 mg and a 50 mg vial are 8,746 DKK and 1,749 DKK, respectively, was retrieved from Medicinpriser.dk (February 2024).

Table 27. Drug acquisition costs

Drug	Dosing schedule*	Dose unit*	Standard package size	Alt. package size	AIP per standard vial, DKK	AIP per alt. vial, DKK	Source
EV	Days 1, 8, 15 of each 28-day cycle	1.25 mg/kg	30 mg	20 mg	7,173.30	4,782.20	Medicinpriser.dk, February 2024 [76]
V	Day 1 of each 21-day cycle	320 mg/m^2	250 mg	50 mg	8,746.00	1,749.01	Medicinpriser.dk, February 2024 [76]

The cost year is 2024 for all costs.
* Dosing schedule and dosing units for all treatments were based on the EV-301 trial [15,31].
AIP = apotekernes indkøbspris; EV = enfortumab vedotin; V = vinflunine

Table 28 summarizes the dose intensity and utilization weights used to calculate drug and drug administration costs. Dose intensities for EV and V were estimated based on data from the EV-301 study. The utilization weights as well as dose intensity can be modified with user specified values.

Table 28. Dose intensity and utilization weights

Arm	Relative dose intensity*, %	Utilization weights, %	Source
EV	XXXXXXXX	Not applicable	EV-301, all patients randomized to EV arm
V	XXXXXXXX		EV-301, all patients randomized to receive V

* Dose intensity for all treatments were based on the EV-301 trial [15,31].
D = docetaxel; DPV = docetaxel, paclitaxel, or vinflunine; P = paclitaxel; V = vinflunine

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

Administration costs (Table 29) were obtained from DRG tariffs 2024. The administration frequency of EV and V were based on the dosing schedule from the EV-301 study protocol (ISN/Protocol 7465-CL-0301). As all drugs in the model are administered IV, the cost per administration were assumed to be the same. To determine the administration cost the code DC679M was used as both diagnosis and procedure code for administration of medication IV. Based on the selected diagnosis- and procedure codes, the 17MA98 DRG-code was applied in the model. The cost per administration is 1,989 DKK (Table 29).

Table 29. Administration costs for IV administered treatments (EV and V)

Delivery type(s)	Cost per administration*, 2024 DKK	Diagnosis/Procedure code	DRG Tariff (2024)
Outpatient visit – consultation	1,989	|DC679M|Kræft i urinblæren med metastaser|	|17MA98|MDC17 1-dagsgruppe, pat. mindst 7 år|[68]

The cost year is 2024 for all costs.
* The cost per administration was assumed to be the same, regardless the drug administered. To determine the administration cost the code DC679M was used as both diagnosis and procedure code for administration of medication IV. Based on the selected diagnosis- and procedure codes, the 17MA98 DRG-code was applied in the model.
EV = enfortumab vedotin; V = vinflunine

11.4 Disease management costs

The disease management costs vary by health state but not by treatments. The medical costs associated with health states account for costs of outpatient visits (including visits to hospital-based physicians, nurses, or general practitioners), emergency department (ED) visits, and hospitalizations (including inpatient and intensive care unit stays).

Costs of each resource are shown in Table 30. Specifically, outpatient costs were obtained from Tariff 17MA98. Costs per bed day for hospitalization visits were based on a long-term DRG (2024) tariff. The frequencies for all the visits are based on Flannery et al. (2018) [77]. This was a retrospective cohort study of patients identified in the SEER database with a new primary diagnosis of stage IV bladder cancer between January 2007 and December 2011. Health care visits

were collected for treated and untreated patients and categorized as bladder cancer related, adverse event related, or other. Health care visits were further classified by setting of care: outpatient, emergency, inpatient, skilled nursing facility, and hospice. We included only bladder cancer related visits in the model, and to reflect Danish practice and comments from DMC on the version 1.0 dossier for Padcev, only outpatient and emergency visits have been included [3]. DMC stated that due lake of transparency in the calculation of the hospitalisation, they have excluded the hospitalisation cost in the analysis, but they also stated that the impact of hospitalisation was marginal.

Monthly resource use and costs by health state are summarized in Table 31. Overall, the monthly pre-progression disease management cost was 8,228 DKK and the monthly post-progression disease management cost was 7,445 DKK. All costs were inflated to 2024 DKK.

Table 30. Unit medical costs

Medical care	Unit cost, DKK/period	Period	Diagnosis/ Procedure code	Sources and key assumptions
Hospital-based physician visits	1,989	per visit	|DC679M|Kræft i urinblæren med metastaser|	|17MA98|MDC17 1-dagsgruppe, pat. mindst 7 år|[68]
ED visits	1,989	per visit	|DC679M|Kræft i urinblæren med metastaser|	|17MA98|MDC17 1-dagsgruppe, pat. mindst 7 år|[68]

The cost year is 2024 for all costs.
*The model provides the user with the option of including palliative care costs. If palliative care costs inclusion is selected, the specified cost per visit will be used. The base case scenario does not include palliative care costs and the resource use frequency is therefore set to 0 in the base case.
DMC = Danish Medicines Council; ED = emergency department; ICU = intensive care unit; LOS = length of stay

Table 31. Healthcare resource use (HRU) by health state

Medical care	Pre-progression HRU per month	Post-progression HRU per month	Sources and key assumptions
Hospital-based physician visits	3.79	3.04	Flannery 2018 [77]: Number of outpatient visits per patient per month.
ED visits	0.10	0.23	Flannery 2018 [77]: Number of ED visits per patient per month

ED = emergency department; HRU = healthcare resource use; ICU = intensive care unit; KEE = key external expert; NHS = National Health Service

11.5 Costs associated with management of adverse events

AE costs were calculated for EV and comparator arms based on rates of grade ≥3 treatment-emergent AEs and unit costs per AE. The inputs of AE rates were obtained from the EV-301 study safety cohort data cut 15 July 2020 since data was not available for the later data cut. In the base case, AEs rates for EV were derived from the EV-301 study ITT population; those for V were derived from the EV-301 V subgroup.

In general, AEs of Grade 3 or 4 are managed by the oncology department in the outpatient setting. Febrile neutropenia is a more severe condition and requires in-hospitalisation and specialist care with a unit cost of 37,129 DKK. AEs affecting the blood and the blood forming organs like neutropenia, neutrophil- and white cell count decrease will not require hospitalization and are expected to be managed by the oncology department. DMC wrote in Padcev 1 version assessment report that on average, fatigue and asthenia is associated with a regional resource consumption management equivalent to an outpatient visit (DRG 11MA98) [3]. The clinical expert advising the DMC suggested that general physical health deterioration would not require any specific treatment. The expert also noted that AEs would not be expected to lead to significant costs as their frequencies are in line with what would be expected for other therapies.

Grade 3/4 AEs were included in the model if they affected ≥ 5% of patients receiving any treatment considered in the model. The costs associated with each of the AEs were derived from DRG Takster 2024 by combining diagnosis and procedure codes [68].

Adverse reaction costs for each treatment were calculated as a sum product of incidence of adverse reaction (as observed in the EV-301 trial follow-up period) and the unit costs for the management of it. This estimate was applied once in the 1st model cycle when all patients begin on treatment and are in the 'progression-free' health state. The rationale behind using this approach (compared the approach of calculating per-cycle probability of AE and applying it over the treatment duration) was that the AE rates remain unchanged over the extended treatment duration as toxicity events tend to occur at the start of the treatment. The overall cost for management of AEs per patient was XXXXXXXX for patients assigned to EV compared with XXXXXXXX for patients assigned to V.

Table 32. AE unit costs

Grade 3/4 AEs ≥ 5%	Unit cost, 2024 DKK	Diagnosis/Procedure code	Sources – 2024 DRG Tariffs
Anaemia	2,111	|DD649|Anæmi UNS|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
Neutropenia	2,111	|DD709A|Neutropeni og agranulocytose forårsaget af lægemiddel|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
Febrile neutropenia	37,129	|DD709A|Neutropeni og agranulocytose forårsaget af lægemiddel|	|16MA03|Granulocytose forårsaget af lægemiddel|[68]
Rash maculo-papular	1,625	|DR219|Hududslæt UNS|	| 09MA98| MDC09 1-dagsgruppe, pat. mindst 7 år|[68]
Decreased appetite	1,847	|DR630|Appetitløshed|	|10MA98| MDC10 1-dagsgruppe, pat. Mindst 7 år|[68]
Hyperglycemia	5,103	|DR739|Hyperglykæmi UNS|	|23MA03|Symptomer of fund, u. kompl. Bidiag.|[68]

Grade 3/4 AEs ≥ 5%	Unit cost, 2024 DKK	Diagnosis/Procedure code	Sources – 2024 DRG Tariffs
Neutrophil count decreased	2,111	|DD728|Anden forstyrrelse i hvide blodlegemer|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
White blood cell count decreased	2,111	|DD728|Anden forstyrrelse i hvide blodlegemer|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
Fatigue	1,550		|11MA98| MDC11 1-dagsgruppe, pat. mindst 7 år (assumed by Medicinrådet, Padcev Assessment 2022 [3,68]
Constipation	7,818	| DK590| Forstoppelse|	|06MA11 |Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.|[68]
Asthenia	1,550		|11MA98| MDC11 1-dagsgruppe, pat. mindst 7 år (assumed by Medicinrådet, Padcev Assessment 2022 [3,68]
General physical health deterioration	0		Assumed the same as fatigue†
Abdominal pain	7,818	|DR101|Mavesmerter lokaliseret til øvre abdomen |	|06MA11 |Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.|[68]

The cost year is 2024 for all costs.
* Assumption aligned with prior submission of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy.
† Assumption.
AE = adverse events

11.6 Subsequent treatment costs

Costs of concomitant treatments, and subsequent treatment post progression were assumed to be comparable across treatment arms and therefore were not considered in the base case analysis.

11.7 Patient costs

[Patient costs are based on per hour costs of patient time for medical visits and procedures as well as on costs for transportation to and from hospital visits. Patient cost inputs are presented in Table 33, and the time for medical visits and procedures used in the model is presented in Table 34. Patients' effective time spent on treatment was based on the time required for infusion of EV (30 minutes) and V (20 minutes) as per the respective SmPCs. These durations were also in line with

the DMC assessment of avelumab for first-line maintenance treatment. Patient time for monitoring and management of AEs was also based on the avelumab assessment.

Table 33. Patient cost inputs

Unit cost input	Unit cost, 2024 DKK	Sources
Patient time cost per hour	182 per hour	Medicinrådet, 2022 [3]
Patient transportation costs*	140 per visit	

The cost year is 2024 for all costs.
* Costs for transportation to and from the hospital for treatment, based on the DMC assumption of 14 km distance to hospital.
DMC = Danish Medicines Council

Table 34. Patient time inputs

Unit cost input	Patient time (minutes)	Sources
Infusion, vinflunine	20	Medicinrådet, 2022 [3]
Infusion, EV	30	
Outpatient clinic visit	30	
Admission, per day	4,320 (3 days)	
Oncologist visit	30	

CT = computed tomography; EV = enfortumab vedotin

11.8 Other costs

No terminal care costs were included in the base-case analysis. This is based on the assumption that the tariffs applied to disease management and management of adverse events are average costs of all medical services related to the treatment and that the terminal care costs by principle are covered by these tariffs. To test the potential impact of the inclusion of terminal care, a scenario analysis where the terminal care costs have been included is presented in section 8.7.3.

12. Results

12.1 Base case overview

Table 35 below provides an overview of the base case model settings applied in the analysis.

Table 35. Base case overview

Feature	Description
Patient characteristics	Based on ITT population of EV-301 (age, percent male, weight, height, BSA)
Comparator	Vinflunine (V)
Type of model	Three-state partitioned survival model with monthly cycle (i.e., 30.4 days)
Time horizon	10 years [3]
Annual discount rates	3.5% for cost and health outcomes [65]
Treatment line	2nd line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in EV-301. Danish population weights were used to estimate health-state utility values
Included costs	Treatment costs (drug and administration) Medical costs (outpatient visits, hospitalization, emergency room visits, intensive care unit visits) AE costs Patient costs
Dosage of pharmaceutical	Based on weight
Average time on treatment (i.e., DOT)	Parametric extrapolation based on data from EV-301 trial for EV (pre-selected for V) and V subgroup, EV (pre-selected V) and V: log-normal extrapolations based on AIC-BIC criteria and visual inspection (KM vs model curve).
Parametric function for PFS	Parametric extrapolation for EV (pre-selected V) and V subgroup data from EV-301 trial EV (pre-selected V) and V: log-logistic extrapolations based on AIC-BIC criteria and visual inspection (KM vs model curve)
Parametric function for OS	Parametric extrapolation for EV (pre-selected V) and V subgroup data from EV-301 trial EV (pre-selected V) and V: log-logistic extrapolations based on AIC-BIC criteria and visual inspection (KM vs model curve)

AE = adverse event; AIC = Akaike information criterion; BIC = Bayesian information criterion; DOT = duration of treatment; EQ-5D-5L=-EuroQol-5 dimension-5 level Instrument; EV = enfortumab vedotin; ITT = intention to treat; KM = Kaplan-Meier curve; OS = overall survival; PFS = progression-free survival; V = vinflunine

12.1.1 Base case results (pre-selected V subgroup) vs V

Table 36 below presents the clinical and economic outcomes for each EV and V cohorts as well as base case incremental cost-effectiveness results. All results are over the lifetime horizon and discounted.

Over the 10 years horizon, treatment with EV was estimated to add [redacted] LYs compared to treatment with V (Total LY of EV vs V: [redacted] vs [redacted]). Patients receiving EV spent longer in the pre-progression health state compared to patients on V ([redacted] years vs [redacted] years). This leads to an increase in QALY of [redacted] over V (Total QALY of EV vs V: [redacted] vs [redacted]).

Total costs per patient were estimated to be [redacted] DKK for treatment with EV and [redacted] DKK for treatment with V (Incremental total costs of [redacted] DKK per patient with EV compared to V). Of these costs, drug and administration costs were the largest component ([redacted] DKK per patient for EV and [redacted] DKK per patient for V) followed by the medical costs ([redacted] DKK per patient for EV and [redacted] DKK per patient for V). Per patient costs due to treatment-emergent AEs were [redacted] DKK for EV and [redacted] DKK for V. EV was estimated to have higher medical costs than V, which is largely related to longer PFS and OS for patients on EV (i.e., the longer survival duration means that patients stay on treatment longer and incur more healthcare visits).

The model estimates that the introduction of EV in Denmark will result in an incremental cost of [redacted] per LY gained or [redacted] per QALY gained in adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor.

Table 36. Base case results, EV vs V.

Per patient (Discounted)	EV	V	Difference (EV minus V)
LY gained			
Total LY gained	[redacted]	[redacted]	[redacted]
LY gained pre-progression	[redacted]	[redacted]	[redacted]
LY gained post-progression	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
QALYs: Pre-progression	[redacted]	[redacted]	[redacted]
QALYs: post-progression	[redacted]	[redacted]	[redacted]
Costs, DKK			
Treatment costs, Total	[redacted]	[redacted]	[redacted]
Pre-progression drug costs	[redacted]	[redacted]	[redacted]
Pre-progression administrative costs	[redacted]	[redacted]	[redacted]

Per patient (Discounted)	EV	V	Difference (EV minus V)
Medical costs, total	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Pre-progression disease management costs	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Post-progression disease management costs	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Adverse reactions costs	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Patient costs	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Total costs	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Incremental results			
Incremental costs, DKK			XXXXXXXXXX
Incremental life years			XXXX
Incremental QALYs			XXXX
ICER (per LY), DKK			XXXXXXXXXX
ICER (per QALY), DKK			XXXXXXXXXX

EV = enfortumab vedotin; ICER = incremental cost-effectiveness ratio; LY life years; QALY = quality-adjusted life years; V = vinflunine

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

One-way sensitivity analyses

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. Confidence intervals, where available, were used to define the lower and upper bounds of model parameters. If a SE was reported, this was used to set bounds according to the assumed distribution. Alternatively, when uncertainty information was not available, lower and upper bounds were calculated based on the assumption that the SE was 25% of the mean deterministic value.

In deterministic sensitivity analyses, **Error! Reference source not found.**, the ICER for EV vs. V ranged from XXXXXXXXXX DKK/QALY to XXXXXXXXXX DKK/QALY. The key model drivers included pre-progression utility in the vinflunine subgroup, vinflunine drug cost, and pre-progression utility in the EV subgroup (Figure 16). One of the main baseline characteristics in the model that differs from the Danish population is the average population weight (Danish average 75kg compared to the base case mean value of 73.9kg used in the model). However, varying the mean body weight (low input value – 72.5kg; high input value – 75.17kg) had a minor impact on the ICER compared to the base case ICER, Figure 16.

Table 37. One-way sensitivity analyses results

Parameter	Base-case input	One-way sensitivity analysis input		ICER (ΔCost/ΔQALY)	
		Low input value	High input value	Low input value	High input value
Utility					
Pre-progression, EV ±95% CI	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Pre-progression, V ±95% CI	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Post-progression, EV ±95% CI	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Post-progression, V ±95% CI	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Baseline Characteristics					
Mean age (years)±95% CI	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Male (%)±95% CI	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Average BSA (m^2)±95% CI (affects drug cost of comparators)	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Average weight (kg)±95% CI (affects drug cost of EV)	XXXX	XXXX	XXXX	XXXXXXXXXX	XXXXXXXXXX
Costs, DKK					
Pre-progression disease management costs±25%	XXXXXXXX	XXXXXXXX	XXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
Post-progression disease	XXXXXXXX	XXXXXXXX	XXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX

Parameter	Base-case input	One-way sensitivity analysis input		ICER (ΔCost/ΔQALY)	
		Low input value	High input value	Low input value	High input value
management costs±25%					
Pre-progression patient costs±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression patient costs±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EV admin cost±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EV patient cost±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
V drug cost±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
V admin cost±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
V patient cost±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EV, AE costs ±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
V, AE costs±25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity					
EV, dose intensity±95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
V, dose intensity±95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 16. Deterministic sensitivity analysis results ranked by impact on ICER values (EV vs. V)

Scenario analyses

In addition to the one-way sensitivity analyses, scenario analysis was performed to test the impact of change in key inputs and assumptions on the CE estimate. Table 38 below lists the scenarios conducted around the base case analysis presented above. These scenarios included alternate time horizons, discount rates, extrapolations of OS, PFS and DoT (to test structural uncertainties), drug wastage, utility, cost inputs, and population.

Additionally, since the cost-effectiveness of V has not previously been assessed by the DMC, a scenario was added in the sensitivity analysis using the cost of taxanes instead of vinflunine in the comparator arm to understand how the results would change if V had the same price as taxanes. This scenario compared the efficacy of EV (ITT) vs. DPV, with DP costs replacing V costs in the DPV arm, i.e., efficacy of EV vs. DPV and costs of EV vs. DP. Due to the lower acquisition cost of DP compared to V alone, the scenario using ITT as efficacy population and DPV as comparator with DP costs used for V in the DPV arm was the scenario with the largest impact on the ICER. However, this scenario assumes the efficacy of DPV and the cost of DP which underestimates the cost in the comparator arm. In addition, D and P are not considered relevant comparators in this group of frail patients.

The scenario using ITT as efficacy population and DPV as comparator (to reflect EV-301 trial) had a similar impact on base case CE estimates due to lower acquisition cost of DPV compared to V alone leading to decrease in incremental costs compared to the base case. Following this, using same utility for both EV and V in the pre-progression health states and using most conservative extrapolation function for OS had most impact on the base case CE estimates.

Table 38. Scenario analyses

Parameter	Base Case	Scenario	ICER (cost/QALY), DKK
Time horizon	10 years	30 years	XXXXXXX
Annual discount rates	3.5% for cost and health outcomes	0%	XXXXXXX
		5%	XXXXXXX
OS	EV (pre-selected V) and V: log-logistic extrapolations based on AIC-BIC criteria and visual inspection	Patient level data KM through month 20 followed by log-logistic extrapolation for both EV and V	XXXXXXX
		Most conservative survival function for both EV and V (exponential)	XXXXXXX
PFS	EV (pre-selected V) and V: log-logistic extrapolations based on AIC-BIC criteria and visual inspection	Patient level data KM through month 20 followed by log-logistic extrapolation for both EV and V	XXXXXXX
DOT	EV (pre-selected V) and V: log-normal extrapolations based on AIC-BIC criteria and visual inspection	Patient level data KM through month 20 followed by log-normal extrapolation for both EV and V	XXXXXXX
EV list price per 30 mg and 20 mg vials	Base case assumes dose intensity, wastage, and body weight/BSA distribution in calculation of the drug cost	No wastage	XXXXXXX
Utility	Treatment-specific in the pre-progression state; same utility for all treatments in the post-progression state (Danish utility weights)	No treatment-specific utility in pre-progression state	XXXXXXX
Comparator	EV (preselected for V) vs. V subgroup	ITT as efficacy population and DPV as comparator (to reflect EV-301 trial)	XXXXXXX
		DPV price same as V price given D and P are not used in Denmark)	XXXXXXX
		ITT as efficacy population and DPV as comparator (to reflect EV-301 trial) DP costs used for V in the DPV arm**	XXXXXXX

12.2.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was conducted in which multiple input parameters were varied simultaneously over 5,000 iterations, by sampling their values from uncertainty distributions. Averages of costs, life years and QALYs over the 5,000 iterations were calculated.

Whenever available, the SE of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, variability was assumed as 10% of the mean value.

Parametric time-to-event inputs were varied according to multivariate normal distributions, to account for joint parametric uncertainty. Baseline characteristics such as age, weight, BSA, and percent male were varied according to normal distributions. Dose intensities were also varied using normal distributions. Utility values bound by 0 and 1 were assigned beta distributions. Where uncertainty data were available, costs were assigned gamma distributions to reflect the expected skew.

Probabilistic CE results are illustrated in Table 39, Figure 17 and Figure 18. The probabilistic ICER (XXXXXXXX DKK per QALY) was comparable with the base case result, estimated at XXXXXXXX DKK per QALY. A range of willingness-to-pay (WTP) values for a QALY gained were tested given a lack of ICER threshold to establish cost-effectiveness in Denmark. Across the WTP values tested, treatment with EV had a higher probability of being cost-effective than treatment with V at a WTP value equal to or greater than XXXXXXXX DKK per QALY gained. A convergence plot for the estimated mean ICER is shown in

Figure 19.

The data and assumptions underlying the probabilistic sensitivity analyses are shown in Table 45. Overview of parameters in the PSA in Appendix H.

Table 39. Comparison of probabilistic outcomes and base case outcomes

Probabilistic outcomes	Values
Total cost: Enfortumab Vedotin	XXXXXXXX
Total cost: Vinflunine	XXXXXXXX
Total QALYs: Enfortumab Vedotin	XXXX

Total QALYs: Vinflunine	XXXX
Incremental cost: Enfortumab Vedotin vs. Vinflunine	XXXXXXXX
Incremental QALYs: Enfortumab Vedotin vs. Vinflunine	XXXX
Probabilistic ICER	XXXXXXXX
Base case outcomes	
Base case incremental cost: EV vs. Vinflunine	XXXXXXXX
Base case incremental QALYs: EV vs. Vinflunine	XXXX
Base case ICER	XXXXXXXX

Figure 17. Scatterplot of probabilistic sensitivity analysis

Figure 18. Cost-effectiveness acceptability curve

Figure 19. Convergence plot

13. Budget impact analysis

Number of patients

Astellas estimate that 25-48 patients are eligible for EV within the given indication in Denmark per year. In the budget impact assessment 48 patients per year is used (Table 40), which is based on DMC assumption from Padcev assessment report. [3] The yearly uptake in the budget impact analysis is assumed to be 100% from year 1 to year 5, which was also an assumption by DMC in the same.

Table 40. Number of patients expected to be treated over the next five-year period - if EV is introduced

Year	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
EV	48	48	48	48	48
V	0	0	0	0	0
			Non-recommendation		
EV	0	0	0	0	0
V	48	48	48	48	48

EV = enfortumab vedotin; V = vinflunine

Budget impact

The budget impact analysis for years 1 to 5 with and without a recommendation for reimbursement of EV are shown below (Table 41). The total budget impact is [redacted] DKK in year 1 and increases to [redacted] DKK in year 5. The calculations are based on the assumption that all 48 patients will start treatment on day 1 of each year.

Table 41. Expected budget impact of recommending the EV over 5 years

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended (	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

It was not possible to obtain Danish expert validation for the inputs for this assessment, however, the chairman of the expert committee was consulted at the dialogue meeting. In addition, the following experts were consulted.

14.1 Nordic Clinical Experts – Validation of inputs

Jan Oldenburg - Norway
Clinical Oncologist, Akershus University Hospital

14.2 Experts from University XXXXXX – Global model development

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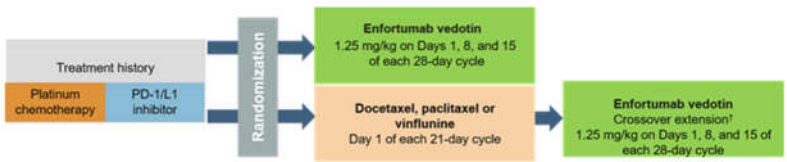
Appendix A. Main characteristics of studies included

Trial name: EV – 301	NCT number: NCT03474107 [15]
Objective	Compare the overall survival (OS) of participants with la/mUC r treated with enfortumab vedotin to the OS of participants treated with chemotherapy.
Publications – title, author, journal, year	Rosenberg al. EV-301 long-term outcomes: 24-month findings from the phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. Ann Oncol. 2023 Nov;34(11):1047-1054 Powles et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med 2021;384:1125-35. DOI: 10.1056/NEJMoa2035807
Study type and design	A multinational, randomized, open-label, Phase III study comparing the efficacy and safety of enfortumab vedotin with chemotherapy in patients with previously treated la/mUC (platinum-based chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting with disease progression/relapse during or after PD-1/L1 inhibitors). The study consisted of three phases: screening, treatment, and follow-up. The screening took place up to 28 days prior to randomization. The treatment phase started with Cycle 1 and continued to subsequent 28-day or 21-day cycles (for Arm A and Arm B, respectively) until one of the discontinuation criteria was met or upon study termination, or study completion, whichever occurred first. A study schematic is presented in **Figure a**. **Figure a. Study schematic for EV-301** 
Sample size (n)	A total of 608 patients at 191 centers in 19 countries (of which 3 were in Denmark - Herlev, Rigshospitalet, and Odense) were randomly assigned to receive EV (301 patients) or chemotherapy preselected by the investigator (307 patients)
Main inclusion and exclusion criteria	**Inclusion criteria** • Subject is legally an adult according to local regulation at the time of signing informed consent. • Subject has histologically or cytologically confirmed urothelial carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Patients with urothelial carcinoma (transitional cell) with squamous differentiation or mixed cell types are eligible. • Subject must have experienced radiographic progression or relapse during or after a checkpoint inhibitor (CPI) (anti-programmed cell death protein 1 (PD1) or anti-programmed death-ligand 1 (PD-L1)) for locally advanced or metastatic disease. Patients who discontinued CPI treatment due to toxicity are eligible provided that the patients have evidence of disease progression following discontinuation. The CPI need not be the most recent therapy. Patients for whom the most recent therapy has been a non-CPI-based regimen are eligible if the patients have progressed/relapsed during or after the patients' most recent therapy. Locally

advanced disease must not be amenable to resection with curative intent per the treating physician.

- Subject must have received a platinum containing regimen (cisplatin or carboplatin) in the metastatic/locally advanced, neoadjuvant or adjuvant setting. If platinum was administered in the adjuvant/neoadjuvant setting subject must have progressed within 12 months of completion.
- Subject has radiologically documented metastatic or locally advanced disease at baseline.
- An archival tumor tissue sample should be available for submission to central laboratory prior to study treatment. If an archival tumor tissue sample is not available, a fresh tissue sample should be provided. If a fresh tissue sample cannot be provided due to safety concerns, enrollment into the study must be discussed with the medical monitor.
- Subject has ECOG PS of 0 or 1
- The subject has the following baseline laboratory data:
    - absolute neutrophil count (ANC) ≥ 1500/mm3
    - platelet count ≥ 100 × 109/L
    - hemoglobin ≥ 9 g/dL
    - serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for patients with Gilbert's disease
    - creatinine clearance (CrCl) ≥ 30 mL/min as estimated per institutional standards or as measured by 24 hour urine collection (glomerular filtration rate [GFR] can also be used instead of CrCl)
    - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 3 x ULN for patients with liver metastases
- Female subject must either:
    - Be of nonchildbearing potential: Postmenopausal (defined as at least 1 year without any menses for which there is no other obvious pathological or physiological cause) prior to screening, or documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
    - Or, if of childbearing potential: Agree not to try to become pregnant during the study and for at least 6 months after the final study drug administration, and have a negative urine or serum pregnancy test within 7 days prior to Day 1 (Females with false positive results and documented verification of negative pregnancy status are eligible for participation), and if heterosexually active, agree to consistently use a condom plus 1 form of highly effective birth control per locally accepted standards starting at screening and throughout the study period and for at least 6 months after the final study administration.
- Female subject must agree not to breastfeed or donate ova starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.
- A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:
    - Agrees to use a male condom starting at screening and continue throughout the study treatment and for at least 6 months after final study drug administration. If the male subject has not had a vasectomy or is not sterile as defined below the patients female partner(s) is utilizing 1 form of highly effective birth control per locally accepted standards starting at screening and continue throughout study treatment and for at least 6 months after the male subject receives final study drug administration.
- Male subject must not donate sperm starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.

- Male subject with a pregnant or breastfeeding partner(s) must agree to abstinence or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for at least 6 months after the final study drug administration.
- Subject agrees not to participate in another interventional study while on treatment in present study.

Inclusion Criteria for COE:

- Subject is eligible for the COE if they continue to meet all inclusion criteria from the main protocol in addition to the following when the patient is evaluated for eligibility to participate in the COE portion of the study:
- Institutional review board (IRB)/ independent ethics committee (IEC) approved written COE informed consent and privacy language as per national regulations (e.g., health insurance portability and accountability act [HIPAA] Authorization for US sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
- Subject was randomized to Arm B and is either currently on study treatment or has discontinued study treatment due to intolerance, AE or progression of disease, has not started a new systemic anticancer treatment and is still participating in the follow up phase of the study.

Exclusion criteria

- Subject has preexisting sensory or motor neuropathy Grade ≥ 2.
- Subject has active central nervous system (CNS) metastases. Patients with treated CNS metastases are permitted on study if all the following are true:
    - CNS metastases have been clinically stable for at least 6 weeks prior to screening
    - If requiring steroid treatment for CNS metastases, the subject is on a stable dose ≤ 20 mg/day of prednisone or equivalent for at least 2 weeks
    - Baseline scans show no evidence of new or enlarged brain metastasis
    - Subject does not have leptomeningeal disease
- Subject has ongoing clinically significant toxicity (Grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery). Subject with ≤ Grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may be enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated). Patients with ongoing ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded. Patients with ongoing immunotherapy related colitis, uveitis, or pneumonitis or patients with other immunotherapy related AEs requiring high doses of steroids (> 20 mg/day of prednisone or equivalent) are excluded.
- Subject has prior treatment with EV or other monomethyl auristatin E (MMAE)-based Antibody drug conjugates (ADCs).
- Subject has received prior chemotherapy for urothelial cancer with all available study therapies in the control arm (i.e., both prior paclitaxel and docetaxel in regions where vinflunine is not an approved therapy, or prior paclitaxel, docetaxel and vinflunine in regions where vinflunine is an approved therapy).
- Subject has received more than 1 prior chemotherapy regimen for locally advanced or metastatic urothelial cancer, including chemotherapy for adjuvant or neo-adjuvant disease if recurrence occurred within 12 months of completing therapy. The substitution of carboplatin for cisplatin does not constitute a new regimen provided no new chemotherapeutic agents were added to the regimen.
- Subject has history of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Patients with nonmelanoma skin cancer, localized prostate cancer

	treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed. • Subject is currently receiving systemic antimicrobial treatment for viral, bacterial, or fungal infection at the time of first dose of EV. Routine antimicrobial prophylaxis is permitted. • Subject has known active Hepatitis B (e.g., hepatitis B surface antigen (HBsAg) reactive) or active hepatitis C (e.g., hepatitis C virus (HCV) Ribonucleic Acid (RNA) [qualitative] is detected). • Subject has known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2). • Subject has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug. • Subject has radiotherapy or major surgery within 4 weeks prior to first dose of study drug. • Subject has had chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug. • Subject has known hypersensitivity to EV or to any excipient contained in the drug formulation of EV; OR subject has known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells. • Subject has known hypersensitivity to the following: docetaxel or to any of the other excipients listed in product label, including polysorbate 80, paclitaxel, or to any of the other excipients listed in product label, such as macrogolglycerol ricinoleate 35 (Ph.Eur.); and vinflunine or to any of the other excipients listed in product label such as other vinca alkaloids (vinblastine, vincristine, vindesine, vinorelbine). • Subject has known active keratitis or corneal ulcerations. • Subject has other underlying medical condition that would impair the ability of the subject to receive or tolerate the planned treatment and follow-up. • History of uncontrolled diabetes mellitus within 3 months of the first dose of study drug. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained. **Exclusion Criteria for COE** • Subject will be excluded from participation in the COE if they meet any of the exclusion criteria listed in the main protocol or if any of the following apply when the patient is evaluated for eligibility to participate in the COE portion of the study: • Subject has been diagnosed with a new malignancy while on Arm B in the EV-301 study. Patients with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.
Intervention	EV was administered to 301 patients at a dose of 1.25 mg per kilogram of body weight by means of intravenous infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle.
Comparator(s)	Chemotherapy was selected by the investigator before randomization and was one of the following:

	• 117 patients received docetaxel at a dose of 75 mg per square meter of body-surface area, administered intravenously over 60 minutes. • 112 patients received paclitaxel at a dose of 175 mg per square meter, administered intravenously over 3 hours. • 78 patients received vinflunine (in regions where it is approved for the treatment of urothelial carcinoma) at a dose of 320 mg per square meter, administered intravenously over 20 minutes. The use of vinflunine was capped at 35% of the patients in this trial. The chemotherapy treatments were administered on day 1 of a 21-day cycle.
Follow-up time	Patients had a follow-up visit 30 days (+ 7 days) after their last dose of drug for safety assessments. If a subject discontinued study drug prior to undocumented radiographic disease progression (i.e. PFS1), the subject was to enter the post-treatment follow-up period and continue to undergo imaging assessments every 56 days (± 7 days) until PFS1 was documented, or the subject started another anticancer treatment, whichever occurred earlier. Enrollment was initiated in June 2018. At the pre-planned interim analysis on 15 July 2020, the efficacy boundary had been crossed, and at the recommendation of the IDMC, the study was stopped early for efficacy analysis. The protocol was amended to allow for patients in the chemotherapy arm to cross over to receive EV. The estimated study completion date is February 28, 2022. Radiographic imaging was performed at baseline and every 8 weeks. Bone scintigraphy was performed in all patients at screening; repeat scanning was performed at least every 8 weeks in patients with a positive scan. Imaging of the brain was performed, if clinically indicated, at baseline and throughout the trial. Patients were followed until radiographic disease progression, until discontinuation criteria were met, or until trial completion. Patients who discontinued treatment before disease progression underwent imaging assessments every 8 weeks until documented disease progression or initiation of a different anticancer treatment, whichever occurred earlier. After radiographic disease progression had occurred, patients entered the long-term follow-up phase and were followed at least every 3 months from the date of the follow-up visit for vital status until death, loss to follow-up, withdrawal of consent, or termination of the trial.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was overall survival evaluated according to RECIST, version 1.1. Secondary endpoints included; Progression-free Survival on study therapy (PFS1) per RECIST, version 1.1 and Overall Response Rate (ORR) (Complete Response (CR) and Partial Response(PR)) per RECIST V1.1, safety assessed by Adverse Events, number of participants with laboratory value abnormalities and/or adverse events, number of participants with vital signs abnormalities and/or adverse events and patient-reported outcome assessed by quality of life: EuroQOL 5-dimensions (EQ-5D -5L) questionnaire. **Other endpoints:** Disease Control Rate (DCR) (CR + PR + stable disease [SD]) per RECIST V1.1, Duration of Response (DoR) per RECIST V1.1, Safety assessed by 12- lead electrocardiogram, Safety assessed by 12- lead electrocardiogram (ECG), and patient-reported outcome assessed by quality of life: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) were included as secondary endpoints in the study, but the results are not presented in this application

Method of analysis	All efficacy analyses were intention-to-treat analyses. The KM method was used to estimate rates of progression-free survival, overall survival, and duration of response, and a stratified log-rank test for treatment comparisons. In addition, the stratified Cox proportional hazards model (same stratification factors as used for stratified log-rank test) was used to estimate the HR and the corresponding 95% CIs for PFS and OS. For ORR and disease control rate the comparison between Arm A and Arm B was performed using the stratified CMH test. In addition, for each endpoint the corresponding 95% CI was constructed based on the estimated rates. The formal statistical comparison of Arm A and Arm B was conducted only per the planned multiplicity adjustment rule. Additional sensitivity analysis for ORR and DCR included the comparison of ORR and DCR, respectively, regardless of confirmation.
Subgroup analyses	Pre-planned subgroups included age group, sex, geographic region, ECOG PS score, liver metastasis presence, preselected chemotherapy group, primary site of tumor, previous systemic therapies, and response to previous CPI status.
Other relevant information	A post hoc statistical analysis was conducted based on the randomized phase 3 study to evaluate Enfortumab Vedotin vs chemotherapy. It specifically investigates the treatment effects in a subpopulation of subjects (target population) who have been pre-selected for treatment with the comparator Vinflunine. [18]

Appendix B. Efficacy results per study

Results per study

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall-survival	*EV*	*207/301*	*12.91 months (11.01–14.92)*	*3.97*	*N/A*	*N/A*	*HR: 0.70*	*0.58-0.85*	*0.001*	*Overall survival was estimated for each treatment arm with the use of KM method and comparisons between groups were conducted with the use of the stratified log-rank test.*	[15]
	Chemo-therapy	*237/307*	*8.94 months (8.25–10.25)*								
Median progression-free survival	*EV*	*231/301*	*5.55 months (5.32-6.28)*	*1.84*	*N/A*	*N/A*	*HR: 0.63*	*0.53-0.76*	*<0.001*	*Progression-free survival was estimated for each treatment arm with the use of KM method and comparisons between groups were conducted with the use of the stratified log-rank test.*	[15]
	Chemo-therapy	*248/307*	*3.71 months (3.52-3.94),*								
Overall response rate	*EV*	*119/288*	*41.3% (35.57, 47.25)*	*22.7*	*N/A*	*N/A*				*ORR was compared with the use of a stratified CMH-test.*	[15]
	Chemo-therapy	*55/296*	*18.6% (14.32, 23.49)*								
Disease control rate	*EV*	*207/288*	*71.9% (66.3-77.0)*	*18.5*	*N/A*	*N/A*				*Disease control rate was compared with the use of a stratified CMH-test.*	[15]
	Chemo-therapy	*158/296*	*53.4% (47.5-59.2)*								
	EV	*81/119*	*7.62 months (5.68, 11.17)*	*0.59*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*The duration of response was analyzed with the use of the KM method.*	[15]

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median Duration of response	*Chemo-therapy*	*42/ 55*	*8.21 months (5.68-9.56)*								
Complete response	*EV*	*20/ 288*	*6.9%*	*3.5*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*CMH- test*	[15]
	Chemo-therapy	*10/ 296*	*3.3%*								
Quality of life, EORTC QLQ-C30 (baseline)	*EV*	[redacted]	[redacted]	*0.75*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[19]
	Chemo-therapy	[redacted]	[redacted]								
Quality of life, EORTC QLQ-C30 (12 weeks) *(11 month FU)*	*EV*	[redacted]	[redacted]	*3.42*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[19]
	Chemo-therapy	[redacted]	[redacted]								
Quality of life, EORTC QLQ-C30 (12 weeks) *(11 month FU)*	*EV*	[redacted]	[redacted]	*2.17 (SE: 1.86)*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Mixed model repeated measures*	[19]
	Chemo-therapy	[redacted]	[redacted]								
Quality of life, EORTC	*EV*	[redacted]	[redacted]	*2.22*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[19]

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
QLQ-C30 (End of treatment) ***(11 month FU)***	*Chemo-therapy*	XXXX	XXXXXXXXXXXX XXXX								
Quality of life, EQ-5D-5L (baseline) ***(11 month FU)***	*EV*	XXXX	XXXXXXXXXXXX XXXX	*-0.15*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	***Descriptive statistics were used.***	[19]
	Chemo-therapy	XXXX	XXXXXXXXXXXX XXXX								
Quality of life, EQ-5D-5L (12 weeks) ***(11 month FU)***	*EV*	XXXX	XXXXXXXXXXXX XXXX	*2.82*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	***Descriptive statistics were used.***	[19]
	Chemo-therapy	XXXX	XXXXXXXXXXXX XXXX								
Quality of life, EQ-5D-5L (12 weeks) ***(11 month FU)***	*EV*	XXXX	XXXXXXXXXXXX XXXX	*1.77 (SE: 1.79)*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Mixed model repeated measures*	[19]
	Chemo-therapy	XXXX	XXXXXXXXXXXX XXXX								
Quality of life, EQ-5D-5L (end of treatment) ***(11 month FU)***	*EV*	XXXX	XXXXXXXXXXXX XXXX	*2.39*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	***Descriptive statistics were used.***	[19]
	Chemo-therapy	XXXX	XXXXXXXXXXXX XXXX								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Overall TEAE (11 month FU)	*EV*	*290/296*	*98.0%*	*1*	*-1.22-3.41**	*0.320**	*RR: 0.99***	*0.97-1.01***	*0.325***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	*288/291*	*99.0%*								
Overall TEAE (drug-related) (11 month FU)	*EV*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Descriptive statistics were used.*	[17]
	Chemo-therapy	[redacted]	[redacted]								
Serious TEAEs (11 month FU)	*EV*	*138/296*	*46.6%*	*2.6*	*-5.42-10.58**	*0.527**	*RR: 1.06***	*0.89-1.27***	*0.522***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	*128/291*	*44.0%*								
Serious TEAEs (drug-related) (11 month FU)	*EV*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Descriptive statistics were used.*	[17]
	Chemo-therapy	[redacted]	[redacted]								
TEAEs Grade ≥3 (11 month FU)	*EV*	*210/296*	*70.9%*	*4.6*	*-2.90-12.04**	*0.230**	*RR: 1.07*	*0.96-1.19***	*0.228***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	*193/291*	*66.3%*								
	EV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Descriptive statistics were used.*	[17]

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
TEAEs Grade ≥3 (drug-related) (11 month FU)	*Chemo-therapy*	[redacted]	[redacted]								
TEAEs leading to dose reduction (11 month FU)	*EV*	*101/ 296*	*34.1%*	*6.3*	*-1.18-13.68**	*0.099**	*RR: 1.23***	*0.96-1.56***	*0.101***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	*81/ 291*	*27.8%*								
TEAEs leading to dose reduction (drug-related) (11 month FU)	*EV*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Descriptive statistics were used.*	[17]
	Chemo-therapy	[redacted]	[redacted]								
TEAEs leading to dose inter-ruption (11 month FU)	*EV*	*180/ 296*	*60.8%*	*31.6*	*23.73-38.90**	*<0.001**	*RR: 2.08***	*1.70-2.55***	*<0.001***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	*85/ 291*	*29.2%*								
TEAEs leading to dose inter-ruption (drug-	*EV*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Descriptive statistics were used.*	[17]
	Chemo-therapy	[redacted]	[redacted]								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
related) (11 month FU)											
TEAEs leading to treatment withdrawal (11 month FU)	*EV*	*51/ 296*	*17.2%*	*0.3*	*-5.84- 6.45**	*0.924**	*RR: 0.98***	*0.69- 1.40***	*0.925***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	*51/ 291*	[redacted]								
TEAEs leading to treatment withdrawal (drug-related) (11 month FU)	*EV*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Descriptive statistics were used.*	[17]
	Chemo-therapy	[redacted]	[redacted]								
TEAEs leading to death (11 month FU)	*EV*	*21/ 296*	*7.1%*	*1.6*	*-2.44- 5.68**	*0.426**	*RR: 1.29***	*0.69- 2.42***	*0.428***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	*16/ 291*	*5.5%*								
TEAEs leading to death (drug-related) (11 month FU)	*EV*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Descriptive statistics were used.*	[17]
	Chemo-therapy	[redacted]	[redacted]								
TEAEs leading to death, excluding	*EV*	*11/ 296*	*3.7%*	*0.1*	*-3.17- 3.39**	*0.949**	*RR: 0.98***	*0.43- 2.23***	*0.968***	*Descriptive statistics were used.*	[20]
	Chemo-therapy	11/ 291	3.8%								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
disease progression (11 month FU)											
TEAEs leading to death, excluding disease progression (drug-related) *(11 month FU)*	EV	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	Descriptive statistics were used.	[17]
	Chemo-therapy	XXXX	XXXX								

* Absolute difference CI calculated using: $D - \sqrt{(\rho_1 - l_1)^2 + (u_2 - \rho_2)^2}$ to $D + \sqrt{(\rho_2 - l_2)^2 + (u_1 - \rho_1)^2}$

** Relative risk (RR) calculated using: $RR = \frac{a/(a+b)}{c/(c+d)}$, with the SE of the log relative risk being: $SE\{\ln(RR)\} = \sqrt{\frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d'}}$, and the 95% CI being:

$95\%\ CI = \exp(ln(RR) - 1.96 * SE\{ln(RR)\})\ to\ \exp(ln(RR) + 1.96 * SE\{ln(RR)\})$

Table A3b Results of EV-301 (NCT03474107) – Vinflunine subgroup											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Overall survival was estimated for each treatment arm with the use of KM method and comparisons between groups were conducted with the use of a 2-sided unstratified log-rank test.*	[18]
	Vinflunine	XXXX	XXXX								
Median PFS	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*2-sided unstratified log-rank test.*	[18]
	Vinflunine	XXXX	XXXX								
Median DoR (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*2-sided unstratified log-rank test.*	[21]
	Vinflunine	XXXX	XXXX								
Quality of life, EORTC QLQ-C30 (baseline) (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[19]
	Vinflunine	XXXX	XXXX								
Quality of life, EORTC QLQ-C30 (12 weeks) (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Mixed model repeated measures*	[19]
	Vinflunine	XXXX	XXXX								

Table A3b Results of EV-301 (NCT03474107) – Vinflunine subgroup											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Quality of life, EQ-5D-5L (baseline)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[19]
	Vinflunine	XXXX	XXXX								
(11 month FU)											
Quality of life, EQ-5D-5L (12 weeks) (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Mixed model repeated measures*	[19]
	Vinflunine	XXXX	XXXX								
Overall TEAE (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
Serious TEAEs (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
Serious TEAEs excluding those related to disease progression	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21
	Vinflunine	XXXX	XXXX								
(11 month FU)											

Table A3b Results of EV-301 (NCT03474107) – Vinflunine subgroup											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Severe TEAEs (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
Severe TEAEs excluding those related to disease progression (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
TEAEs Grade ≥3 (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
TEAEs Grade ≥3 (Drug-related) (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
Not Severe (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
Not Severe TEAEs excluding those related to disease	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								

Table A3b Results of EV-301 (NCT03474107) – Vinflunine subgroup											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Reference
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
progression (11 month FU)											
TEAEs leading to drug discontinuation	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								
TEAEs leading to drug discontinuation excluding those related to disease progression (11 month FU)	*Enfortumab Vedotin*	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	*Descriptive statistics were used.*	[21]
	Vinflunine	XXXX	XXXX								

* Absolute difference CI calculated using: $D - \sqrt{(\rho_1 - l_1)^2 + (u_2 - \rho_2)^2}$ to $D + \sqrt{(\rho_2 - l_2)^2 + (u_1 - \rho_1)^2}$

** Relative risk (RR) calculated using: $RR = \frac{a/(a+b)}{c/(c+d)}$, with the SE of the log relative risk being: $SE\{\ln(RR)\} = \sqrt{\frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}}$, and the 95% CI being:

$95\%\ CI = \exp(ln(RR) - 1.96 * SE\{ln(RR)\})\ to\ \exp(ln(RR) + 1.96 * SE\{ln(RR)\})$

Appendix C. Comparative analysis of efficacy

N.A.

Appendix D. Extrapolation

D.1 Extrapolation of OS

D.1.1 Data input

Efficacy input (OS and PFS) and treatment duration were based on the EV-301 study and were extrapolated beyond the follow-up of the study to assess the CE of EV vs comparators over a lifetime horizon.

D.1.2 Model

Parametric functions considered for OS, PFS, and DoT extrapolation included exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions. The suitability of parametric survival models was evaluated based on the following criteria suggested by the systematic survival model selection process by National Institute for Health and Care Excellence(NICE) DSU TSD14:[69]

- **Akaike information criterion (AIC)/Bayesian information criterion (BIC) tests**: These criteria can be used to evaluate relative fit of different parametric survival models. Lower AIC and BIC values indicate better (complexity-adjusted) goodness-of-fit to the data.
- **Visual inspection**: Visual inspection evaluates visually how well a parametric survival model fits the observed KM. Along with the statistical fit (i.e., AIC/BIC), the parametric survival model that most closely follows the observed KM curve could be considered as the best fit.
- **Examination of the log-cumulative hazard plots (for OS and PFS)**: Hazard function implied by the parametric survival model varies by the distribution assumed (e.g., exponential models assumed constant hazard rate, Gompertz models implied a monotonic hazard etc.). Log-cumulative hazard plots are often constructed to evaluate whether the hazard function used in each parametric survival model show clinically suitable and plausible shape (i.e., non-monotonic, monotonic, or constant hazard functions).
- **Testing the proportional hazards assumption (for OS and PFS)**: The PH assumption needs to be evaluated when HRs are applied to a base survival curve for the comparisons between a reference arm (i.e., EV for this CEA) with comparators (i.e., chemotherapy arms). In addition, Schoenfeld residual test was conducted to examine the PH assumption and ensure that the treatment effect is proportional over time between reference and comparator arms.

D.1.3 Proportional hazards

The PH assumption between EV (V subgroup) and V arms couldn't be clearly determined. The proportional log cumulative hazard functions between the EV (V subgroup) and V arms cross (Figure 20) while the Schoenfeld residuals tests yielded non-significant test results (Figure 21).

Figure 20. Log cumulative hazard plots for OS

Figure 21. Schoenfeld residuals plots for OS

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

The selected base-case OS extrapolation approach for the EV (pre-selected V subgroup) and V arm was a parametric extrapolation with the log-logistic distribution This approach was supported by AIC/BIC statistics below.

Table 42. Statistical goodness of fit for OS extrapolation of EV (pre-selected V subgroup) and V subgroups

OS	Enfortumab Vedotin		Vinflunine	
Functional Form	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	XXXX	XXXX	XXXX	XXXX
Weibull	XXXX	XXXX	XXXX	XXXX
Log-Logistic	XXXX	XXXX	XXXX	XXXX
Lognormal	XXXX	XXXX	XXXX	XXXX
Gompertz	XXXX	XXXX	XXXX	XXXX
Generalized Gamma	XXXX	XXXX	XXXX	XXXX

D.1.5 Evaluation of visual fit

The figure below shows a comparison between the observed KM curves and the extrapolated curves.

(a) EV (V subgroup) **(b) V**

Figure 22. Parametric models for OS

D.1.6 Evaluation of hazard functions

The smoothed hazard plots below suggest a reasonably good fit of log-logistic and log-normal functions for both arms.

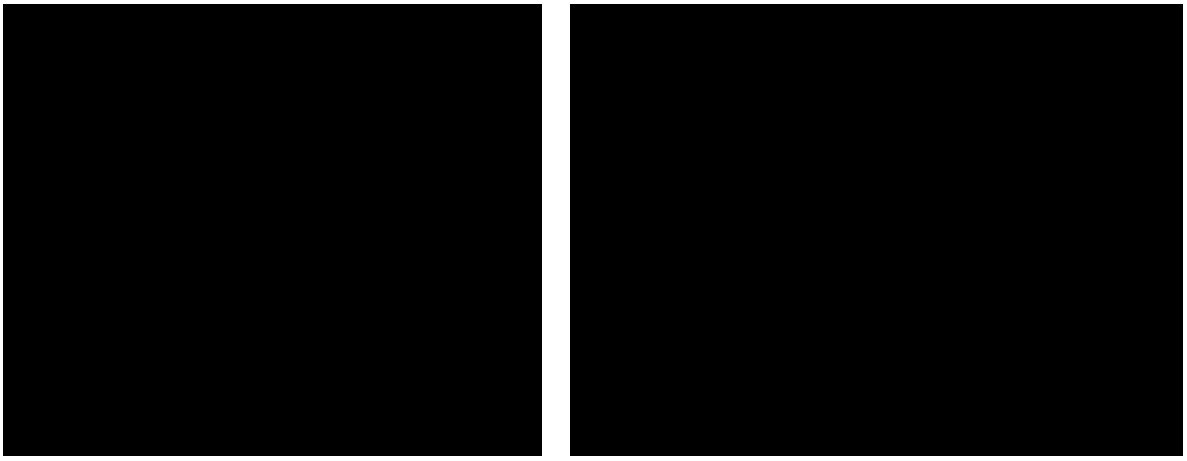


Figure 23. Observed hazard rate over time: with vs without smoothing for OS

Figure 24. Observed (smoothed) and predicted (all models) hazard rates over time ENDPOINT OS (only)

D.1.7 Validation and discussion of extrapolated curves

NA

D.1.8 Adjustment of background mortality

Adjustment of background mortality in line with DMC guidelines.

D.1.9 Adjustment for treatment switching/cross-over

NA

D.1.10 Waning effect

NA

D.1.11 Cure-point

NA

D.2 Extrapolation of PFS

D.2.1 Data input

See D.1

D.2.2 Model

See D.1

D.2.3 Proportional hazards

The PH assumption between EV (V subgroup) and V arms couldn't be clearly determined. The proportional log cumulative hazard functions between the EV (V subgroup) and V arms cross (Figure 25) while the Schoenfeld residuals tests yielded non-significant test results (Figure 26).

Figure 25. Log cumulative hazard plots for PFS

Figure 26. Schoenfeld residuals plots for PFS

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

The selected base-case PFS extrapolation approach for the EV (pre-selected V subgroup) and V arm was a parametric extrapolation with the log-logistic distribution This approach was supported by AIC/BIC statistics below.

Table 43. Statistical goodness of fit for PFS extrapolation of EV (pre-selected V subgroup) and V subgroups

PFS	Enfortumab Vedotin		Vinflunine	
Functional Form	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	XXXX	XXXX	XXXX	XXXX
Weibull	XXXX	XXXX	XXXX	XXXX
Log-Logistic	XXXX	XXXX	XXXX	XXXX
Lognormal	XXXX	XXXX	XXXX	XXXX
Gompertz	XXXX	XXXX	XXXX	XXXX
Generalized Gamma	XXXX	XXXX	XXXX	XXXX

D.2.5 Evaluation of visual fit

The figure below shows a comparison between the observed KM curves and the extrapolated curves.

(a) EV (V subgroup) **(b) V**

Figure 27. Parametric models for PFS

EV = enfortumab vedotin; KM = Kaplan-Meier; PFS = progression-free survival; V = vinflunine

D.2.6 Evaluation of hazard functions

NA

D.2.7 Validation and discussion of extrapolated curves

NA

D.2.8 Adjustment of background mortality

Adjustment of background mortality in line with DMC guidelines.

D.2.9 Adjustment for treatment switching/cross-over

NA

D.2.10 Waning effect

NA

D.2.11 Cure-point

NA

D.3 Extrapolation of DoT

D.3.1 Data input

See D.1

D.3.2 Model

See D.1

D.3.3 Proportional hazards

N.A.

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

The selected base-case DoT extrapolation approach for the EV (pre-selected V subgroup) and V arm was a parametric extrapolation with the log-normal distribution. This approach was supported by AIC/BIC statistics below.

Table 44. Statistical goodness of fit for DoT extrapolation of EV (pre-selected V subgroup) and V subgroups

DoT	Enfortumab Vedotin		Vinflunine	
Functional Form	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	XXXX	XXXX	XXXX	XXXX
Weibull	XXXX	XXXX	XXXX	XXXX
Log-Logistic	XXXX	XXXX	XXXX	XXXX
Lognormal	XXXX	XXXX	XXXX	XXXX
Gompertz	XXXX	XXXX	XXXX	XXXX
Generalized Gamma	XXXX	XXXX	XXXX	XXXX

D.3.5 Evaluation of visual fit

The figure below shows a comparison between the observed KM curves and the extrapolated curves.

(a) EV (V subgroup) **(b) V**

Figure 28. Parametric models for DoT

D.3.6 Evaluation of hazard functions

NA

D.3.7 Validation and discussion of extrapolated curves

NA

D.3.8 Adjustment of background mortality

Adjustment of background mortality in line with DMC guidelines.

D.3.9 Adjustment for treatment switching/cross-over

NA

D.3.10 Waning effect

NA

D.3.11 Cure-point

NA

Appendix E. Serious adverse events

Serious Treatment-emergent Adverse Events Reported for ≥ 1% of Subjects in Either Treatment Arm (SAF)

Preferred Term (MedDRA v24.0)†	Overall Incidence, n (%)							
	30 Jul 2021				15 Jul 2020			
	Enfortumab Vedotin (n = 296)		Chemotherapy (n = 291)		Enfortumab Vedotin (n = 296)		Chemotherapy (n = 291)	
	All Causality	Treatment-related	All Causality	Treatment-related	All Causality	Treatment-related	All Causality	Treatment-related
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection bacterial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignant neoplasm progression‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Term (MedDRA v24.0)†	Overall Incidence, n (%)							
	30 Jul 2021				15 Jul 2020			
	Enfortumab Vedotin (n = 296)		Chemotherapy (n = 291)		Enfortumab Vedotin (n = 296)		Chemotherapy (n = 291)	
	All Causality	Treatment-related	All Causality	Treatment-related	All Causality	Treatment-related	All Causality	Treatment-related
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculopapular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Escherichia urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydronephrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Term (MedDRA v24.0)†	Overall Incidence, n (%)							
	30 Jul 2021				15 Jul 2020			
	Enfortumab Vedotin (n = 296)		Chemotherapy (n = 291)		Enfortumab Vedotin (n = 296)		Chemotherapy (n = 291)	
	All Causality	Treatment-related	All Causality	Treatment-related	All Causality	Treatment-related	All Causality	Treatment-related
Malaise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urosepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Delirium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All randomized subjects who received any amount of study drug (SAF).

Sorting order: descending by the overall number of subjects of the enfortumab vedotin arm by preferred term. In case of ties, ascending alphabetic order by preferred term is applied.

Grey highlighted cells indicate a change in data since the primary analysis (data cutoff: 15 Jul 2020).

Treatment-related were adverse events with a reasonable possibility of relationship as assessed by the investigator, or were missing relationship.

SAF: safety analysis set.

† MedDRA v23.0 was used for the primary analysis

‡ Because of a data transcription error during the writing of the primary CSR, 3 (1.0%) subjects each in the enfortumab vedotin and chemotherapy arm were reported as having a treatment-related TEAE of malignant neoplasm progression while there were no treatment-related TEAEs of malignant neoplasm progression. This mistake has been corrected in the above in-text table.

Source: Astellas Pharma, data on file [17]

Appendix F. Health-related quality of life

N.A.

Appendix G. Probabilistic sensitivity analyses

The parameters varied in the probabilistic sensitivity analysis are shown in Table 45 below.

Table 45. Overview of parameters in the PSA

Parameter	Description
Base case efficacy and duration of treatment parameters	
log(HR)s of OS and PFS	log(HR)s of OS and PFS for comparators vs. EV in the base-case were varied based on normal distributions. The mean and SE of log(HR)s were estimated by cox regression using EV-301 data.
Parametric function estimations for OS, PFS and DoT	Parametric function estimations used in the base-case were varied using multivariate normal distributions. The SEs of the parameters were estimated using Cholesky decomposition.
Utility	
Pre-progression by treatment	Pre-progression and post-progression utilities values were varied using beta distributions. Mean utility values and SEs were estimated using EV-301 data as specified in Jensen et al (2021). [66]
Post-progression by treatment	
Baseline characteristics	
Age	Baseline characteristics were varied using normal distributions. Means and SEs were obtained from EV-301 data.
Gender	
BSA	
Weight	
AE costs	
AE costs	AE costs were varied using gamma distributions. SEs were assumed to be 10% of mean.
Medical costs	
Pre-Progression disease management costs	Pre-progression and post-progression medical costs were varied using gamma distributions.

Parameter	Description
Post-Progression disease management costs	SEs were assumed to be 10% of mean.
Treatment costs	
EV	Acquisition and administration costs for each drug are modelled using gamma distributions. SEs were assumed to be 10% of mean.
V	
Dose intensity	
EV	Dose intensities are modelled using normal distributions. Means and SEs were obtained from EV-301 ITT population.
V	

Appendix H. Literature searches for the clinical assessment

N.A

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

N.A

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

N.A

Appendix K. Overview of results in the hard-to-treat population

At the ESMO Congress held on September 16-21, 2021, a poster reporting the analysis of hard-to-treat subgroups from EV-301, was presented [31]. The subgroups characterized as hard-to-treat including those with poor prognostic factors included age ≥65 years (64% of all EV and DPV patients), presence of liver metastasis (31% of all EV and DPV patients), primary upper tract disease (33% of EV patients; 35% of DPV patients), and nonresponse to prior PD-1/L1 inhibitor (69% of EV patients, 70% of DPV patients). Analyses of prespecified subgroups characterized as hard-to-treat were conducted and reported for OS, PFS, and ORR. The statistical analyses included Kaplan-Meier (KM) analyses and log-rank test to compare OS and PFS, Cox proportional hazard (PH) model to estimate the hazard ratio (HR), and Cochran-Mantel-Haenszel (CMH) test to compare response and disease control rates between groups.

Kaplan Meier estimates of OS – Hard-to-treat subgroups

OS benefit for EV was maintained across the hard-to-treat subgroups as shown in Figure 29 A, B, C and D below. The OS was longer in the EV arm compared with the chemotherapy arm, consistent with median OS for the overall population.

In the subgroup "age ≥65 years" (Figure 29A below), EV demonstrated a 25.5% reduction in the risk of death (HR=0.745, [95% CI: 0.558, 0.995]). A total of 85 (44.0%) deaths occurred in the EV arm compared with 101 (51.5%) in the chemotherapy arm. The corresponding median OS was 14.32 months [95% CI: 10.05, 17.15] in the EV arm compared with 9.46 months [95% CI: 8.44, 13.70] in the chemotherapy arm.

In the subgroup with presence of "liver metastasis" (Figure 29B below), EV demonstrated a 34% reduction in the risk of disease progression or death (HR=0.660, [95% CI: 0.456, 0.957]). A total of 53 (57.0%) deaths occurred in the EV arm compared with 63 (66.3%) in the chemotherapy arm. The median OS was 9.63 months [95% CI: 6.80, 11.63] in the EV arm and 5.95 months [95% CI: 4.93, 7.10] in the chemotherapy arm.

In the population with "primary upper tract disease" (Figure C below), EV demonstrated a 15.2% reduction in the risk of death (HR=0.848, [95% CI: 0.567, 1.269]). A total of 44 (44.9%) deaths occurred in the EV arm and 52 (48.6%) in the chemotherapy arm. The median OS was 12.62 months [95% CI: 10.05, 15.34] in the EV arm and 10.91 months [95% CI: 8.05, 14.06] in the chemotherapy arm.]

In the population with "nonresponse to prior PD-1/L1 inhibitor" (Figure D below), EV demonstrated a 24.3% reduction in the risk of disease progression or death (HR=0.757, [95% CI: 0.580, 0.988]). A total of 100 (48.3%) deaths occurred in the EV arm and 120 (55.8%) in the chemotherapy arm. The corresponding median OS was 11.63 months [95% CI: 9.99, 15.18] in the EV arm and 9.17 months [95% CI: 7.95, 10.74] in the chemotherapy arm.

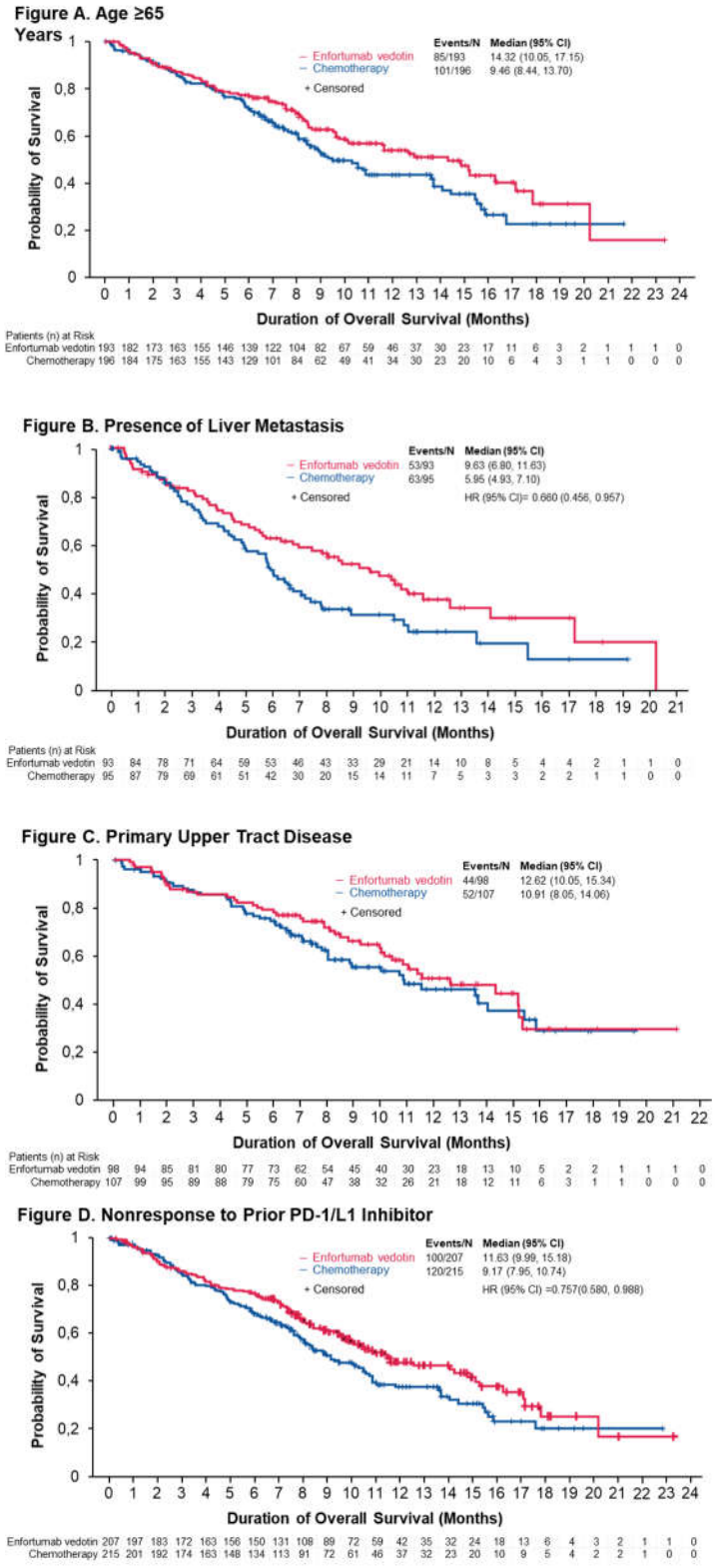


Figure 29. Kaplan-Meier estimates of OS by subgroups - hard-to-treat.

Source: Rosenberg et al, ESMO 2021 [31]

Kaplan-Meier estimates of PFS1 – Hard-to-treat subgroup

PFS benefit for EV was maintained hard-to-treat across most subgroups as shown in Figure 30 A, B, C and D below.

In the subgroup age "≥65 years" (Figure A below), EV demonstrated a 38.4% reduction in the risk of disease progression or death (HR=0.616, [95% CI: 0.485, 0.781]). A total of 126 (65.3%) deaths or progression events occurred in the EV arm compared with 151 (77.0%) in the chemotherapy arm. The corresponding median PFS was 5.65 months [95% CI: 5.22, 7.16] in the EV arm compared with 3.78 [95% CI: 3.52, 4.90] in the chemotherapy arm.

In the subgroup with presence of "liver metastasis" (Figure B below), EV demonstrated a 40.3% reduction in the risk of disease progression or death (HR=0.597, [95% CI: 0.428, 0.833]). A total of 71 (76.3%) deaths or progression events occurred in the EV arm compared with 75 (78.9%) in the chemotherapy arm. The median PFS was 4.14 months [95% CI: 3.71, 5.55] in the EV arm and 2.63 months [95% CI: 2.07, 3.55] in the chemotherapy arm.

In the population with "primary upper tract disease "(Figure C below), EV demonstrated a 28.4% reduction in the risk of disease progression or death (HR=0.716, [95% CI: 0.551, 1.003]). A total of 63 (64.3%) deaths or progression events occurred in the EV arm and 74 (69.2%) in the chemotherapy arm. The median PFS was 5.62 months [95% CI: 5.32, 7.29] in the EV arm and 3.78 months [95% CI: 2.23, 5.39] in the chemotherapy arm.

In the population with "nonresponse to prior PD-1/L1 inhibitor" (Figure D below), EV demonstrated a 30.3% reduction in the risk of disease progression or death (HR=0.697, [95% CI: 0.556, 0.873]). A total of 146 (70.5%) deaths or progression events occurred in the EV arm and 160 (74.4%) in the chemotherapy arm. The corresponding median PFS was 5.42 months [95% CI: 4.44, 5.65] in the EV arm and 3.65 months [95% CI: 3.35, 3.84] in the chemotherapy arm.

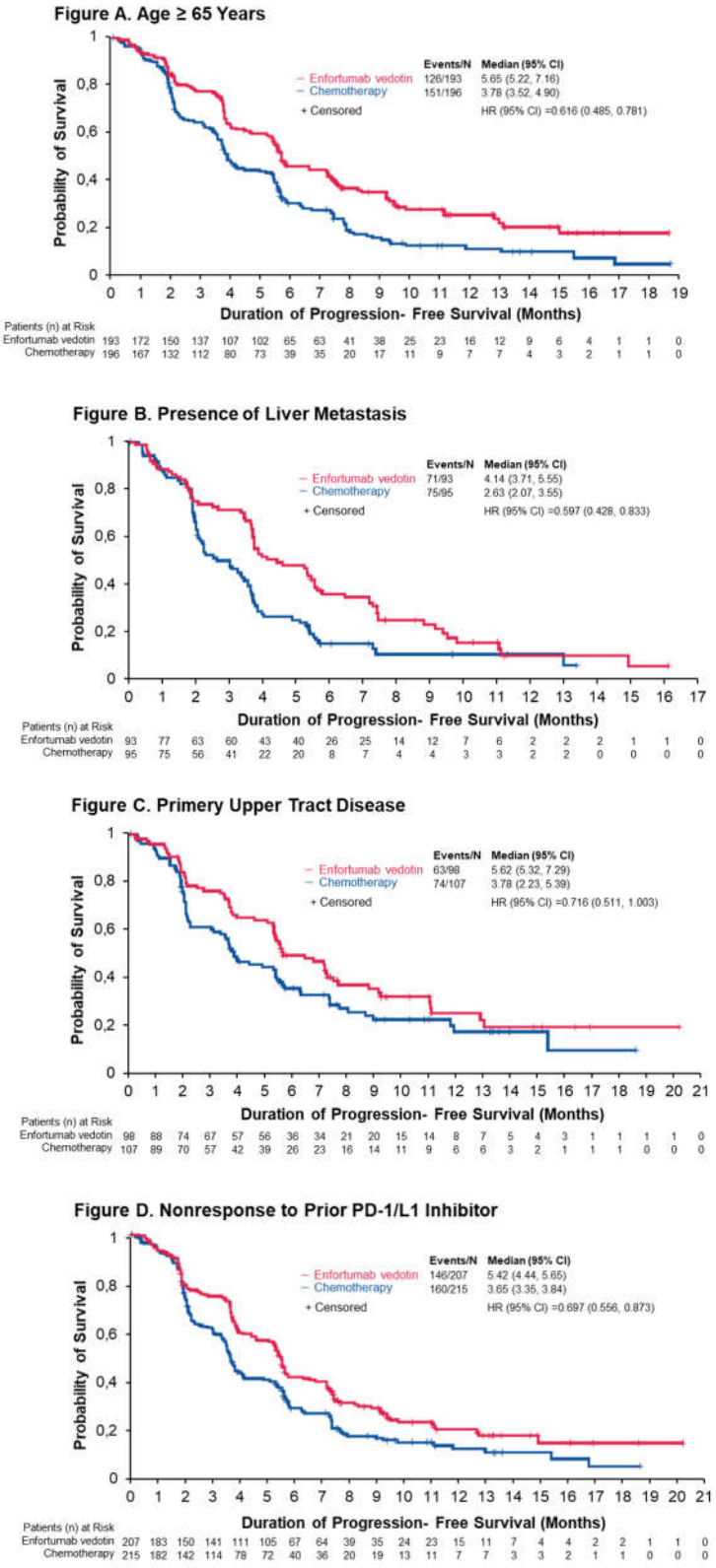


Figure 30. Kaplan-Meier estimates of PFS1 by subgroups - hard-to-treat.

Source: Rosenberg et al, ESMO 2021 [31]

Overall response rate – Hard-to-treat subgroup

The ORRs reported across all hard-to-treat subgroups were similar to that of the overall population in EV-301 [15]. In the subgroup age ≥65 years EV demonstrated an ORR of 40.8% [95% CI: 33.59, 48.23] relative to 19.9% [95% CI: 14.48, 26.27] in the chemotherapy arm. In the subgroup with presence of liver metastasis EV demonstrated an ORR of 35.5% [95% CI: 25.83, 46.09] relative to 10.8% [95% CI: 5.28, 18.89] in the chemotherapy group. In the subgroup with primary upper tract disease EV demonstrated an ORR of 43.9% [95% CI: 33.87, 54.27] relative to 19.0 [95% CI: 12.04, 27.87] in the chemotherapy arm. Lastly, the subgroup with nonresponse to prior PD-1/L1 inhibitor EV demonstrated an ORR of 39.7% [95% CI: 32.85, 46.86] relative to 17.4% [95% CI: 12.49, 23.25] in the chemotherapy arm.

Treatment-related adverse events of Grade 3 or higher – Hard-to-treat subgroup

The incidence of grade 3 or higher TRAEs that occurred in at least 5% of the populations were in each hard-to-treat subgroup similar to that of the overall EV-301 safety population.

Table 46. Incidence of Grade ≥3 Treatment-Related Adverse Events (Safety Population)

Adverse event	All		Age ≥65 Years		Presence of Liver Metastasis		Primary Upper Tract Disease		Nonresponse to Prior PD-1/L1 Inhibitor	
	EV N=296	DPV N=291	EV N=190	DPV N=188	EV N=90	DPV N=92	EV N=96	DPV N=102	EV N=202	DPV N=202
Maculopa-pular rash	22 (7.4)	0	14 (7.4)	0	8 (8.9)	0	10 (10.4)	0	19 (9.4)	0
Fatigue	19 (6.4)	13 (4.5)	15 (7.9)	12 (6.4)	5 (5.6)	5 (5.4)	9 (9.4)	5 (4.9)	10 (5.0)	5 (2.5)
Decreased neutrophil count	18 (6.1)	39 (13.4)	14 (7.4)	26 (13.8)	5 (5.6)	7 (7.6)	9 (9.4)	18 (17.6)	10 (5.0)	27 (13.4)
Neutro-penia	14 (4.7)	18 (6.2)	7 (3.7)	15 (8.0)	5 (5.6)	4 (4.3)	6 (6.3)	7 (6.9)	9 (4.5)	10 (5.0)
Anemia	8 (2.7)	22 (7.6)	5 (2.6)	15 (8.0)	3 (3.3)	3 (3.3)	6 (6.3)	5 (4.9)	6 (3.0)	12 (5.9)
Decreased white blood cell count	4 (1.4)	20 (6.9)	4 (2.1)	14 (7.4)	0	3 (3.3)	1 (1.0)	9 (8.8)	2 (1.0)	15 (7.4)
Febrile neutro-penia	2 (0.7)	16 (5.5)	2 (1.1)	11 (5.9)	2 (2.2)	6 (6.5)	2 (2.1)	7 (6.9)	2 (1.0)	10 (5.0)

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