Medicinrådet

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

Vers. 1.0

Bilagsoversigt

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

01.09.2022
DBS/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.09.2022
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)

Forhandlingsresultat

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

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Padcev (enfortumab vedotin)	20 mg	1 stk.	4.782,20	[redacted]	[redacted]
Padcev (enfortumab vedotin)	30 mg	1 stk.	7.173,30	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling og er gældende dagen efter godkendelse. Såfremt Medicinrådet ikke anbefaler Padcev (enfortumab vedotin), indkøbes lægemidlet til AIP. [redacted]

Informationer fra forhandlingen

[redacted].

Konkurrencesituationen

Der er i dag ingen andre lægemidler som har indikation til behandling af patienter med lokalt fremskreden eller metastatisk urotelial cancer efter svigt af platinbaseret kemoterapi samt svigt af en PD-1/-L1-hæmmer.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Pakningspris SAIP	Antal pakninger pr. behandlings periode	SAIP lægemiddelpris pr. behandlings periode
Padcev (enfortumab vedotin)	20 mg/ 1,25 mg/kg på dag 1, 8 og 15 i 28-dages cyklusser, iv*	1 stk.	[redacted]	116 (7,7 mdr.)	[redacted]
Padcev (enfortumab vedotin)	30 mg/ 1,25 mg/kg på dag 1, 8 og 15 i 28-dages cyklusser, iv*	1 stk.	[redacted]	77 (7,7 mdr.)	[redacted]
Javlor (vinflunin)	25 mg/ml /320 mg/m^2 hver 3. uge/ iv**	10 ml	[redacted]	22 (6,1 mdr.)	[redacted]

Note: Behandlingsperioden for Padcev (enfortumab vedotin) er 7,7 måneder og Javlor (vinflunin) er 6,1 måneder
* Beregning af lægemiddelforbruget for Padcev (enfortumab vedotin er baseret på en antaget gennemsnitlig vægt på 73,9 kg (se Medicinrådets vurderingsrapport)
** Beregning af lægemiddelforbruget for Javlor (vinflunin) er baseret på en antaget gennemsnitlig legemsoverflade for patienter på 1,9 m^2 (se Medicinrådets vurderingsrapport)
*** Ved justeret dosisintensitet (79% af startdosis) er lægemiddelprisen pr. behandlingsperiode [redacted] for Padcev (enfortumab vedotin)
**** Ved justeret dosisintensitet (91 % af startdosis) er lægemiddelprisen pr. behandlingsperiode [redacted] for Javlor (vinflunin)

Status fra andre lande

Norge: Under vurdering [1]
Sverige: Under vurdering [2]
England: Ikke vurderet. Mangel på evidens [3]

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/enfortumab-vedotin
[2] https://www.tlv.se/lakemedel/kliniklakemedelsuppdraget/pagaende-halsoekonomiska-bedomningar.html
[3] https://www.nice.org.uk/guidance/ta797

Medicinrådet

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 1.0

Refences were made using Vancouver style. A reference placed before a full stop refers to the sentence just ended. A reference placed after a full stop refers to the just ended paragraph or until the previous placed reference.

Any information that are confidential is highlighted in [redacted] throughout this application and appendix.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Contents

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1. Basic information

Contact information	
Name	Sara Nordling
Title	Associate Director Market Access
Phone number	+45 2272 0283
E-mail	sara.nordling@astellas.com

Overview of the pharmaceutical	
Proprietary name	PADCEV™
Generic name	Enfortumab Vedotin (EV) [1]
Marketing authorization holder in Denmark	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden Holland
ATC code	ATC code L01FX13 (new from 2022 index, previous ATC code L01XC36). [2]
Pharmacotherapeutic group	Nectin-4-directed antibody-drug conjugate (ADC) [1].
Active substance(s)	Enfortumab Vedotin [1].
Pharmaceutical form(s)	White to off-white lyophilized powder and solvent for solution for infusion [1].
Mechanism of action	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. [1]
Dosage regimen	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]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, 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. [3]
Other approved therapeutic indications	Not applicable

Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Not applicable
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]
Orphan drug designation	Not applicable

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2. 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

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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

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3. Tables and Figures

3.1 Table of tables

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

3.2 Table of figures

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

4. Summary

4.1 The medical condition, patient population, and indication

Urothelial carcinoma (UC) is the most common type of bladder cancer (BC), accounting for more than 90% of all cases of BC. Risk factors include smoking, age (incidence increases over age 45 years), and sex; the incidence of BC is approximately 4-fold higher in men than women.[4,5] UC is often characterized clinically by the extent of invasion and can be non-muscle invasive (NMIBC), muscle-invasive (MIBC), or metastatic [6]. Regional metastasis is referred to as locally advanced urothelial carcinoma, and distant metastasis is referred to as metastatic urothelial carcinoma [7].

In Denmark, the number of patients living with BC has been estimated to be approximately 21,000 people [8]. According to the Danish Medicines Council (DMC), the incidence of patients with locally advanced or metastatic urothelial carcinoma (la/mUC) that initiate 1st line treatment is approximately 150 per year. Approximately 25-48 patients are expected to benefit from enfortumab vedotin (EV; PADCEV™) in 2nd line [9]. The number of eligible patients was calculated based on recommendations from experts in the DMC and data from a Danish population-based, medical chart review which assessed the real-world treatment patterns and overall survival in la/mUC patients treated with chemotherapy in Denmark in the pre-immunotherapy era [9,10].

EV is the first antibody-drug conjugate (ADC) approved for use in la/mUC. EV as monotherapy is indicated for treatment of adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1(PD-1/L1) inhibitor [3]. The submission covers the technology's full marketing authorization for this indication. [1,11]

4.2 Current treatment, placement in the guideline, and choice of comparator

In Denmark, two treatment algorithms for the treatment of la/mUC exist. The guidelines were defined by the Danish Bladder Cancer Group (DaBlaCa) in 2019 and by the DMC in 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.

In 1st line, the current treatment of la/mUC consists of cisplatin for cisplatin-eligible patients [4,9,12]. The cisplatin-ineligible patients with negative PD-1/L1 biomarker are treated with carboplatin in combination with gemcitabine or gemcitabine monotherapy [4,9,12]. Cisplatin-ineligible patients with positive PD-1/L1 biomarker expression can be treated with carboplatin in combination with gemcitabine, gemcitabine monotherapy, or immunotherapy with the checkpoint inhibitors pembrolizumab or atezolizumab [9].

Patients who have been treated with platinum-based chemotherapy and are progression-free are recommended maintenance treatment with avelumab. According to the DMC guideline, the recommended treatment in 2nd line, after platinum-based chemotherapy and avelumab or immunotherapy, is vinflunine (V) or reinduction of platinum-based chemotherapy. [9] The DaBlaCa also recommends taxanes (docetaxel (D) and paclitaxel (P)), but these are according to experts not widely used in Danish clinical practice [9,12].

4.2.1 Placement in guideline

EV is, based on the discussion with the DMC at the dialogue meeting, expected to replace V in the treatment algorithm for the treatment of UC. 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 [1,13]. Thus, the current placement of V in the DMC guideline is considered off-label, whereas the placement of EV as monotherapy in 2nd line after PD-1/L1 inhibitor

and platinum-containing chemotherapy agrees with the label of EV. In addition, 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].

4.2.2 Choice of comparator

V is, as the treatment recommended in the DMC treatment guideline for an indication similar to that of EV, considered the most relevant comparator for this application [9]. To reflect other national guidelines D and P will also be presented as comparators but are of less interest due to the limited use in Danish clinical practice [9,12].

4.3 Clinical Value

A head-to-head study comparing EV with the relevant comparators, V, D, and P exists and thus, a literature search was omitted, in agreement with the DMC guideline [15]. The study, EV-301, is a global, open-label, Phase III randomized controlled trial (RCT) comparing the efficacy and safety of EV with the Investigator's choice of chemotherapy (D, P, and V) in patients with la/mUC who have previously been treated with a platinum-based chemotherapy and a PD-1/L-1 inhibitor [15]. EV-301 is a confirmatory trial design based on EV-201, Cohort 1, a single-arm, open-label, multicenter trial designed to assess the efficacy and safety of EV in patients with la/mUC who have previously received systemic therapy with a PD-1/PD-L1 inhibitor [15,16]. The findings of EV-201 granted EV FDA accelerated approval and is also considered relevant in this application as it provides more mature survival data to support the EV-301 study [15–17]. In addition, supplementary analyses based on the EV-301 trial are included to ensure transparency and to ensure that all evidence relevant for this application is presented and assessed. These supplementary analyses include a subgroup analyses of a hard-to-treat population, and an unpublished post hoc subgroup analysis of patients who were pre-selected to receive V (that is, the V population) and then randomized to either V or EV [18,19].

4.3.1 Efficacy

In the intention-to-treat (ITT) population it was demonstrated that EV significantly prolonged the primary endpoint overall survival (OS) compared with chemotherapy, median OS: 12.88 vs 8.97 months, respectively; and reduced the risk of death, hazard ratio (HR): 0.70; [95% confidence interval (CI): 0.56, 0.89]; p=0.001). The key secondary endpoints included progression-free survival (PFS) (median PFS: 5.55 vs 3.71 months for EV and chemotherapy arms, respectively; p<0.001), and overall response rate (ORR) (40.6% vs 17.9% for EV and chemotherapy arms, respectively; p<0.001). [15] The hard-to-treat subgroups retained the OS benefit for EV across all subgroups. The median OS was in all subgroups longer for EV compared with chemotherapy, consistent with the median OS for the overall population. [19]

In the post hoc V population, similar results to the ITT population were seen, with EV resulting in longer median OS compared with V (median OS: [redacted], respectively; HR= [redacted]) as well as prolonged PFS (median PFS: [redacted] respectively; HR= [redacted] 18] Similarly, the hard-to-treat subgroups retained the OS benefit for EV across all subgroups. The median OS was in all subgroups longer for EV compared with chemotherapy, consistent with the median OS for the overall population. [19]

Data from data cut-off July 2021 supported that EV significantly prolonged the primary endpoint OS compared with chemotherapy, median OS: 12.91 vs. 8.94 months, respectively; and reduced the risk of death, (HR=0.70; [95% CI: 0.58, 0.85]; p=0.001). Median PFS for both the EV and chemotherapy arm were similar to the previous data cut at July 2020 (5.55 and 3.71 months, respectively). [20]

Patients enrolled in Cohort 1 in EV-201 had also previously received platinum-based chemotherapy treatment and a PD1/L1 inhibitor. [redacted] [15,16,21]

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4.3.2 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). 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 improvement in pain.[22]

4.3.3 Safety

EV was generally well-tolerated in both the ITT and the V subgroup populations, with similar treatment-emergent discontinuation rates compared with chemotherapy, as demonstrated by EV-301 data (ITT: 17.2% vs 17.5% experienced treatment-emergent adverse events (TRAEs) leading to treatment withdrawal; 7.1% vs 5.5% experienced treatment-emergent adverse events (TEAEs) leading to death [15]. The safety profile in the hard-to-treat subgroups was consistent with that observed in the overall population in EV-301. No new safety signals were observed. [19]

In the V subgroup [redacted] experienced serious TEAEs; and [redacted] experienced TEAE leading to drug discontinuation, respectively [18].

4.4 Economic Value

A partitioned survival model was developed to assess the cost-effectiveness of EV vs V in patients with la/mUC previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor. 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.

In the base case, the disease course of the target population was estimated over a lifetime horizon (i.e., 33 years with the target cohort's baseline age at 67 years old). Both costs and outcomes were discounted at 3.5% annually. Efficacy (i.e., OS and PFS), duration of treatment (DoT), dose intensity, and utility by health state data were based on the subgroup analysis of EV-301 comparing EV with V. The OS extrapolations were piecewise fits for OS (Kaplan-Meier for 15 months followed by exponential for EV and Weibull for V) and single fit with log-logistic function for PFS for both EV and V. Treatment and administration costs while receiving EV (drug cost of [redacted] per month and administration cost of 6,646 DKK per month) or V (drug cost of [redacted] per month and administration cost of 2,954 DKK per month) are incurred based on the median DoT of approximately [redacted] and [redacted] for EV and V, respectively.

In the base case analysis, treatment with EV resulted in a gain of [redacted] quality-adjusted life-years (QALYs) over V (total QALYs: [redacted] The treatment cost per patient (drug and administration cost) was estimated to [redacted]. Total costs per patient were estimated to be [redacted] for treatment with EV and V, respectively. Total medical costs (in addition to the anti-cancer treatments) for EV and V were [redacted] respectively. The incremental cost-effectiveness ratio (ICER) was estimated to be [redacted] per QALY gained for EV vs V.

The results in the base case analysis were consistent with the majority of the univariate sensitivity analyses as well as most of the explored scenarios. The probabilistic ICER, estimated at [redacted] per QALY, was comparable to the base-case result. In deterministic sensitivity analyses (DSA), the ICER for EV vs V ranged from [redacted] DKK. The key model drivers were V drug cost, pre-progression utility in the V arm, and pre-progression utility in the EV arm.

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To summarize, the CEA estimates that treatment with EV results in an incremental cost of [redacted] per patient compared to treatment with V. These incremental costs are due to the higher medical costs incurred during EV treatment (driven by longer PFS and OS for patients treated with EV) as well as the higher treatment cost of EV. These incremental costs yielded a gain of [redacted] QALYs per patient for patients receiving EV due to the improved OS and maintained QoL during the pre-progression phase.

4.5 Budget Impact analysis

The budget impact assessment is based on the cost-effectiveness model and uses the key parameters (e.g., extrapolated OS, PFS, and DoT curves, cost inputs, etc.) In the budget impact analysis it is assumed that the population for whom EV is indicated will be approximately [redacted] patients per year based on a range of [redacted] per year. Thus, an annual incidence of [redacted] patients and an assumed uptake of [redacted] among eligible patients in year 1, [redacted] uptake in year 2, and [redacted] uptake thereafter, were used in the budget impact analysis. The budgetary impact of introducing EV was estimated at DKK [redacted] in year 5.

4.6 Final remarks

Patients with la/mUC have limited treatment options and their outcomes are poor. La/mUC is an incurable disease with a 5-year survival rate of 7%. There are currently no standard therapies indicated for patients who are progressing after platinum-containing chemotherapy and PD-1/L1 inhibitors.

EV has been investigated as part of a comprehensive clinical trial program and has demonstrated improved efficacy compared with chemotherapy. EV provides a novel therapeutic option for patients with la/mUC in the post-platinum-containing chemotherapy and PD-1/L1 inhibitor setting, filling a large unmet need for a population who previously had limited treatment options and poor outcomes [11,23].

EV is the first and only targeted treatment to extend survival vs. single-agent chemotherapy in the post-PD-(L)1 setting, demonstrating a 3.9-month OS improvement and 30% reduction in the risk of death. The survival benefit of EV was consistent across subgroups and supported by significant improvements in PFS and ORR. Patients treated with EV maintained overall QoL and experienced reduced pain symptoms.

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5. The patient population, the intervention, and choice of comparator(s)

5.1 The medical condition and patient population

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]

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].

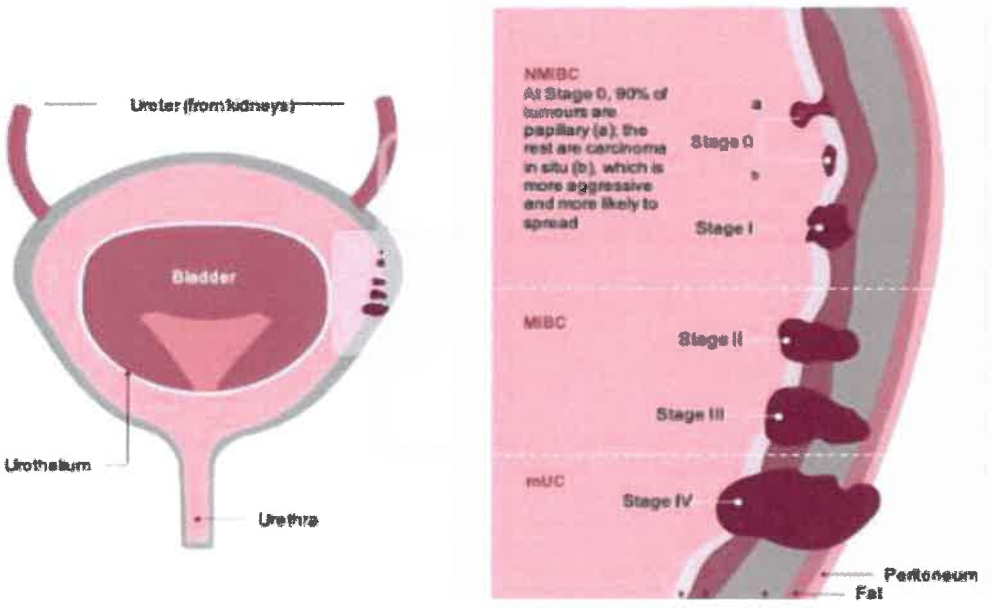

Figure 1. Staging of urothelial carcinoma*.

* Figure adapted from Bedirk, 2017

MIBC= Muscle-invasive bladder cancer; mUC= metastatic urothelial cancer; NMIBC= Non-muscular invasive bladder cancer.

Sources: [30]

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5.1.1 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 [31] . 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].

5.1.2 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]

5.1.3 Prognosis and unmet need

A recent 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]

5.1.4 Epidemiology and population characteristics

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 10th most common cancer worldwide, with 573,300 newly diagnosed cases in 2020 [50]. In the years 2015-2019, 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 2018 it was estimated that 21,000 people in Denmark were living with a diagnosis of BC or UC [8]. Further, a recent Danish study in a real-world setting reported that approximately 1100 patients are diagnosed with UTC in Denmark every year (Table 1), 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 and prevalence of urinary tract cancer in the years 2015 to 2019.

Year	2015	2016	2017	2018	2019
Incidence of invasive UTC in Denmark [10]	1,100	1,100	1,100	1,100	1,100
Prevalence of BC in Denmark	Not available	14,000 [8]	Not available	Not available	Not available

BC= Breast cancer; UTC= Urothelial tract cancer

Sources: [10]

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 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

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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	2022	2023	2024	2025	2026
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

5.1.5 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.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The European Association of Urology (EAU) updated its guidelines in January 2021 after the European Medicines Agency (EMA) approval 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 published in 2019. 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

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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 [9,53]. 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].

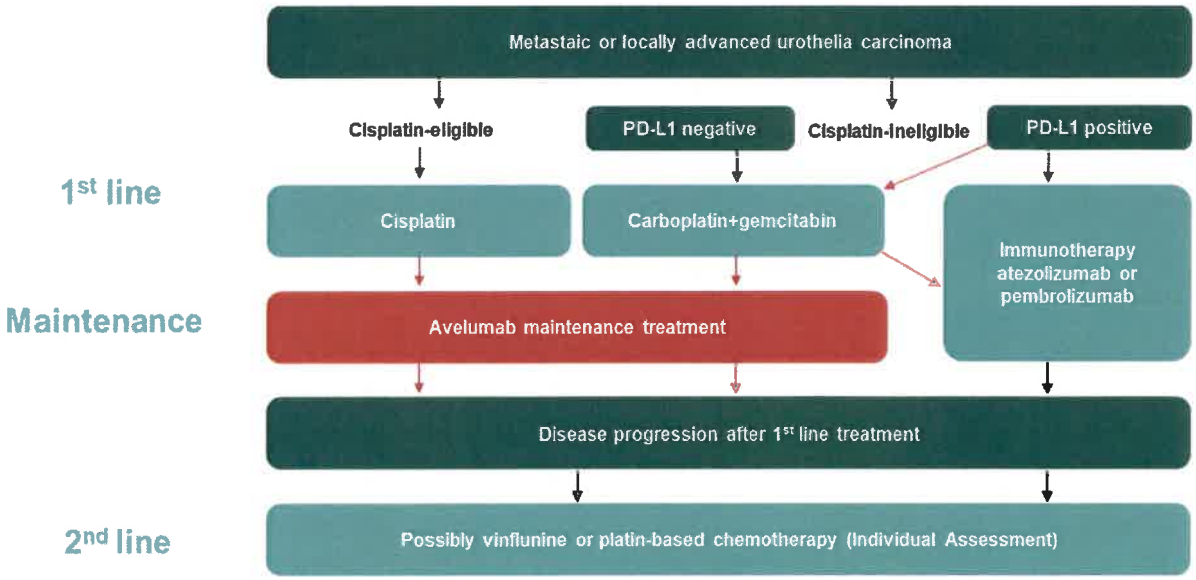

Figure 2. Current treatment algorithm for UC in Denmark, adapted from the appendix of the DMC assessment of avelumab as maintenance treatment for UC.

* Vinflunine is indicated for adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum containing regimen. The recommendation of using vinflunine after failure of a prior platinum containing chemotherapy and PD-1/L1 inhibitor is considered off-label.

PD-L1= programmed death-ligand 1

Source: [9]

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5.2.2 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 [53]. 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, vinflunine 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 D and P will also be presented as comparators but are of less interest due to the limited use in Danish clinical practice.

Additionally, since the cost-effectiveness of V has not previously been assessed by the DMC, 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.

5.2.3 Description of the comparator(s)

Descriptions of the comparators, V, D, and P, are provided in Table 3, Table 4, and Table 5, respectively.

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Table 3. Description of vinflunine.

Vinflunine	
Generic name (ATC-code)	Vinflunine (L01CA05) [13]
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 [49].
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate) [49].
Posology	The recommended dose is 320 mg/m^2 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/m^2. 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/m^2 every 3 weeks for the subsequent cycles. [49]
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. [49] According to a Swedish key expert, the majority of patients treated with vinflunine need to undergo a small vena-porta surgery before initiating vinflunine and then removal surgery post progression [49,54].
Dosing	320 mg/m^2 [49]
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 [49].
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 [49].
Need for diagnostics or other tests (i.e., companion diagnostics)	No need [49]
Packaging	25 mg/ml x 2 ml or 25 mg/ml x 10 ml [55].

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]

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Table 4. 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.[47]
Pharmaceutical form	Concentrate for solution for infusion. [47]
Posology	Not specified for UC in the European Public Assessment Report (EPAR) or the Summary of Product Characteristics (SmPC)
Method of administration	Infusion. [47]
Dosing	Not specified for UC in EPAR or SmPC
Should the pharmaceutical be administered with other medicines?	Due to the significant risk of hypersensitivity reactions and fluid retention, all patients should be premedicated with oral corticosteroids.[56]
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 or other tests (i.e., companion diagnostics)	No [47]
Packaging	20 mg/ml x 1 ml, x 4ml or 8 ml [56,57]

ATC= Anatomical therapeutic classification; EPAR= European Public Assessment Report; SmPC= Summary of Product Characteristics; UC= Urothelial cancer

Sources: [47,56,57]

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Table 5. Description of paclitaxel.

Paclitaxel	
Generic name (ATC-code)	Paclitaxel (L01CD01) [58]
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. [48]
Pharmaceutical form	Powder for dispersion for infusion. [48]
Posology	Not specified for UC in EPAR or SmPC
Method of administration	Infusion [48]
Dosing	Not specified for UC in EPAR or SmPC
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. [48]
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. [48]
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 [59,60]

ATC= Anatomical therapeutic classification; EPAR= European Public Assessment Report; SmPC= Summary of Product Characteristics; UC= Urothelial cancer

Sources: [48,58–60]

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5.3 The intervention

A description of the intervention EV is provided in Table 6.

Table 6. Description of enfortumab vedotin.

Enfortumab vedotin	
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 [1].
Method of administration	Intravenous infusion [1].
Treatment duration/criteria for end of treatment	Until disease progression or unacceptable toxicity [1].
Should the pharmaceutical be administered with other medicines?	No [1].
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, and for ocular disorders. [1] 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)). [1]
Need for diagnostics or other tests (i.e., companion diagnostics)	No [1]

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

Sources: [1]

5.3.1 Placement in Guideline

EV is, based on the discussion with the DMC at the dialogue meeting, expected to replace V in the treatment algorithm for the treatment of UC. 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.

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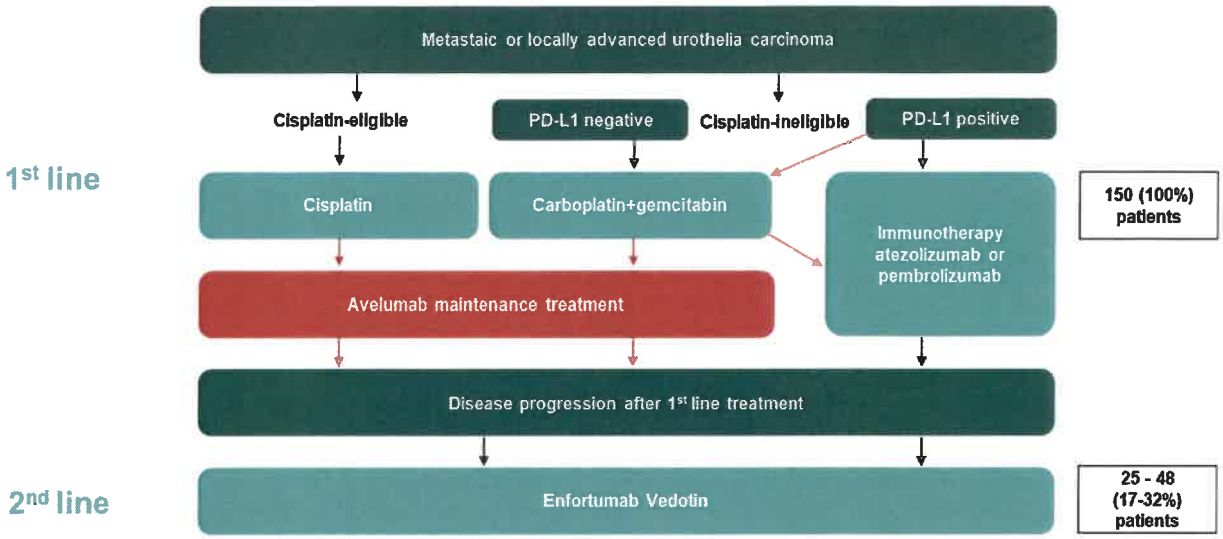

Figure 3. Treatment algorithm with possible placement of EV in guideline, including number of patients eligible for EV.

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]

5.4 Summary

In Denmark, the number of patients living with BC has been estimated to be approximately 21,000 [8]. According to the DMC, the incidence of patients with la/mUC that initiate 1st line treatment is approximately 150 per year. The DMC estimated that approximately 25 patients will be eligible for 2nd line treatment. [9] EV is, based on the discussion with the DMC at the dialogue meeting, expected to replace V in the treatment algorithm for the treatment of UC. 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 [1,13]. 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 [1,9,13,14] V is, as the treatment recommended in the DMC treatment guideline for an indication similar to that of EV, considered the most relevant comparator for this application [9]. To reflect other national guidelines D and P will also be presented as comparators but are of less interest due to the limited use in Danish clinical practice [9,12].

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A head-to-head study comparing EV with the relevant comparators, V, D, and 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]. EV-301 is a confirmatory trial design based on EV-201, cohort 1, a single-arm, open-label, multicenter trial designed to assess the efficacy and safety of EV in patients with la/mUC who have previously received platinum-based chemotherapy and a PD-1/L-1 inhibitor [16]. The findings of EV-201, Cohort 1, granted EV Food and Drug Administration (FDA) accelerated approval and the study is also considered relevant in this application as it provides more mature survival data to support the EV-301 study [17]. In addition, supplementary analyses based on the EV-301 trial are included to ensure transparency and to ensure that all evidence relevant for this application is presented and assessed.

6.1.1 List of relevant studies

The studies relevant to this assessment are listed in Table 7. Detailed study characteristics are provided in Appendix B.

Table 7. Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma, Powles T. et al. N Engl J Med, 2021;384:1125-1135	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 Expected completion: 28.02.2023	Enfortumab vedotin vs. docetaxel, vinflunine, and paclitaxel for patients with locally advanced or metastatic urothelial cancer treated with chemotherapy
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.	A Study to Evaluate Enfortumab Vedotin Versus (vs) Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial	NCT03474107	Start: 27.06.2018 Expected completion: 28.02.2023	Enfortumab vedotin vs. docetaxel, vinflunine, and paclitaxel for patients with locally advanced or metastatic urothelial cancer treated with chemotherapy

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Mamtani R, Rosenberg JE, Powles T, Sonpavde GP, Loriot Y, Duran I, et al. ASCO 2021, Abstr No 4539.	Cancer (EV-301)			
Analysis of Hard-to-Treat Subgroups From EV-301, a Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy for Previously Treated Advanced Urothelial Carcinoma. Rosenberg JE, Powles T et al. ESMO 2021, Abstr No 698P	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 Expected completion: 28.02.2023	Enfortumab vedotin vs. docetaxel, vinflunine, and paclitaxel for patients with locally advanced or metastatic urothelial cancer treated with chemotherapy
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	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 Expected completion: 28.02.2023	Enfortumab vedotin vs. docetaxel, vinflunine, and paclitaxel for patients with locally advanced or metastatic urothelial cancer treated with chemotherapy

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy, Rosenberg, J. E. et al. J Clin Oncol, 2019;37(29):2592-2600	A Study of Enfortumab Vedotin for Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer (EV-201)	NCT03219333	Start: 08.10.2017 Expected completion: 31.05.2025	EV compared with EV in two cohorts Cohort 1: patients with locally advanced or metastatic urothelial cancer who previously received a CPI and previously received platinum-containing chemotherapy Cohort 2: patients with locally advanced or metastatic urothelial cancer who previously received a CPI and are platinum-naïve and cisplatin-ineligible

An overview of completed and ongoing trials on EV, that are not included in this assessment is provided in Table 8. The trials were identified at clinicaltrials.gov on August 26, 2021, using the search term *Enfortumab Vedotin*. The studies are primarily based on non-European patients or other indications and were thus deemed irrelevant for this application.

Table 8. List of completed and ongoing studies not included in the assessment.

Study Title	Status	NCT number	Dates of study (start and expected completion date)	Official Title
A Study of Intravesical Enfortumab Vedotin for Treatment of Patients with Non-muscle Invasive Bladder Cancer (NMIBC)	Recruiting	NCT05014139	Start: 07.12.2021 Expected completion: 31.05.2028	A Study of Intravesical Enfortumab Vedotin for Treatment of Patients With Non-muscle Invasive Bladder Cancer (NMIBC)
A Study to Evaluate Enfortumab Vedotin (ASG-22CE) in Chinese Subjects with Locally Advanced or Metastatic Urothelial Cancer Who Previously Received Platinum-containing Chemotherapy and PD 1/PD-L1 Inhibitor Therapy	Active, not recruiting	NCT04995419	Start: 22.07.2021 Expected completion: 31.05.2024	A Single-arm, Open-label, Multi-center Phase II Study of Enfortumab Vedotin (ASG-22CE) in Chinese Subjects with Locally Advanced or Metastatic Urothelial Cancer Who Previously Received Platinum-containing Chemotherapy and PD 1/PD-L1 Inhibitor Therapy (EV-203)

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Study Title	Status	NCT number	Dates of study (start and expected completion date)	Official Title
A Study of Enfortumab Vedotin in Japanese Subjects with Locally Advanced or Metastatic Urothelial Carcinoma	Recruitment completed	NCT03070990	Start: 24.04.2017 Completion: 25.02.2019	An Open-label, Randomized, Phase I Safety and Pharmacokinetic Study of Enfortumab Vedotin (ASG-22CE) in Japanese Patients with Locally Advanced or Metastatic Urothelial Carcinoma
Testing Combination Erdafitinib and Enfortumab Vedotin in Metastatic Bladder Cancer After Treatment with Chemotherapy and Immunotherapy	Recruiting	NCT04963153	Start: 13.10.2021 Expected completion: 01.09.2023	Phase Ib trial evaluating the effect and safety of erdafitinib and enfortumab vedotin in treating patients with bladder cancer that has spread to other places in the body (metastatic).
Sacituzumab Govitecan Plus EV in Metastatic UC	Recruiting	NCT04724018	Start: 20.05.2021 Expected completion: 01.05.2023	Single-center, open-label, nonrandomized phase I trial testing the safety and efficacy of Sacituzumab Govitecan and Enfortumab for people with metastatic urothelial carcinoma (mUC) progressing on platinum-based chemotherapy and PD1/L1 inhibitors
Cabozantinib in Combination with Enfortumab Vedotin for Locally Advanced or Metastatic Urothelial Cancer	Recruiting	NCT04878029	Start: 23.07.2021 Expected completion: 21.01.2025	A Phase I/Ib Open-Label, Single-Arm Study of Cabozantinib in Combination with Enfortumab Vedotin (EV) in the Treatment of Locally Advanced or Metastatic Urothelial Cancer
A Study to Evaluate Enfortumab Vedotin in Subjects with Previously Treated Locally Advanced or Metastatic Malignant Solid Tumors (EV-202)	Recruiting	NCT04225117	Start: 09.03.2020 Expected completion: 30.04.2024	An Open-label, Multicenter, Multicohort, Phase II Study to Evaluate Enfortumab Vedotin in Subjects with Previously Treated Locally Advanced or Metastatic Malignant Solid Tumors (EV-202)
Treatment Combination of Durvalumab, Tremelimumab, and Enfortumab Vedotin or Durvalumab and	Not yet recruiting	NCT04960709	Start: 05.08.2021 Expected completion: 08.09.2028	A Phase III Randomized, Open-Label, Multicenter Study evaluating the Efficacy and Safety of Durvalumab in Combination with Tremelimumab and

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Study Title	Status	NCT number	Dates of study (start and expected completion date)	Official Title
Enfortumab Vedotin in Patients with Muscle Invasive Bladder Cancer Ineligible to Cisplatin (VOLGA)				Enfortumab Vedotin or Durvalumab in Combination With Enfortumab Vedotin for Perioperative Treatment in Patients Ineligible for Cisplatin Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer
An Expanded Access Treatment Protocol of Enfortumab Vedotin in Subjects with Locally Advanced or Metastatic Urothelial Carcinoma	Approved for marketing	NCT04136808	N/A	A Multicenter, Open-label, Expanded Access Treatment Protocol of Enfortumab Vedotin in Subjects with Locally Advanced or Metastatic Urothelial Carcinoma (EV-901)

6.2 Summary

A head-to-head study comparing EV with the relevant comparators, vinflunine, docetaxel, and paclitaxel exists and thus, a literature search was omitted, in agreement with the DMC guideline [15]. EV-301 is a confirmatory trial design based on EV-201, cohort 1, a single-arm, open-label, multicenter trial designed to assess the efficacy and safety of EV in adult patients with la/mUC who have previously received platinum-based chemotherapy and a PD-1/L-1 inhibitor [15,16]. The findings of EV-201, Cohort 1, granted EV FDA accelerated approval and the study is also considered relevant in this application as it provides more mature survival data to support the EV-301 study. [15,16,21,31]

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7. Efficacy and safety

7.1 Efficacy and safety 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

7.1.1 Relevant studies

In the following sections 7.1.1.1 and 7.1.1.2, the studies EV-301 and EV-201 are described, respectively. The descriptions include a brief overview of the study designs, the statistical methodology used to analyze the data, prespecified and post hoc subgroup analyses relevant to this application as well as a summary of the population baseline characteristics.

7.1.1.1 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. [15,31]

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. [15,31]

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 4. [15,31]

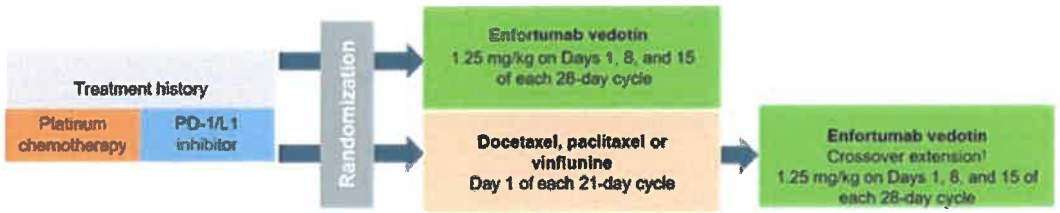

Figure 4. Study schematic of EV-301.

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

Sources: [15,31]

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. [15,31]

7.1.1.1.1 Statistical analysis and definition of subgroups

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. This application details data from the interim efficacy analysis that 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. [15,31]

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 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] Table 9 provides an overview and descriptions of the analyses set in EV-301 and the number of patients in the different populations.

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Table 9. Description of study analyses sets in EV-301 and the number of patients in the different analyses sets and treatment arms.

Analysis set	Description			
Full analysis set (FAS)	The FAS consisted of all subjects who were randomized. This analysis set complies with the intent-to-treat principle that includes all randomized subjects. The FAS was the primary analysis set for efficacy analyses except for response-related efficacy endpoints. Demographic and baseline characteristics were summarized for the FAS.			
Population	**Enfortumab Vedotin**		**Chemotherapy**	
Total ITT	EV (ITT)	301	DPV	307
Pre-selected V subgroup	EV (pre-selected V)	73 (24%)	V (subgroup)	78(25%)
Response evaluable set (RES)	The RES was defined as all subjects in the FAS who had measurable disease (per RECIST v1.1) per investigator at baseline. The RES was used for primary efficacy analysis of response-related endpoints (e.g., ORR and DCR). Subjects were analyzed based on the randomized treatments.			
Population	**Enfortumab Vedotin**		**Chemotherapy**	
Total ITT	EV (ITT)	288	DPV	296
Pre-selected V subgroup	EV (pre-selected V)	70 (24%)	V (subgroup)	75 (25%)
Safety analysis set (SAF)	The SAF consisted of all subjects who received any amount of study drug and was used for safety analyses. Subjects were analyzed based on actual treatment received.			
Population	**Enfortumab Vedotin**		**Chemotherapy**	
Total ITT	EV (ITT)	296	DPV	291
Pre-selected V subgroup	EV (pre-selected V)	71(24%)	V (subgroup)	75(26%)

DCR= Disease control rate; FAS= Full analysis set; RECIST= Response Evaluation Criteria in Solid Tumors; ORR= Overall response rate; RES= Response evaluable set; SAF= Safety analysis set.

Sources: [18,31]

A post hoc analysis was conducted to specifically investigate the treatment effects in a subpopulation of subjects who had been pre-selected for treatment with the comparator vinflunine (that is, the vinflunine population) and then randomized to either vinflunine or EV. Results from this analysis are presented alongside the ITT analyses to better reflect Danish clinical practice. Despite the post hoc nature of this analysis, randomization has been preserved as the chemotherapy allocation occurred pre-randomization and those patients who were pre-allocated to docetaxel and paclitaxel and then randomized to either docetaxel, paclitaxel, or EV have been removed. [18]

In addition, analyses of prespecified subgroups characterized as hard-to-treat were conducted and reported for OS, PFS, and ORR. The subgroups characterized as hard-to-treat including those with poor prognostic factors included age ≥65 years, presence of liver metastasis, primary upper tract disease, and nonresponse to prior PD-1/L1 inhibitor. The statistical analyses of the hard-to-treat subgroup 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. [19]

7.1.1.1.2 Population characteristics at baseline

Baseline characteristics were generally balanced between populations. In the ITT population, the median age was 68 years (30–88) and 77.3% of patients were men. Visceral disease was present in 77.7% of patients in the EV arm and 81.7% in the chemotherapy arm, liver metastases were present in 30.9% of patients across both arms. [15] In the ITT population, 87.5% had received up to two prior lines of therapy in the locally advanced or metastatic setting; 12.5% had received three or more. The most common PD-1 or PD-L1 inhibitor received was [redacted] followed by [redacted] Overall, prior platinum-based chemotherapy consisted of cisplatin-based chemotherapy regimen only for [redacted] and carboplatin-based chemotherapy regimen only for [redacted] had received both. [15,31]

Similar baseline characteristics were reported for the vinflunine subgroup, where the median age was [redacted] and a slightly greater proportion of patients were male [redacted]. Visceral disease was present in [redacted] in the EV arm and [redacted] in the vinflunine arm, and liver metastases were present in [redacted] and [redacted] respectively. In the EV arm [redacted] had received up to two prior lines of therapy and [redacted] had received three or more. In the vinflunine arm [redacted] had received up to two prior lines of therapy and [redacted] had received three or more. The most common PD-1/L1 inhibitor received was pembrolizumab [redacted] followed by atezolizumab [redacted] and durvalumab [redacted] the EV arm and durvalumab [redacted] atezolizumab [redacted] and pembrolizumab [redacted] the vinflunine arm. Overall, prior platinum-based chemotherapy consisted of cisplatin-based chemotherapy regimen only for [redacted] of patients and carboplatin-based chemotherapy regimen only for [redacted] of patients; [redacted]

An overview of all baseline characteristics is provided in Appendix C.

7.1.1.2 EV-201

EV-201 is a global, Phase II, single-arm, two-cohort, multicenter study that enrolled patients with la/mUC previously treated with a PD-1/L1 inhibitor therapy; patients enrolled in Cohort 1 had also previously received platinum-based chemotherapy treatment [16], while those recruited to Cohort 2 were platinum-naïve and cisplatin-ineligible [62].

Treatment consisted of intravenous EV 1.25 mg/kg (based on actual body weight with a maximum dose of 125 mg) over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, investigator decision, start of subsequent anticancer therapy, pregnancy, or study termination by the study sponsor [16,62]. A study schematic of EV-201 is presented in Figure 5 [16].

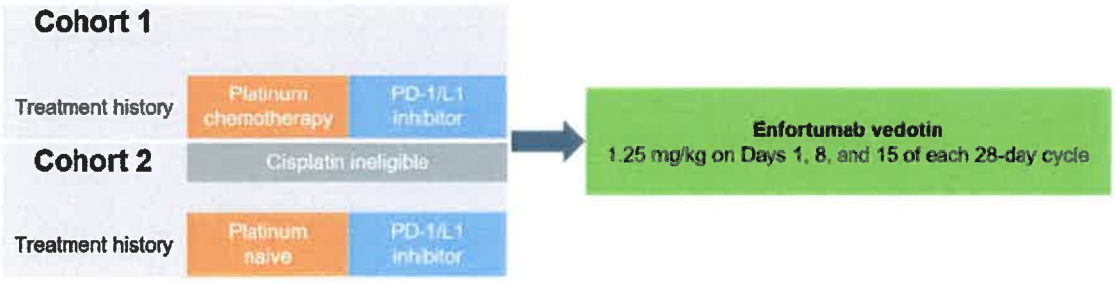

Figure 5. Study schematic of EV-201.

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

Sources: [16,21]

The results presented in section 7.1.2.2 are based on Cohort 1 as of September 2020 [redacted] [16,21].

Patients in Cohort 2 received no prior platinum-containing chemotherapy and were ineligible for treatment with cisplatin at the time of enrollment; these patients are not of interest to this application and are therefore not discussed further [62]. As the EV-201 Cohort 1 aligns to the population under consideration in this application, all further mention of EV-201 data relates to the EV-201 Cohort 1 [16].

The primary endpoint was ORR, defined as the proportion of patients whose best OR was a confirmed complete response (CR) or partial response (PR) according to RECIST version 1.1 as determined by blinded independent central review (BICR). Secondary endpoints included duration of response (DoR), defined as the time from the first documented response to the first documented progressive disease (PD) per RECIST v. 1.1 or death due to any cause, PFS, defined as the time from the start of study treatment to first documented PD as determined by BICR or death due to any cause, and OS, defined as the time from the start of study treatment to the date of death due to any cause determined by investigator. Safety was assessed using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 and graded according to the NCI CTCAE version 4.03. [16,21]

7.1.1.2.1 Population characteristics at baseline

Patient demographics and clinical characteristics were broadly similar to those in the EV-301 study, although fewer patients in the EV-201 study were male (70% vs 79%) and more patients had an ECOG score of 1 (68% vs 60%), and visceral metastases (90% vs 78%). [16]

An overview of all baseline characteristics is provided in Appendix C.

7.1.2 Efficacy and safety – results per study

In section 7.1.2.1, results from EV-301 are presented. As per agreement with the DMC, 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. The subgroup data is included to better reflect Danish clinical practice where vinflunine currently is recommended in 2nd line according to the DMC treatment algorithm (before approval of EV). In addition, a comparison between the safety profiles of the EV (ITT) and vinflunine (subgroup) is presented. This is done because the EV (ITT) population is larger and provides greater power compared with the EV (pre-selected V) population. Lastly, 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, PFS, ORR), from hard-to-treat subgroups is presented.

The EV-301 data presented in this assessment is based on the primary analysis (cut-off date 15 July 2020). This was based on the pre-specified interim analysis where the EV-301 study reached its primary endpoint. At the time of dossier preparation and submission, this was the latest data cut available. At the time of the primary analysis further efficacy follow-up analysis was not planned. However, based on request of a regulatory authority an additional efficacy post-hoc analysis was conducted (cut-off date 30th July 2021), and has in the meantime become available. Data from the data cut-off from July 2020 was used as primary efficacy data in the dossier to comply with the DMC's principles regarding unpublished data, however OS, PFS and safety from the most recent data cut (July 2021) have been added in the clinical section, confirming that overall survival benefit is maintained with EV over 23.75 months (95%CI: 23.10, 24.51) of follow-up [63].

In section 7.1.2.2 survival data from EV-201 are presented to support the findings of EV-301. The most recent data cut (September 2020) of EV-201 provides more mature survival data with median follow-up of [redacted] compared

with the most recent data cut (July 2021) of EV-301 with a median follow-up of 23.75 months. Thus, the survival data from EV-201 will be used in the health economic section to assess the external validity of the model predicted OS. [20,21,63]

7.1.2.1 EV-301

7.1.2.1.1 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 (in days) was calculated as: (Date of death or censored) – (Date of randomization) + 1.

The primary analysis population for OS was the FAS. The distribution of OS was estimated for each treatment arm using KM methodology and the primary analysis on comparing Arm A and Arm B was conducted using the log-rank test stratified by ECOG PS (0 vs 1), region (US, EU, or the Rest of World) and liver metastasis status (Yes vs No) per interactive response technology (IRT). In addition, the stratified Cox PH model (same stratification factors as used for stratified log-rank test) was used to estimate the HR and the corresponding 95% CIs. The final (primary) analysis was to be performed when approximately 439 OS events had been observed (occurred July 2021) [20]. One planned interim analysis was to be performed when approximately 285 OS (about 65% of the total OS events) events had been observed (occurred July 2020). [15]

Kaplan Meier estimates of OS - ITT

At data cut-off 15 July 2020 (median follow-up 11.1 months), 301 deaths had been reported; 134 deaths in the EV (ITT) arm and 167 deaths in the DPV arm. EV reduced the risk of death vs. DPV by 30.0% (HR=0.70 [95% CI; 0.56, 0.89], 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 (12.88 months [95% CI; 10.58, 15.21] vs 8.97 months [95% CI; 8.05, 10.74]), Figure 6. [15]

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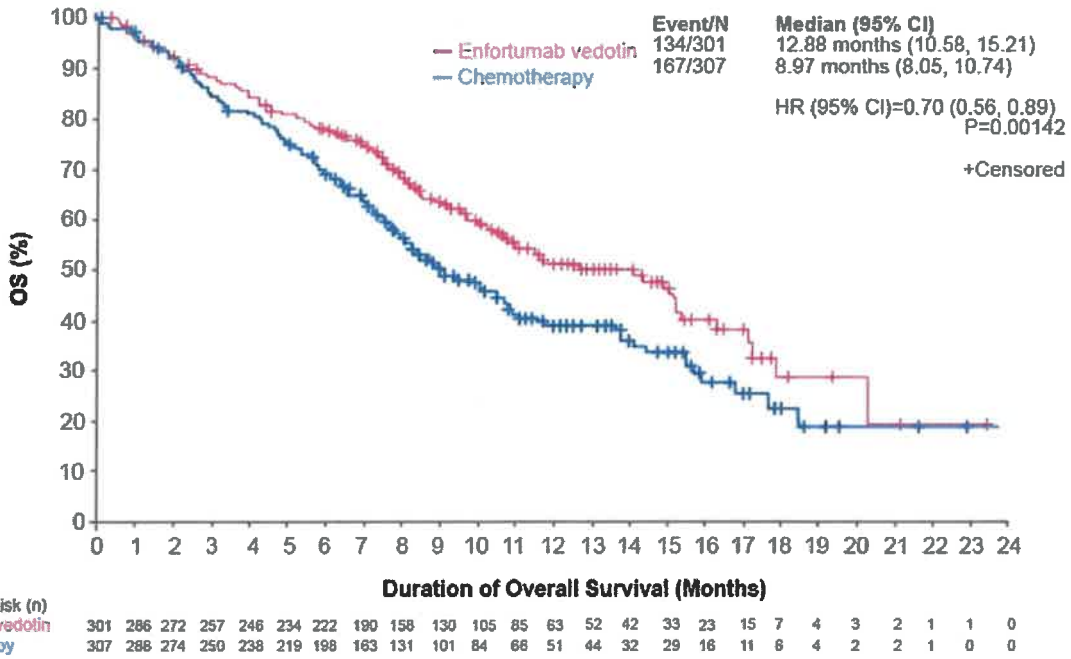


Figure 6. Kaplan-Meier estimates of OS, ITT population (Data cut-off 15 July 2020).

CI= Confidence interval; HR= Hazard ratio; ITT= Intention-to-treat; OS= Overall survival

Sources: [15]

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 7. [20]

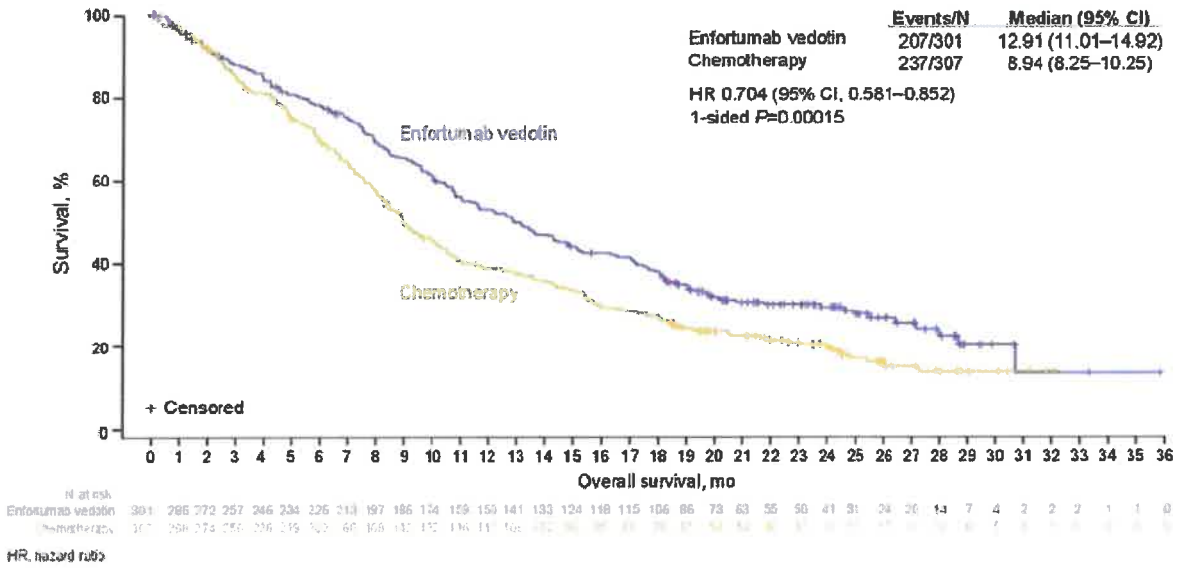


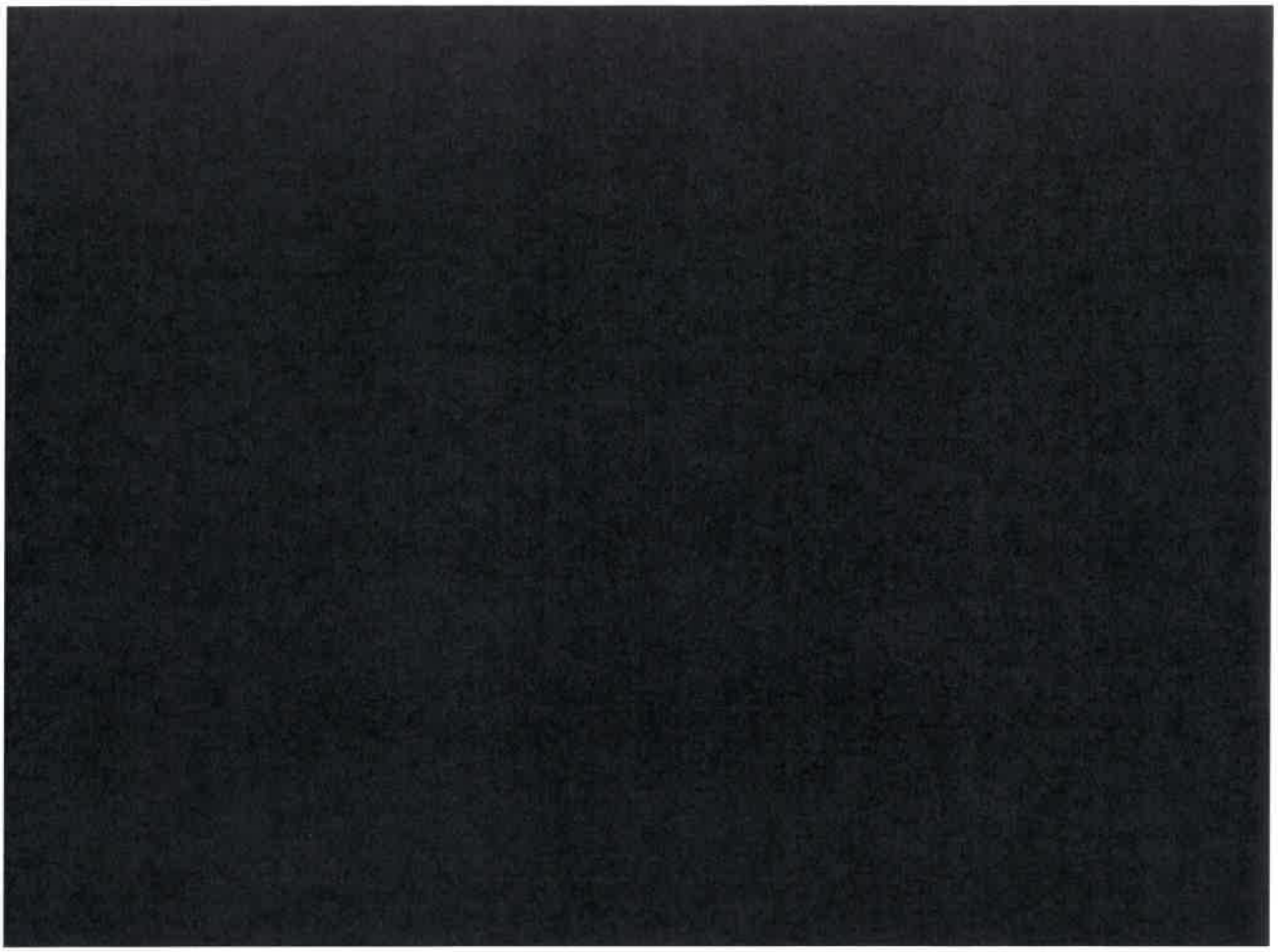
Figure 7. Kaplan-Meier estimates of OS, ITT population (Data cut-off 30 July 2021)

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

Source: [20]

Kaplan Meier estimates of OS – Vinflunine subgroup

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 [redacted] occurred in the EV (pre-selected V) arm compared with [redacted] in the vinflunine (subgroup) arm; the corresponding median OS was [redacted] in the EV (pre-selected V) arm compared with [redacted] in the vinflunine (subgroup) arm as presented in Figure 8. In pre-selected V subgroup EV demonstrated a [redacted] reduction in the risk of death with a [redacted] compared with the vinflunine (subgroup) arm. [18] The reduction in the risk of death in the vinflunine subgroup was maintained at the data cut July 2021, [redacted]. It should be noted that the data reported on the vinflunine subgroup based on the 2020 data-cut was estimated using stratified cox proportional hazard models whereas the vinflunine subgroup data based on the 2021 data-cut was estimated using unstratified cox proportional hazards models.



7.1.2.1.2 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]

Kaplan-Meier estimates of PFS1 - ITT

At data cut-off 15 July 2020 (median follow-up 11.1 months) 432 PFS1 events had been reported (201 and 231 events in the EV and chemotherapy arms, respectively), and EV significantly improved PFS1 compared to DPV, with a 38.0% reduction in the risk of disease progression or death (HR=0.62, [95% CI: 0.51, 0.75], p<0.001). Median PFS was longer in the EV (ITT) arm compared with the DPV arm (5.55 months, [95% CI: 5.32, 5.82] vs 3.71 months, [95% CI: 3.52, 3.94]), Figure 9. [15]

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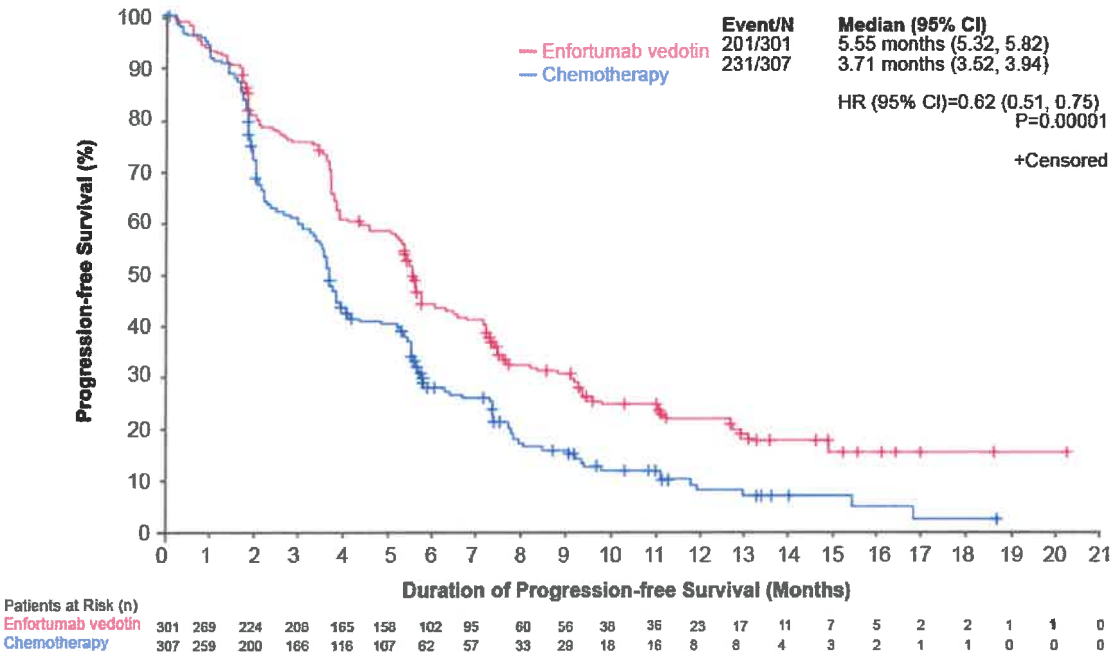


Figure 9. Kaplan-Meier estimates of PFS, ITT population (Data cut-off 15 July 2020).

CI= Confidence interval; HR= Hazard ratio; ITT= Intention-to-treat; PFS= Progression-free survival

Sources: [15]

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 10. [20]

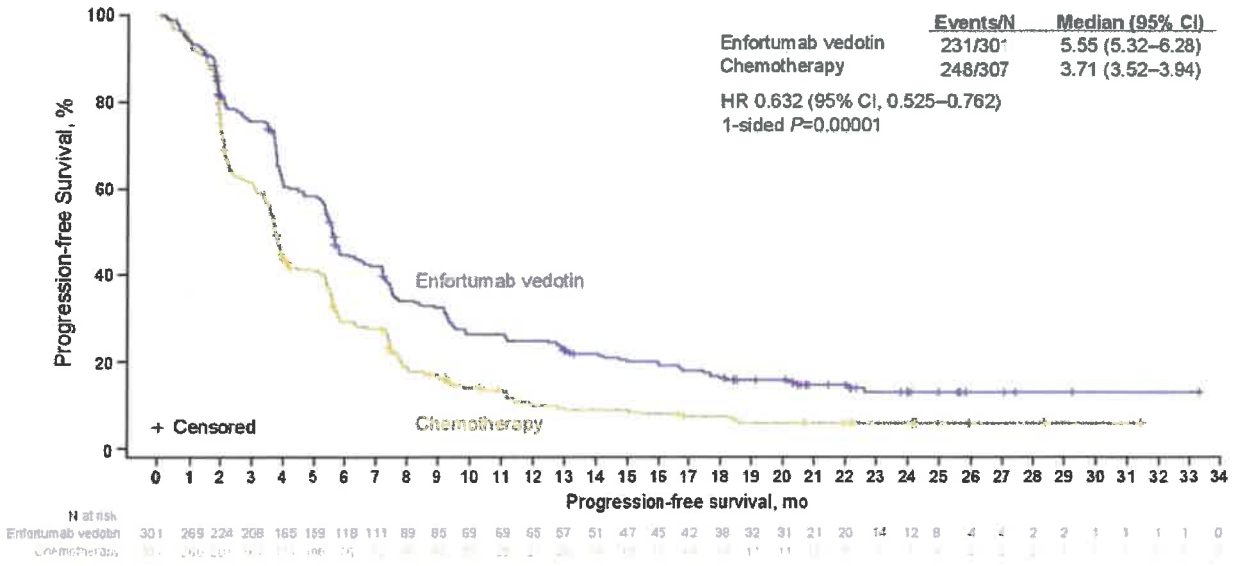


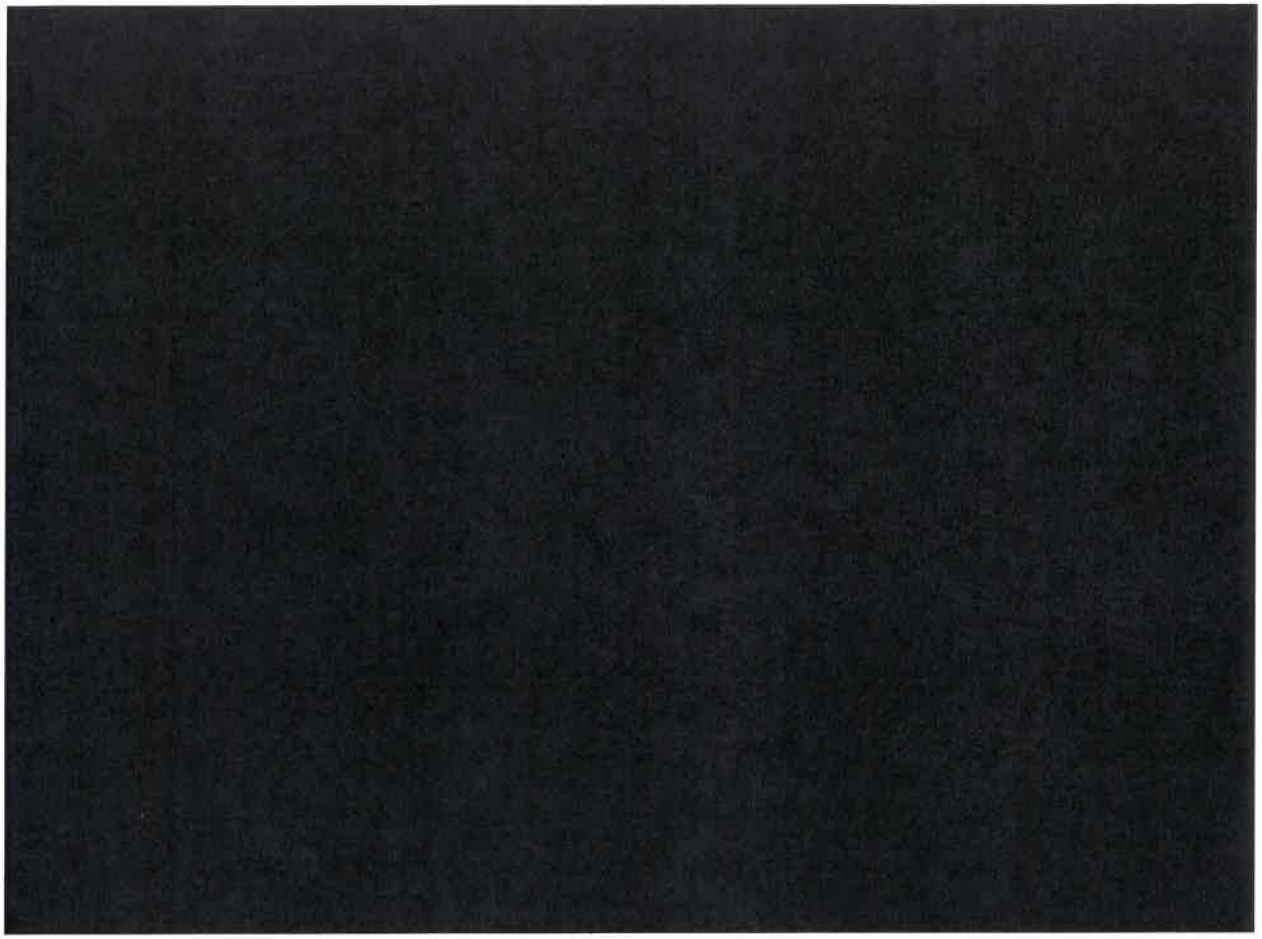
Figure 10. Kaplan-Meier estimates of PFS, ITT population (Data cut-off 30 July 2021).

CI= Confidence interval; HR= Hazard ratio

Source: [20]

Kaplan-Meier estimates of PFS1 - Vinflunine subgroup

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 [redacted] deaths or progression events [redacted] occurred in the EV (pre-selected V) arm compared with [redacted] events [redacted] in the V (subgroup) arm; the corresponding median PFS was [redacted] compared with [redacted] in the EV (pre-selected V) and vinflunine (subgroup) arm respectively, as presented in [redacted] In the pre-selected V population, EV demonstrated a [redacted] reduction in the risk of disease progression or death [redacted] [18]



7.1.2.1.3 Clinical response

The clinical response 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. The comparison of ORR between Arm A and Arm B was performed using the stratified CMH test. The primary analysis was performed on the RES. In addition, ORR for each arm was estimated and the corresponding 95% CI constructed. The formal statistical comparison of ORR between Arm A and Arm B was conducted only per the planned multiplicity adjustment rule. Additional sensitivity analysis for ORR included the comparison of ORR regardless of confirmation. [15]

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. For subjects in the RES who achieved confirmed complete response or partial response, the distribution of DoR was estimated using KM method by each treatment arm. [15]

DCR is defined as the proportion of participants with a CR, PR, or stable disease based on RECIST V1.1. The comparison of DCR between Arm A and Arm B was performed using the stratified CMH test. In addition, DCR for each arm was estimated and the corresponding 95% CI constructed. The formal statistical comparison of Arm A and Arm B was conducted only per the planned multiplicity adjustment rule. Additional sensitivity analysis for DCR included the comparison of DCR regardless of confirmation. [15]

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Clinical response - ITT population

An overview of the clinical response; ORR, DCR, and DoR in the ITT population is presented in Table 10.

The confirmed ORR in the RES was two times higher in the EV (ITT) arm than in the DPV arm, 40.6%, [95% CI: 34.90, 46.54] vs. 17.9%, [95% CI: 13.71, 22.76], P < 0.001, respectively. In the EV (ITT) arm, 4.9% achieved CR compared with 2.7% in the DPV arm (RR=1.80). A median DoR of 7.39 months, [95% CI: 5.59, 9.46] was reported in the EV (ITT) arm and 8.11 months, [95% CI: 5.65, 9.56] in the DPV arm. In the ITT population, the median time to response was 1.87 months, [range: 1.1, 5.7] in the EV (ITT) arm and 1.91 months [range: 1.2, 8.6] in the DPV arm. DCR was significantly higher in the EV (ITT) arm than in the DPV arm (71.9%, [95% CI: 66.30, 76.99] vs 53.4%, [95% CI: 47.52, 59.17], P < 0.001). [15]

Table 10. Clinical response, response-evaluable set.

	EV (N = 288)	Chemotherapy (N = 296)	RR **
Best overall response, n (%)			
Complete response	14 (4.9)	8 (2.7)	1.80
Partial response	103 (35.8)	45 (15.2)	2.35
Stable disease	90 (31.3)	105 (35.5)	0.88
Progressive disease	44 (15.3)	83 (28.0)	0.54
Not evaluable	37 (12.8)	55 (18.6)	0.69
ORR, n (%) [95% CI]	117 (40.6) [34.90, 46.54]	53 (17.9) [13.71, 22.76]	
p-value	<0.001*		
Disease control rate, n (%) [95% CI]	207 (71.9) [66.30, 76.99]	158 (53.4) [47.52, 59.17]	
p-value	<0.001*		
Duration of response, median months [95% CI]	7.39 [5.59, 9.46]	8.11 [5.65, 9.56]	
Time to response, median months	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]

The overall clinical response was also consistent at the data cut-off 30 July 2021 . The confirmed ORR in the RES was two times higher in the EV (ITT) arm than in the DPV arm, 41.3%, [95% CI: 35.57, 47.25] vs. 18.6%, [95% CI: 14.32, 23.49], P < 0.001, respectively. DCR was significantly higher in the EV (ITT) arm than in the DPV arm (71.9%, [95% CI: 66.30, 76.99] vs 53.4%, [95% CI: 47.52, 59.17], P < 0.001). [20]

Clinical response – Vinflunine subgroup

An overview of the clinical response; ORR, DCR, and DoR in the vinflunine subgroup is presented in Table 11.

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The confirmed ORR in the RES was more than two times higher in the EV (pre-selected V) arm than in the V (subgroup) arm, 40.0%, [redacted] 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]

Table 11. Clinical response, response-evaluable set, vinflunine subgroup.

[redacted]		
ORR, n (%) [95% CI]	28 (40.0)	12 (16.0)
[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]

7.1.2.1.4 Patient-reported outcomes – Quality of life

The humanistic value of EV was assessed 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. [22,64]

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. [22,64]

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]

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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. [22,64]

The following domains and overall scores were analyzed:

- EORTC QLQ-C30
  - Global health Status/QoL Scale: Global health status/QoL
  - Functional scales: Physical functioning, role functioning, emotional function, cognitive function, and social functioning
  - Symptom scales: Fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea.
  - Other scale: Financial difficulties
- EQ-5D-5L: EQ-5D-5L utility index, EQ-5D-5L visual analogue scale (VAS)

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. [22,64]

Baseline compliance rates were comparable for the EV and chemotherapy treatment arms in both EORTC QLQ-C30 (90.7% and 88.6% respectively) and the EQ-5D-5L (91.0% and 89.9%, respectively). A similar number of patients in each arm completed QoL assessments at each visit, with a slight decrease post-Week 12. [22,64]

EORTC QLQ-C30

Means and SDs and changes from baseline at each scheduled assessment were reported for each of the QLQ-C30 subscales. The analysis included data from the baseline assessment through the last available data for all subjects in the FAS. [22,64]

EORTC QLQ-C30 results

[redacted]

Table 12. EORTC QLQ-C30 results.

Follow-up time	EV (n=301) Mean (SD)	Chemotherapy (n=307) Mean (SD)
Baseline*	[redacted]	
12 week*		
12 week**	-2.83 (SE: 1.35)	-5.00 (SE: 1.48)
End of treatment visit*	[redacted]	

* Descriptive statistical analysis

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**MMRM analysis

EV= Enfortumab vedotin; ITT= intention to treat; MMRM= mixed model repeated measures; n= sample size; SD: standard deviation; standard error

Source: [64]

Improvement rates were further assessed through logistic regression analyses comparing the proportion of patients achieving confirmed (or sustained) clinically meaningful improvement (i.e. proportion of subjects with confirmed clinically meaningful improvement at two consecutive assessments during the study). On all domains, odds ratios (ORs) were >1, therefore favoring the enfortumab vedotin over the chemotherapy group, except for appetite loss where the odds ratio was 0.96 [0.57; 1.62]. Statistically significant differences were observed for all functioning domains, fatigue, pain, dyspnea and constipation, with more subjects showing a confirmed clinically meaningful improvement compared with subjects in the chemotherapy arm. Across all functioning and most symptom domains improvements were 1.6 to 2.7 times higher with EV compared with chemotherapy, where the greatest difference in confirmed improvement was for pain; there was a 2.7 times higher likelihood of the patients achieving a clinically meaningful reduction in pain with EV than compared with chemotherapy. [22] An overview of the confirmed improvements on QLQ-C30 subscales is provided in Figure 12.

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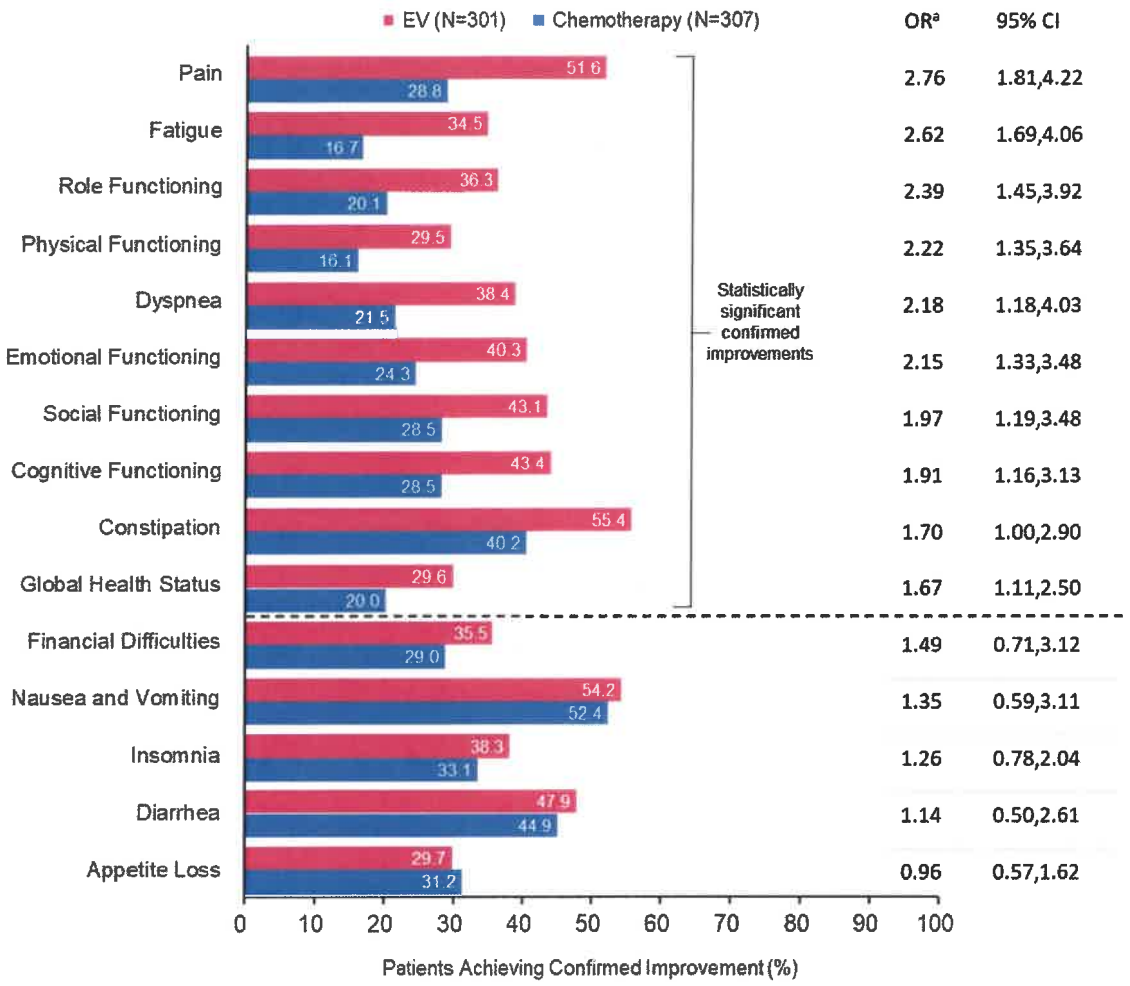

Figure 12. Confirmed Improvements on QLQ-C30 Subscales Based on Primary Thresholds.

CI= Confidence interval; EV= Enfortumab vedotin; OR= overall response

Sources: [22]

EORTC QLQ-C30 results – Vinflunine subgroup

[redacted]

EQ-5D-5L

[redacted]

EQ-5D-5L results

[redacted]

Follow-up time	EV (n=301) Mean (SD)	Chemotherapy (n=307) Mean (SD)
[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: [64]

[redacted]

EQ-5D-5L results – Vinflunine subgroup

[redacted]

7.1.2.1.5 Safety Profile

Safety analyses, which were performed with the use of descriptive statistics, included patients who received any amount of trial drug. Prespecified subgroup analyses were conducted, with subgroups defined according to demographic and baseline disease characteristics. All analyses were performed with the use of SAS software Version 9.2 or higher (SAS Institute). In order to identify any events that may have been associated with study procedures and could have led to a change in the conduct of the study, Astellas collected adverse events (AEs) even if the subject had not received the study drug treatment. AE collection began after the signing of the informed consent and was collected until 30 days after the last dose of study drug. [15,31]

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Results from the EV-301 study demonstrate that treatment with EV was tolerable with a manageable safety profile.

	EV (N = 296)	Chemotherapy (N = 291)	RR
TEAE, n (%)	290 (98.0)	288 (99.0)	0.99
Serious TEAE	138 (46.6)	128 (44.0)	1.06
TEAE leading to withdrawal of treatment	51 (17.2)	51 (17.5)	0.98
Grade ≥3 TEAE	210 (70.9)	193 (66.3)	1.07
Drug-related	[redacted]		
TEAE leading to dose reduction	101 (34.1)	81 (27.8)	1.23
TEAE leading to dose interruption	180 (60.8)	85 (29.2)	2.08
TEAE leading to death	21 (7.1)	16 (5.5)	1.29
Death*	130 (43.9)	161 (55.3)	0.79
TEAE leading to death, excluding disease progression	11 (3.7)	11 (3.8)	0.98

*All reported deaths after the first study drug administration.

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

Sources: [15,31]

AEs, including AEs of special interest, were consistent with the known safety profile of EV and no new safety concerns were identified. 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]

Detailed safety results are shown in appendices D and E.

Treatment-emergent adverse events - ITT

A summary of TEAEs in the data cut-of (15 July 2020) is presented in Table 14. At the data cut-off 15 July 2020, the incidence of overall TEAEs was high in both the EV (ITT) arm and DPV arm (98.0% and 99.0%, respectively) [15]. Serious TEAEs were reported in 46.6% of EV (ITT) patients and 44.0% of patients on DPV, and 17.2% in the EV (ITT) arm and 17.5% in the DPV arm experienced TEAEs leading to withdrawal of treatment. TEAEs of Grade 3 or higher occurred in 70.9% in the EV (ITT) arm and 66.3% in the DPV arm, with [redacted] of the patients, respectively, experiencing drug-related Grade ≥3 TEAE. [15,31]

Table 14. Summary of TEAEs, ITT population, Data cut-off 15 July 2020.

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, Table 15. [63]

Note that the safety data presented in Rosenberg 2022 refers to Safety population, which is defined as all patients which received study treatment, while table 3 and 4 refers in the publication to the ITT population [20].

Table 15. Summary of TEAEs, ITT population, Data cut-off 30 July 2021.

	EV (N = 296)	Chemotherapy (N = 291)	RR
TEAE, n (%)	[redacted]		
Serious TEAE			
TEAE leading to withdrawal of treatment			
Grade ≥3 TEAE			
Drug-related			
TEAE leading to dose reduction			
TEAE leading to dose interruption			
TEAE leading to death			

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

Sources: [63]

Treatment-emergent adverse events – Vinflunine subgroup

A summary of TEAEs based on the preselected V subgroup is presented in Table 16. In the subgroups, a similar safety profile to that of the ITT population was observed. 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, while [redacted] respectively experienced serious TEAEs unrelated to disease progression. In this population, EV demonstrated a [redacted] reduction in the risk of serious TEAEs unrelated to disease progression with an HR of [redacted] **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. An overview of the specific TEAEs of Grade ≥3 that occurred in 2% of patients in either treatment arm is presented in Table 62. [18]

Table 16. Summary of TEAEs, vinflunine subgroup.

	EV (N = 71)	Vinflunine (N = 75)	HR, (95% CI)	P-value
TEAE, n (%)	[redacted]			
Serious TEAE				
Severe TEAE				

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Not Severe TEAE	[redacted]
Grade ≥3 TEAE	
Drug-related Grade ≥3 TEAE	
TEAE leading to drug discontinuation	

EV= Enfortumab vedotin; TEAE= Treatment-emergent adverse events; HR= Hazard ratio

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. 98% of the patients in the EV (ITT) arm experienced a TEAE compared with 98.7% of the patients in the V (subgroup) arm, RR=0.99. Only 46.6% of the patients in the EV (ITT) arm experienced serious TEAEs compared with 60% of the patients in the V (subgroup) arm, RR=0.77. An overview of the comparison is provided in Table 17. [15,18]

Table 17. Comparison of TEAEs in EV (ITT) and vinflunine subgroup.

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

7.1.2.1.6 Supplementary efficacy and safety data on the hard-to-treat subgroups

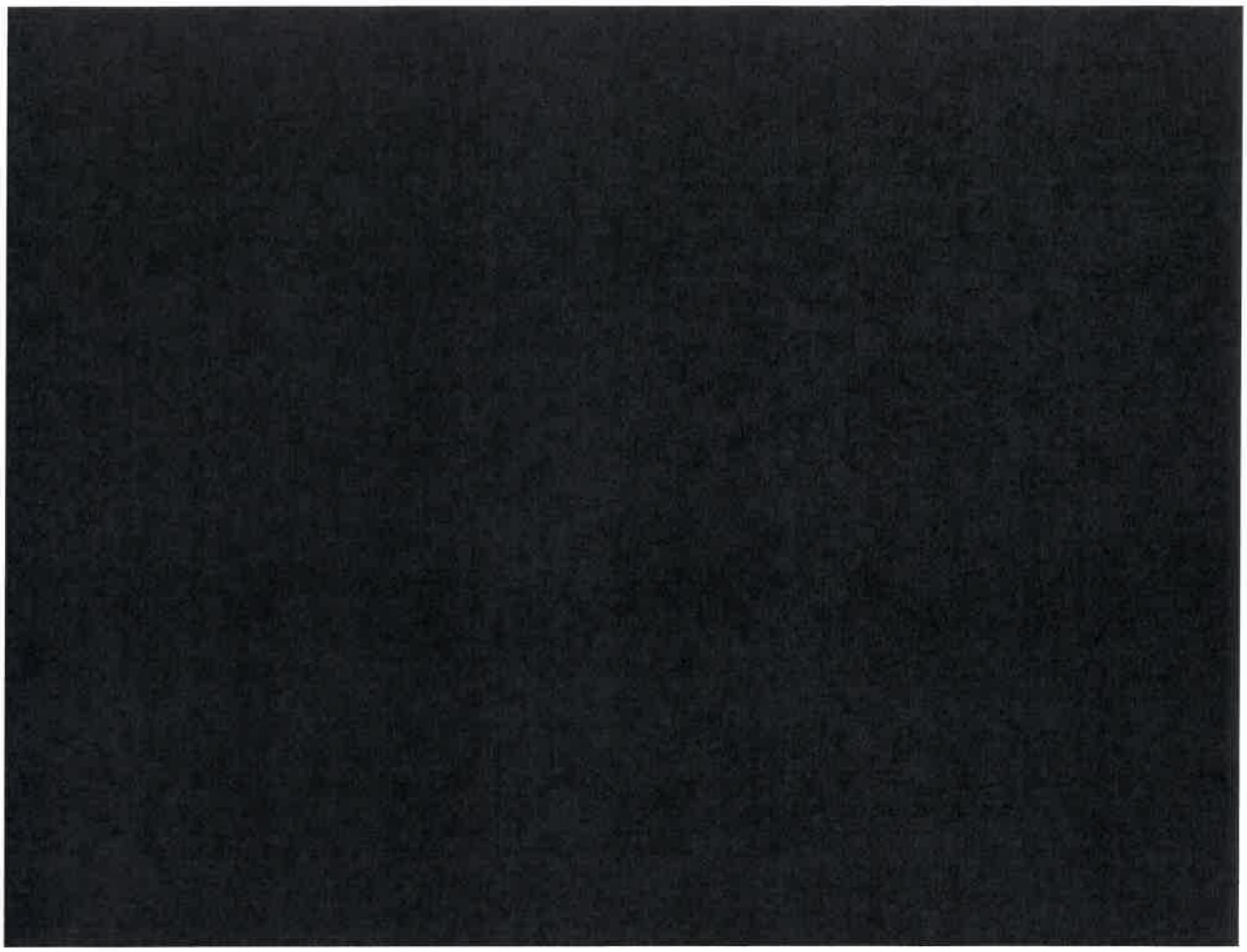
At the ESMO Congress held on September 16-21, 2021, a poster reporting the analysis of hard-to-treat subgroups from EV-301, was presented. The subgroups characterized as hard-to-treat including those with poor prognostic factors included age ≥65 years, presence of liver metastasis, primary upper tract disease, and nonresponse to prior PD-1/L1 inhibitor. Analyses of prespecified subgroups characterized as hard-to-treat were conducted and reported for OS, PFS, and ORR. In summary, the results showed that the OS benefit for EV patients was maintained across the hard-to-treat subgroups, the OS was longer in the EV arm compared with the DPV arm, consistent with median OS for the overall population. The PFS benefit for EV was maintained hard-to-treat across most subgroups, and the ORRs reported across all hard-to-treat subgroups were similar to that of the overall population in EV-301, which supports the unmet need in UC patients. EV provides benefit in the overall population but as stated here, also in the hard-to-treat patients. [19]

Detailed efficacy and safety data of the hard-to-treat subgroups is provided in Appendix K.

7.1.2.2 EV-201, Cohort 1

The EV-201 is an ongoing study with expected completion in 2025. OS data from the updated data cut-off date of 8 September 2020 (median follow-up of 28.4 months) is presented below, all other results from the data cut-off date of 1 March 2019 (median follow-up of 10.2 months) are presented in Table A3d in Appendix D. The later data cut

(September 2020) is used in the health economic section 8 to assess the external validity of the model predicted OS. [16,21]



Further efficacy and safety outcomes are presented in Appendix D and E.

7.1.3 Comparative analyses of efficacy and safety

This assessment does not include comparative analyses of efficacy and safety. In accordance with section 7.1.2 in the DMC application template, the comparative analysis was omitted as a single RCT provides head-to-head evidence of EV and taxane chemotherapy.

7.1.3.1 Method of synthesis

7.1.3.1.1 Meta-analysis

Indirect treatment comparisons have not been conducted as a single RCT provides head-to-head evidence of EV and taxane chemotherapy.

7.1.3.1.2 Indirect and mixed treatment comparisons

Indirect treatment comparisons have not been conducted as a single RCT provides head-to-head evidence of EV and taxane chemotherapy.

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7.1.3.2 Results from the comparative analysis

Not applicable (NA).

7.2 Summary

7.2.1 Efficacy

At the data cut-off July 2020, for the EV-301 ITT population it was demonstrated that EV significantly prolonged the primary endpoint OS compared with DPV, median OS: 12.88 vs 8.97 months, respectively; and reduced the risk of death, HR= 0.70; [95% CI: 0.56, 0.89]; p=0.001). The key secondary endpoints included PFS (median PFS: 5.55 vs 3.71 months for EV and chemotherapy arms, respectively; p<0.001), and ORR (40.6% vs 17.9% for EV and chemotherapy arms, respectively; p<0.001). [15]

Data from data cut-off July 2021 confirmed that EV significantly prolonged the primary endpoint OS compared with chemotherapy, median OS: [redacted] respectively; and reduced the risk of death, [redacted] Median PFS for both the EV and chemotherapy arm were similar to the previous data cut at July 2020 (5.55 and 3.71 months, respectively).[63]

In the post hoc vinflunine population, similar results to the ITT population were seen, with EV resulting in longer median OS compared with vinflunine (median OS: [redacted] respectively; [redacted] as well as prolonged PFS (median PFS: [redacted] respectively; [redacted].[18]

Similarly, the hard-to-treat subgroups retained the OS benefit for EV across all subgroups. The median OS was in all subgroups longer for EV compared with chemotherapy, consistent with the median OS for the overall population. [19]

Patients enrolled in Cohort 1 in EV-201 had also previously received platinum-based chemotherapy treatment [redacted] [21]

7.2.2 Patient-reported outcomes – Quality of life

The humanistic value of EV was assessed using the EORTC QLQ-C30, and the EQ-5D-5L. The assessment showed that patients treated with enfortumab vedotin maintained QoL and had less variability in QoL compared with chemotherapy, with confirmed clinically meaningful improvement in pain. [22]

7.2.3 Safety

EV was generally well-tolerated in both the ITT and the vinflunine subgroup populations, with similar treatment-emergent discontinuation rates compared with DPV, as demonstrated by EV-301 data cut-off July 2020 (ITT: 17.2% vs 17.5% experienced TEAEs leading to treatment withdrawal; 7.1% vs 5.5% experienced TEAEs leading to death [15]).

Similar results were demonstrated in the July 2021 data cut [redacted] patients experiencing TEAEs leading to treatment withdrawal, and [redacted] experienced TEAEs leading to death, respectively. [63]

In the vinflunine subgroup, [redacted] experienced serious TEAEs; and [redacted] experienced TEAE leading to drug discontinuation [18].

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The safety profile in the hard-to-treat subgroups was consistent with that observed in the overall population in EV-301. No new safety signals were observed. [19]

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8. Health economic analysis

8.1 Model

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. [15,31] 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 (see Table 9 in Section 7.1.1.1 for more details about the population). 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). This and other scenarios will be discussed in Section 8.7. 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 [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 18.

Table 18. Key features of the EV model

Features	Description
Patient population	Adult patients with la/mUC who have been treated with a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor.
Perspective	A limited societal perspective in accordance with the DMC guideline [61]
Time horizon	Lifetime*
Discount rate	3.5% annually for both costs and health effects [65]
Model structure	Three-state (pre-progression, post-progression, and death) partitioned survival model with monthly cycle (i.e., 30.4 days)
Intervention	EV
Comparators	V (base case), DPV (scenario analysis)
Clinical parameters	OS, PFS, DoT, dosing, and grade ≥3 AEs. Clinical inputs for all treatment arms were estimated using individual patient data from the EV-301 study (NCT03474107, data cut-off: July 15 2020). The patient population was based on the EV-301 trial population (Table 9). The base-case analysis used the EV (pre-selected for V) and V subgroups.
Valuation of health effects	EQ-5D-5L estimated utility values by treatment and health state†
Economic parameters	Treatment costs (drug and administration), patient time costs (patient time cost per hour, patient transportation costs to and from hospital), medical costs (outpatient visits,

Features	Description
	hospitalization, emergency room visits, and intensive care unit visits), and AE management costs.
Model outputs	Total costs and by category Total LYs and QALYs and by health states Incremental cost per QALY gained

* In this model, the lifetime horizon is 33 years; since the starting age of the patient population is 67 years, this assumes a maximum patient age of 100 years. Based on an extrapolation of OS data, <1% of patients in any treatment arm are expected to be alive after 33 years. This time horizon was selected so as to capture all meaningful differences in effects and costs between the treatment options. The model assumes that patients will receive treatment until the end of life or unacceptable toxicity.

† Utility scores were estimated based on EQ-5D-5L data from the EV-301 trial and the Danish EQ-5D-5L value set [66].

AE = adverse event; DoT = duration of treatment; DMC = Danish Medicines Council; DPV = docetaxel, paclitaxel, or vinflunine; EQ-5D-5L = EuroQol-5 dimension-5 level Instrument; EV = enfortumab vedotin; IPD = individual patient data; la/mUC = locally advanced or metastatic urothelial carcinoma ; LY = life years; OS = overall survival; PD-1 = programmed cell death ligand-1 ; PD-L1 = programmed cell death ligand-1; PFS= progression-free survival; QALY = quality-adjusted life years; V = vinflunine

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.

A partitioned survival model can be limited due to the lack of explicit structural link between efficacy endpoints (e.g., OS and PFS), making the state transition model a viable alternative to conduct CEA for novel interventions in oncology. However, the impact of this limitation is anticipated to be minor in the current analysis, given that the survival data of EV-301 is mature, with less than 20% of patients alive in both arms in EV-301, and 0% and 15% in the PFS state for chemotherapy and EV, respectively at the end of the trial follow-up period. As the PFS and OS data in EV-301 is close to mature, there is little advantage to a state transition model as the long-term extrapolation period is expected to be similar between a state transition model and a partitioned survival model with mature data. Given the above considerations, the partitioned survival model structure was used to evaluate CE of EV vs comparators.

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 14):

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 [31].

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).

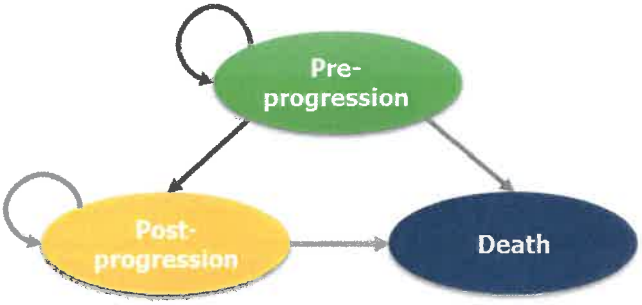

Figure 14. Partition survival structure of the EV model

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.

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Key assumptions applied in the core EV model are summarized in Table 19.

Table 19. Key assumptions of the EV model

Parameter	Assumption
Efficacy	OS and PFS data from the EV-301 study were assumed to reflect the efficacy before and after patients discontinued EV or comparator chemotherapy,* respectively. Subsequent treatment efficacy was not explicitly modelled since a comparable and small proportion of patients on EV and comparator treatments received subsequent treatment after discontinuation.
DoT	The treatment duration of EV and comparators observed in the EV-301 study were assumed to be generalizable to the overall experience of the Danish population.
Utilities	Utilities were assumed to be dependent on health state (pre-progression and post-progression). In addition, pre-progression utilities were assumed to vary by treatment.
Treatment costs	The treatment schedules of EV and comparators specified in the EV-301 study were assumed to be generalizable to clinical practice in Denmark. Dosing intensity of EV and comparators specified in the EV-301 study were assumed to be generalizable to clinical practice in Denmark.
Subsequent treatment costs	The prevalence of subsequent treatment use is comparable between EV and comparators based on data from the EV-301 study and crossover was not allowed in the trial (primary efficacy analysis set), thus costs of these treatments were not accounted for in the EV model.
Medical costs	Medical costs incurred throughout the model time horizon were assumed to be dependent on health states only and independent of treatment arms. 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.
AEs	Costs of AEs were considered as a one-time cost incurred in the first model cycle and were dependent on AE rates in each treatment arm reported from EV-301 safety data set.
Patient costs	Patient costs included patient cost time per hour and patient transportation costs to and from the hospital in accordance with DMC guidance

* Comparator chemotherapy was V in the base-case model and DPV in a scenario analysis.

AE = adverse event; DoT = duration of treatment; DPV = docetaxel, paclitaxel, or vinflunine; EV = enfortumab vedotin; OS = overall survival; PFS= progression-free survival; V = vinflunine

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

Model clinical inputs were based on the EV-301 trial. In addition, the clinical expert present at the dialogue meeting with DMC confirmed the relevance of the trial population and comparators (Table 20) to clinical practice in Denmark.

Table 20. Patient populations used from which base-case model inputs were obtained

Model input	EV arm	Chemotherapy arm
Patient characteristics (age, percent male, weight, height, BSA)	ITT	ITT
OS, PFS, DoT	EV (pre-selected V)	V (subgroup)

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Model input	EV arm	Chemotherapy arm
EQ-5D-5L pre progression	EV (ITT)	V (subgroup)
EQ-5D-5L post progression	ITT	ITT
AE	EV (ITT)	V (subgroup)

AE = adverse event; BSA = body surface area; DoT = duration of trial; EV = enfortumab vedotin; ITT = intention to treat; OS = overall survival; PFS = progression-free survival; V = vinflunine

8.2.1 Presentation of input data used in the model and how they were obtained

For the base case, the model considered EV efficacy data from a subgroup of patients who were pre-selected for V. Patients enrolled in EV-301 who were pre-selected to receive V were then randomized to either V or EV. Those randomized to EV (the EV [pre-selected for V] subgroup) were used to inform EV efficacy and those assigned to V (the V subgroup) were used to inform V efficacy. One scenario analysis described in Section 8.7 considered ITT data for treatment (EV) and comparator (DPV).

As discussed in the above description of model structure (Section 8.1), health state membership was based directly on extrapolated PFS and OS values rather than on transition probabilities, which were not used in the model. Clinical input data are shown in Table 21.

Table 21. Clinical input data used in the model

Name of estimates*	Results from study	Input value used in the model	How is the input value obtained/estimated†
Clinical inputs‡			
OS **EV (pre-selected V), median (95% CI), months** **V subgroup, median (95% CI), months** **EV (pre-selected V) vs. V, HR (95% CI)**	[redacted]	Piecewise extrapolations of EV (pre-selected V) and V subgroup data from EV-301 trial	EV (pre-selected V): KM through month 15 followed by exponential V: KM through month 15 followed by Weibull
PFS **EV (pre-selected V), median (95% CI), months** **V subgroup, median (95% CI), months** **EV (pre-selected V) vs. V, HR (95% CI)**		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)
DoT, EV (pre-selected V), median (95% CI), months **DoT, V, median (95% CI), months**		Patient-level data from EV-301 trial for EV (pre-selected for V): KM curve through month 15; and V subgroup: KM curve through month 14	Patient-level data from EV-301 trial

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Name of estimates*	Results from study	Input value used in the model	How is the input value obtained/estimated†
Pre-progression (EV – Pre-selected V), mean utility (SE)*	[redacted]		Utility scores were estimated based on EQ-5D-5L data from the EV-301 trial and the Danish EQ-5D-5L value set. [66]
Pre-progression (V), mean EQ-5D utility (SE)*			
Post-progression (Full ITT), mean EQ-5D utility (SE)*			
Cost inputs (DKK)**			
EV, Acquisition (per cycle)		[redacted]	
V, Acquisition (per cycle)			
EV, Administration (per cycle)			
V, Administration (per cycle)			
Monthly pre-progression disease management costs			
Monthly post-progression disease management costs			
Adverse reaction costs, EV			Estimate based on rates of AEs in EV-301 trial and on unit costs of AEs from DRG Takster 2022 [68]
Adverse reaction costs, V			
Monthly pre-progression patient cost			Estimate based on patient costs from Medicinradet, 2020‡‡
Monthly post-progression patient cost			
Monthly EV related patient cost			
Monthly V related patient cost			

* Some of these estimates will be presented in other tables in the document. This table is a summary.

† Calculations: If intermediate outcome measures were linked to final outcomes, describe them here (for example, if a change in a surrogate outcome was linked to a final clinical outcome). Explain how the relationship was estimated, what sources of evidence were used, how the sources of evidence were identified (e.g. systematic literature review) and what other evidence exists. Details must be provided in a separate appendix with reference here.

‡ Clinical inputs include HRs for PFS and OS for DPV and V, and duration of treatment inputs. AE inputs, which may be presented in a separate table, include AEs and their incidence and cost of management.

** Cost inputs include all drug acquisition, administration, medical, and patient costs. All costs re expressed in 2022 DKK.

‡‡ Estimated costs for transportation to and from the hospital for treatment (based on DMC assumption of 14 km distance from hospital). [61]

AE = adverse event; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CI = 95% confidence interval; DoT = duration of treatment; DMC = Danish Medicines Council; DPV = docetaxel, paclitaxel, or vinflunine; EQ-5D = EuroQOL-5 dimensions; EV = enfortumab vedotin; HR = hazard ratio; ITT = intention-to treat; KM = Kaplan Meier; NC = not calculable; OS = overall survival; PFS= progression-free survival; SE = standard error; V = vinflunine

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8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

As discussed above, model clinical inputs are based on the EV-301 trial. In addition, the clinical expert present at the dialogue meeting with DMC confirmed the relevance of the trial population and comparators to clinical practice in Denmark.

8.2.2.1 Patient population

The Danish patient population: The patient population relevant for this application is adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor [3]. According to the DMC, the incidence of patients with la/mUC is approximately 150 per year. The DMC estimated that approximately 25 patients will be eligible for 2nd line treatment with EV, whereas evidence from a chart review suggested a patient number of 48 – thus the population that would be indicated for treatment with EV was estimated at between 35 and 48.[9,10,15]

Patient population in the clinical documentation and economic analysis submitted: The patient population in the clinical documentation submitted is adult patients with la/mUC previously treated with a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. This patient population is consistent with the anticipated indication for EV and corresponds to the patient population evaluated in the pivotal phase 3 clinical trial of EV (EV-301 study).[1,31] In particular, all patients included in the EV-301 study experienced radiographic progression or relapse during or after a PD-1/PD/-L1 treatment for la/mUC. The characteristics of the patient population are summarized in Table 22.

Table 22. Patient population*

Important baseline characteristics	Clinical documentation (including source)	Used in the model (number/value including source)
Age (years), mean (SD)	[redacted]	
Age (years), median (range)	68.0 (30.0, 88.0)	68.0 (30.0, 88.0)
Male, n (%)	470 (77.3)	470 (77.3)
Weight (kg), mean (SD)	[redacted]	
Mean BSA, m^2 (SD)		

*The clinical expert present at the dialogue meeting with DMC confirmed the relevance of the trial population and comparators to clinical practice in Denmark. The expert noted that the trial population is younger than that seen in clinical practice.

BSA = body surface area; DMC = Danish Medicines Council; SD = standard deviation

SOURCES: Powles 2021, Astellas Pharma [15,31]

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice: The indication for EV is the treatment of adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor [3]. EV is expected to replace V in the treatment algorithm for the treatment of UC. The clinical expert advising the DMC suggested at the dialogue meeting that EV should replace vinflunine in 2nd line.

Intervention in the clinical documentation and health economic analysis submitted: EV is an ADC for the treatment of patients with la/mUC who have previously been treated with a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. Characteristics of the intervention are summarized in Table 23.

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Table 23. Intervention – EV

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	1.25 mg/kg on Days 1, 8, and 15 of 28-day cycle	1.25 mg/kg on Days 1, 8, and 15 of 28-day cycle	1.25 mg/kg on Days 1, 8, and 15 of 28-day cycle
Length of treatment (time on treatment) **mean [SD]** **median (range) [95% CI]**	NA [redacted]	Patient level data from EV-301 trial for EV (pre-selected for V): KM curve through month 15	
Criteria for discontinuation	Disease progression, protocol-defined discontinuation criterion, study termination, or study completion	Disease progression, protocol-defined discontinuation criterion, study termination, or study completion	Disease progression, protocol-defined discontinuation criterion, study termination, or study completion
The pharmaceutical's position in Danish clinical practice	EV is expected to replace V in the treatment algorithm for the treatment of UC. 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 According to ESMO guidelines, 2021 EV will be the standard of care 2nd line with evidence grade 1, A [14].		

EV = enfortumab vedotin; NA = not available; SD = standard deviation; V = vinflunine

SOURCES: Powles 2021, Astellas Pharma [15,31]

8.2.2.3 Comparators

The current Danish clinical practice: The indication for EV is the treatment adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor [3]. 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 [1,13]. Another guideline, defined by the DaBlaCa, lists taxanes (D and P) as possible treatments [53]. However, taxanes are, according to experts not widely used in Danish clinical practice for this indication [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.

In the base-case model, EV is compared with V. Specifically, data from patients assigned to EV (pre-selected for V) and V subgroups were used to inform the model. In addition, a scenario analysis comparing EV and DPV based on the EV-301 ITT population was also conducted (Section 8.7).

Comparator(s) in the clinical documentation submitted: The efficacy and safety of EV compared with chemotherapy (i.e., D, P or V) for the treatment of patients with la/mUC who have previously been treated with a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor were evaluated in the global, open-label, randomized phase 3 EV-301 study [15,31]. A total of 608 subjects were included in the study (i.e., ITT population). Patients were assigned with a pre-selected control chemotherapy based on investigator's evaluation and then randomized to receive EV (n=301) or the investigator selected control chemotherapy (n=307). Subjects in the EV arm received intravenous infusion of EV on Days 1, 8 and 15 of each 28-day cycle. Subjects in the chemotherapy arm received either docetaxel, paclitaxel or vinflunine via intravenous infusion on Day 1 of every 21-day cycle. Patients in the study would receive the study treatment until the earlier of disease progression, a protocol-defined discontinuation criterion, study termination, or study completion.

Comparator(s) in the health economic analysis submitted: The comparator evaluated in the base-case model was V. The control chemotherapies (i.e. D, P, or V) in the EV-301 study were chosen based on their relevance for the treatment of la/mUC after a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. However, V was deemed the most relevant comparator in Denmark. The DPV scenario (Section 8.7) was included to reflect the full patient population of the EV-301 study. The characteristics of the comparator are summarized in Table 24.

While a number of patients would initiate palliative care (i.e., best supportive care (BSC)) after progressing or relapsing from PD-1/PD-L1 inhibitor, BSC was not considered as a comparator in the EV model due to limited efficacy data. In addition, with several chemotherapies (i.e., D, P, V) available as alternative therapies following PD-1/PD-L1 inhibitor, BSC may be less relevant as a comparator for EV.

Table 24. Comparator – V

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	320 mg/m² on Day 1 of 21-day cycle	320 mg/m² on Day 1 of 21-day cycle	
Length of treatment (time on treatment) **mean [SD]** **median (range) [95% CI]**	[redacted]	Patient level data from EV-301 trial for subgroup: KM curve through month 14	Patient-level data from EV-301 trial
The comparator's position in the Danish clinical practice	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 [13]	V is indicated for adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of prior platinum-containing regimen[13]	In current practice, V is used off-label as a second-line treatment for la/mUC following progression on avelumab. In the future, V may be used off-label in the third-line. Accordingly, the clinical expert advising the DMC at the dialogue meeting also designated vinflunine as the most relevant comparator.

CI = confidence interval; SD = standard deviation; V = vinflunine

SOURCES: Powles 2021, Astellas Pharma [15,31]

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the clinical documentation and health economic analysis submitted: 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 15 2020). [15,31]

The EV-301 study was powered to demonstrate differences in survival between EV and chemotherapies (D, P, or V) in the ITT population [15,31]. 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 [9].

Long-term survival and treatment discontinuation beyond the trial follow-up period were estimated for EV (pre-selected for V) and V. Parametric models of OS, PFS, and DoT were fitted for each treatment (Table 21). Detailed methods of the statistical extrapolation are summarized in Section 8.3.

The most relevant comparator is V, which was used in the base case. DPV was also used as a comparator because it represents the ITT population of the EV 301 trial. Efficacy inputs for OS, PFS and DoT are summarized in Table 25 and Table 26.

Table 25. Summary of base-case efficacy inputs

Inputs	EV (pre-selected for V) subgroup*	V subgroup†
OS	Parametric extrapolation (piecewise), KM curve until month 15 followed by exponential distribution	Parametric extrapolation (piecewise) KM curve until month 15 followed by Weibull distribution
PFS	Parametric extrapolation (one-piece), log-logistic distribution	Parametric extrapolation (one-piece), log-logistic distribution
DoT	Patient-level data from the trial (KM curve through month 15)	Patient-level data from the trial (KM curve through month 14)

DoT = duration of treatment; EV = enfortumab vedotin; OS = overall survival; PFS= progression-free survival; V = vinflunine

* EV patients whose pre-selected therapy is V (n = 73)

† Chemotherapy patients receiving V (n = 78)

SOURCES: [15,31]

Table 26. Relative efficacy of EV (pre-selected for V) vs V based on the EV-301 trial

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study, OS **EV (pre-selected V), median (95% CI), months** **V subgroup, median (95% CI), months** **EV (pre-selected V) vs. V, HR (95% CI)**	[redacted]	EV: Parametric extrapolation (piecewise), KM curve until month 15 followed by exponential distribution V: Parametric extrapolation (piecewise) KM curve until month 15 followed by Weibull distribution
Secondary endpoint, PFS **EV (pre-selected V), median (95% CI), months** **V subgroup, median (95% CI), months** **EV (pre-selected V) vs. V, HR (95% CI)**	[redacted]	EV and V: Parametric extrapolation (one-piece), log-logistic distribution
EV (pre-selected V), DoT, months (median) **V, DoT, months (median)**	[redacted]	Patient-level data from EV-301 trial for EV (pre-selected for V): KM curve through month 15; and V subgroup: KM curve through month 14

CI = confidence interval; DoT = duration of treatment; DPV = docetaxel, paclitaxel, or vinflunine; EV = enfortumab vedotin; HR = hazard ratio; ITT = intention-to treat; NC = not calculable; OS = overall survival; PFS= progression-free survival; V = vinflunine

Source: [18,31]

Relevance of the documentation for Danish clinical practice is shown in Table 27. Additional information regarding relevance of clinical outcomes is presented in Appendix D.

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Table 27. Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study (OS)	The time from randomization to the date of death from any cause. Clinical relevance was investigated with the use of the stratified log-rank test. Minimal clinically important difference [9] Median OS: 3 months OS rate: 5%-points in 12 months	It is assumed that that the standard outcomes in oncology are used in Danish clinical practice.	It is assumed that that the standard measurement methods in oncology are used in Danish clinical practice.
Secondary endpoint (PFS)	The proportion of participants with a complete or partial objective response or a stable disease (at least 7 weeks). Investigator assessed. Evaluated on the basis of RECIST Clinical relevance was investigated with the use of a stratified CMH test.	It is assumed that that the standard outcomes in oncology are used in Danish clinical practice.	It is assumed that that the standard measurement methods in oncology are used in Danish clinical practice.

Cochran-Mantel-Haenszel = CMH; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1.

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation and health economic analysis submitted: The inputs of AE rates were obtained from the EV-301 study safety cohort. 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. Adverse reaction outcomes are summarized in Table 28.

Table 28. Adverse reaction outcomes*

Grade 3 or 4 AEs	Clinical documentation		Used in the model (numerical value)	
	EV (ITT; n=296), n (%)	V (n=75), n (%)	EV (ITT; n=296), n (%)	V (n=75), n (%)
Anemia				
Neutropenia				
Febrile neutropenia				
Rash maculo-papular				

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

*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 [15,31]

8.3 Extrapolation of relative efficacy

The EV model used EV-301 trial data to simulate the impact of EV and comparator on the disease course of patients with la/mUC over a lifetime horizon. As with any oncology clinical trial, EV-301 does not offer data throughout the modelled time horizon. Therefore, extrapolation of the survival data from EV-301 trial was necessary to project the disease progression beyond the trial observed period. Robust statistical models were used to extrapolate efficacy inputs for EV and comparators (described in Section 8.3.1).

The economic model does not account for treatment waning for EV in the analysis given a) the poor prognosis associated with patients with locally advanced / metastatic UC and b) a small proportion of patients surviving beyond 2 years (at 2-year, proportion alive was <30% and proportion progression-free was <8% based on model extrapolation). Due to these reasons, we believe the treatment waning would not have a considerable impact on the result as the proportion of patients surviving after treatment cessation is low.

Modeling the constant treatment effect was further supported by the EV-301 data cut from 30 July 2021 which had a median follow-up of 23.75 months (described in Section 7.1.2). For this 2021 data cut with a longer follow-up, results for the ITT population are available which demonstrate sustained treatment effect of EV (HR of 0.70 vs. DPV arm compared to HR of 0.70 vs. DPV reported by the data cut used in the model analysis) despite treatment cessation by >90% of the patients.

8.3.1 Time to event data – summarized

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 lifetime 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]

- **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.

All survival curve extrapolation was done using R 3.6.3, flexsurv package [70]. For OS and PFS, the proportional hazard assumption between EV (V sub-group) and V arms holds as validated through the reasonable proportional log cumulative hazard functions between the EV (V subgroup) and V arms (Log cumulative hazard plots; Appendix G) and the non-significant test results of the Schoenfeld residuals tests (Schoenfeld residuals plots; Appendix G). The smoothed hazard function and unsmoothed hazard function plots for EV (V subgroup) and V arms are also provided Appendix G.

8.3.1.1 OS

In the base-case model, OS inputs for EV (pre-selected V subgroup; n = 73) and V (n = 78) were derived using individual patient data from the phase 3 EV-301 study. For EV (pre-selected V subgroup) and V, standard parametric models were used to fit an OS curve and extrapolate OS estimates. For the V arm, the core EV model allows for independent parametric survival models or the application of a HR to the EV OS data (see Appendix G). For both treatment arms, estimated OS rates over time were capped by the age-gender adjusted national mortality rates in Denmark (based on Danish life tables)[71].

The selected base-case OS extrapolation approach for the EV (pre-selected V subgroup) arm was a piecewise approach based on the KM curve until month 15 followed by a parametric function with exponential distribution. The selected base-case OS extrapolation approach for the V arm was a piecewise approach based on the KM curve until month 15 followed by a parametric function with Weibull distribution. These approaches were selected based on AIC/BIC statistics (Table 29) and visual fit inspection (Figure 15).

The exponential distribution was statistically the best fit for OS extrapolation for the EV (V) arm based on AIC/BIC statistics (lowest AIC and BIC values; Table 29) and visual fit inspection (Figure 15A). Hence, it was selected to extrapolate data beyond the KM for EV.

For vinflunine, Exponential, Gompertz, and Weibull were the main choices as they scored lowest on the AIC/BIC matrix. The difference in AIC/BIC scores between these three parametric functions was less than 1 point. Upon visual

inspection, exponential function did not seem to fit the observed KM curve from month 12 onwards (Figure 15). Weibull function fits between the Exponential (poor visual fit) and Gompertz (potential underestimation of V OS) extrapolation, and was selected in the base case to estimate OS over the time horizon.

The piecewise approach was chosen because, for both treatments, the remaining sample sizes after month 15 were too small to be representative of the survival trajectories of their respective groups. In this approach, the KM data corresponding to each arm was applied for cycles 0 to 15, post which the extrapolated data from the last observed data point in cycle 15 was applied, i.e. (exponential for EV and Weibull for V).

Statistical goodness of fit and visual validation for the parametric curves are summarized in Table 29 and Figure 15.

Table 29. Statistical goodness of fit for OS extrapolation of EV (pre-selected V subgroup) and V subgroups

Distribution	EV (pre-selected V subgroup)		V subgroup	
	AIC	BIC	AIC	BIC
[redacted]				

AIC = Akaike information criterion; BIC = Bayesian information criterion; EV = enfortumab vedotin; OS = overall survival; V = vinflunine
Grey shaded cells: distribution with the best fit.

[redacted]

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8.3.1.2 PFS

In the base-case model, PFS inputs for EV (pre-selected V subgroup; n = 73) and V (n = 78) were derived using individual patient data from the phase 3 EV-301 study. For EV (pre-selected V subgroup) and V, standard parametric models were used to fit a PFS curve and extrapolate PFS estimates. (For the V arm, the core EV model allows for independent parametric survival models or the application of a HR to the EV PFS data). For all treatment arms, estimated PFS rates over time were capped by the estimated OS rates. Half-cycle correction was applied.

The selected base-case PFS extrapolation approach for the EV (pre-selected V subgroup) arm and the V arm was a parametric function with log-logistic distribution. This approach was selected based on AIC/BIC statistics (Table 30) and visual fit inspection (Figure 16).

Statistical goodness of fit and visual validation figures for the parametric curves fitted for all arms are summarized in Table 30 and Figure 16.

Table 30. Statistical goodness of fit for PFS extrapolation of EV (pre-selected V subgroup) and V subgroups

Distribution	EV (pre-selected V subgroup)		V subgroup	
	AIC	BIC	AIC	BIC
Exponential				
Weibull				
Log-Logistic				
Log-Normal				
Gompertz				
Generalized Gamma				

AIC = Akaike information criterion; BIC = Bayesian information criterion; EV = enfortumab vedotin; ITT = intention to treat; PFS = progression-free survival

Grey shaded cells: distribution with the best fit.

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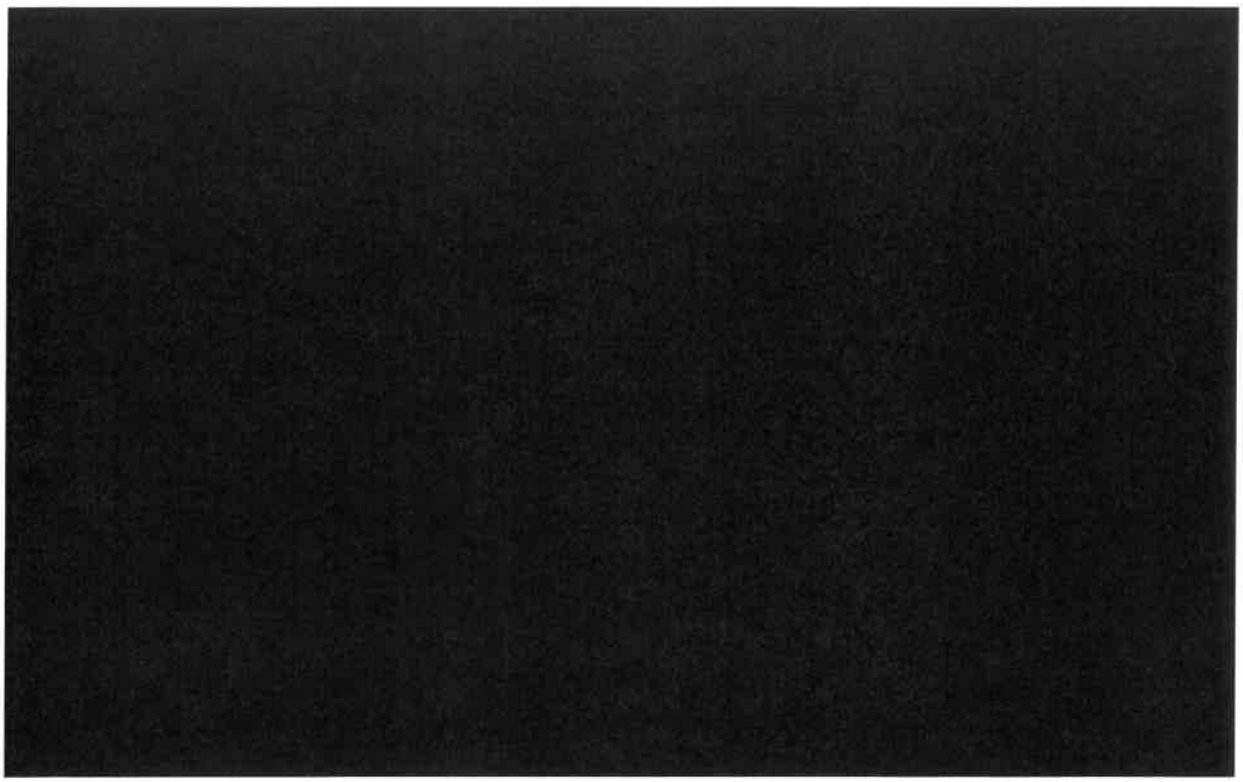

8.3.1.3 DoT

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 based on the ITT population and subgroups by pre-selected chemotherapy to calculate the drug and administration costs. 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 from the EV-301 trial data (through 15 months for the EV subgroup and 14 months for the V subgroup). Parametric functions considered for DoT extrapolation included exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions, which were evaluated based on AIC/BIC (Table 31) and visual inspection (Figure 18). However, as the number at risk dropped to 0 in both EV (pre-selected for V) and V subgroups at 15 months and 14 months (Figure 17), respectively, indicating a complete data set, no extrapolation was deemed necessary.

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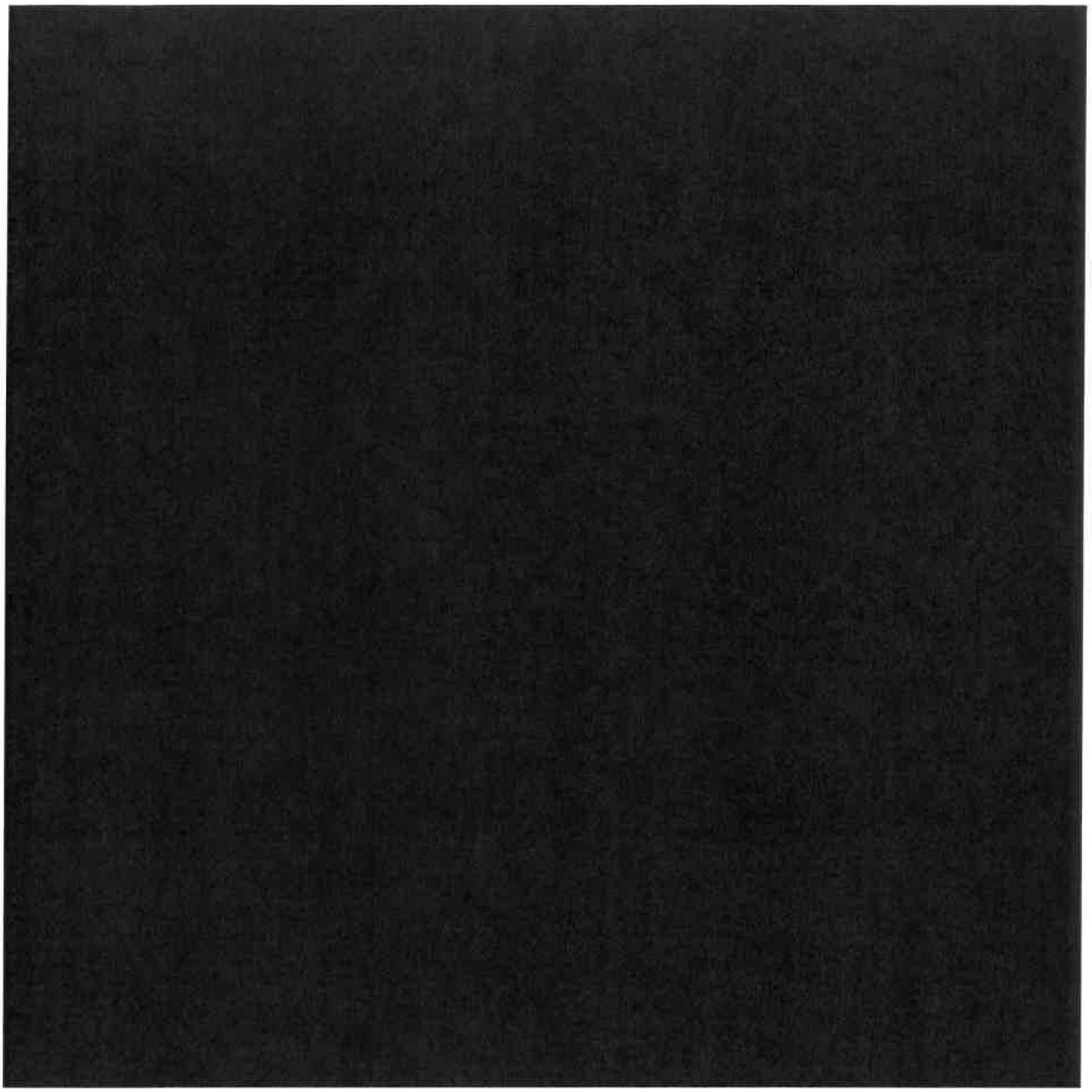

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Table 31. Statistical goodness of fit for DoT extrapolation of EV (pre-selected V subgroup) and V subgroups

Distribution	EV (pre-selected V subgroup)		V subgroup	
	AIC	BIC	AIC	BIC
Exponential				
Weibull				
Log-Logistic				
Log-Normal				
Gompertz				
Generalized Gamma				

AIC = Akaike information criterion; BIC = Bayesian information criterion; EV = enfortumab vedotin; DOT = duration of treatment; V = vinflunine
Grey shaded cells: distribution with the best fit.

[redacted]

In the EV-301 study, there were 587 patients who received at least one dose of the study treatment out of the 608 patients in the ITT-population. Among patients receiving EV (pre-selected V subgroup), [redacted] patients received at least one dose of study drug out of 73 patients randomized, and among patients in the V subgroup, [redacted] patients received at least one dose of study drug out of 78 patients randomized. Extrapolation of treatment duration was therefore estimated among the subset of patients who received study treatment. As the model simulates outcomes for all randomized patients from the ITT population or the pre-selected chemotherapy subgroup, adjustment was applied to the DoT curves in the model to account for patients who did not initiate study treatment at all (i.e., DoT is zero

months). Percentage of patients who received treatment out of the randomized patients for the relevant patient subgroups were used as the adjustment factors for each treatment arm (Table 32).

Table 32. Percentage of randomized patients receiving study treatment in EV-301

Treatment arm	Number of patients received treatment	Number of randomized patients	Percentage*
EV (pre-selected V subgroup)	[redacted]	73	[redacted]
V subgroup		78	

*Percentage of patients who received treatment out of the randomized patients were used as adjustment factors to include untreated patients in the DoT curves used in the core EV model.

EV = enfortumab vedotin; DOT = duration of treatment; V = vinflunine

A scenario was explored with a piecewise fit (KM + parametric function) for DoT (Section 8.7.3) to assess the impact of 5-10% patients remaining on the treatment at the end of the KM cycle at 15-month and 14-month timepoints for EV and V, respectively. Under this scenario, an exponential function was used as the best fit for extrapolation given it reported the lowest values for both AIC and BIC for EV(V) and V (Table 31) as well as passed the visual fit test.

8.3.1.4 Validation of extrapolated efficacy data

To assess the validity of the long-term survival extrapolation, comparisons were made between the observed OS and PFS from the EV-301 trial against the predicted OS and PFS curves from the model (Figure 20 and Figure 21). The predicted curves fitted to the observed data reasonably well for both OS and PFS. The predicted median/mean OS and PFS were close to the observed values (Table 34). Visually, the predicted PFS curves show alignment with the observed curves (Figure 20). The EV-301 reported KM followed by the best parametric fit was used for OS extrapolation of EV and V in the economic model (Figure 21). The 15-month cut-off for KM was selected due to heavy censoring in the tail end of the curve (i.e., less than 10% of the sample remained at risk). The exponential parametric fit for EV's OS post-KM curve resulted in a higher survival than the EV-301 KM curve after month 15. However, this selection of extrapolation is supported by the higher-end tail of the OS data observed for EV in EV-201 cohort 1, which had a much longer median follow-up (28.4 months vs 11.1 months for EV-301 and subgroups). These differences were discussed with clinical experts (University of Sheffield, UK) who suggested that EV-201 patients may exhibit better performance than EV-301 patients due to the amount of pre-selection and pre-treatment (i.e. survivorship bias), but that EV-201 data are still supportive of a higher tail than the EV-301 trial [redacted]

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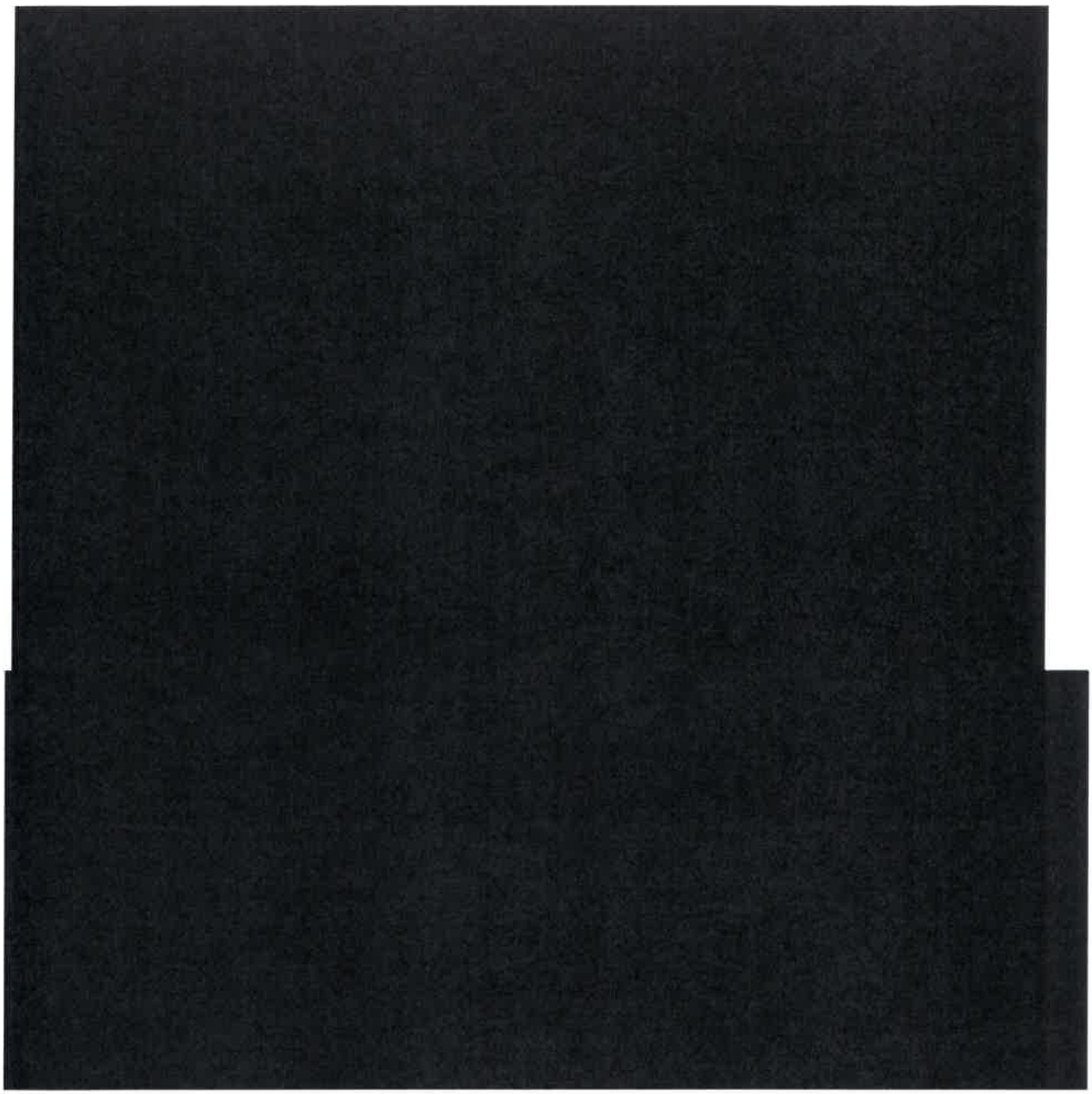

Clinical plausibility of the survival extrapolation was also corroborated via additional validation comparing the extrapolated OS curve for the V arm against data reported from the literature. Bellmunt, et. al. reported that second-line use of V in advanced urothelial carcinoma was associated with a median survival of 6.9 months [43]. A European-based retrospective analysis reported a median OS of 8.3 months in patients who received subsequent systemic treatments (e.g., gemcitabine-carboplatin, gemcitabine-cisplatin, and others) after progressing later line PD-1/PD-L1 inhibitor. These patients were also previously treated with platinum based chemotherapy prior to receiving PD-1/PD-L1 inhibitor [72]. Another study also reported similar results with an estimated median OS of 7.6 months among US patients with la/mUC and treated with taxane monotherapies following PD-1/PD-L1 inhibitor [73]. The literature reported median OS estimates are close to the predicted OS for V (median: [redacted] by the EV model.

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Table 34. Median and mean OS and PFS from observed Kaplan-Meier curves and predictive models

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

*Predicated medians are to the nearest month based on the 1-month cycle length.

EV = enfortumab vedotin; OS = overall survival; PFS = progression-free survival; V = vinflunine

[redacted]

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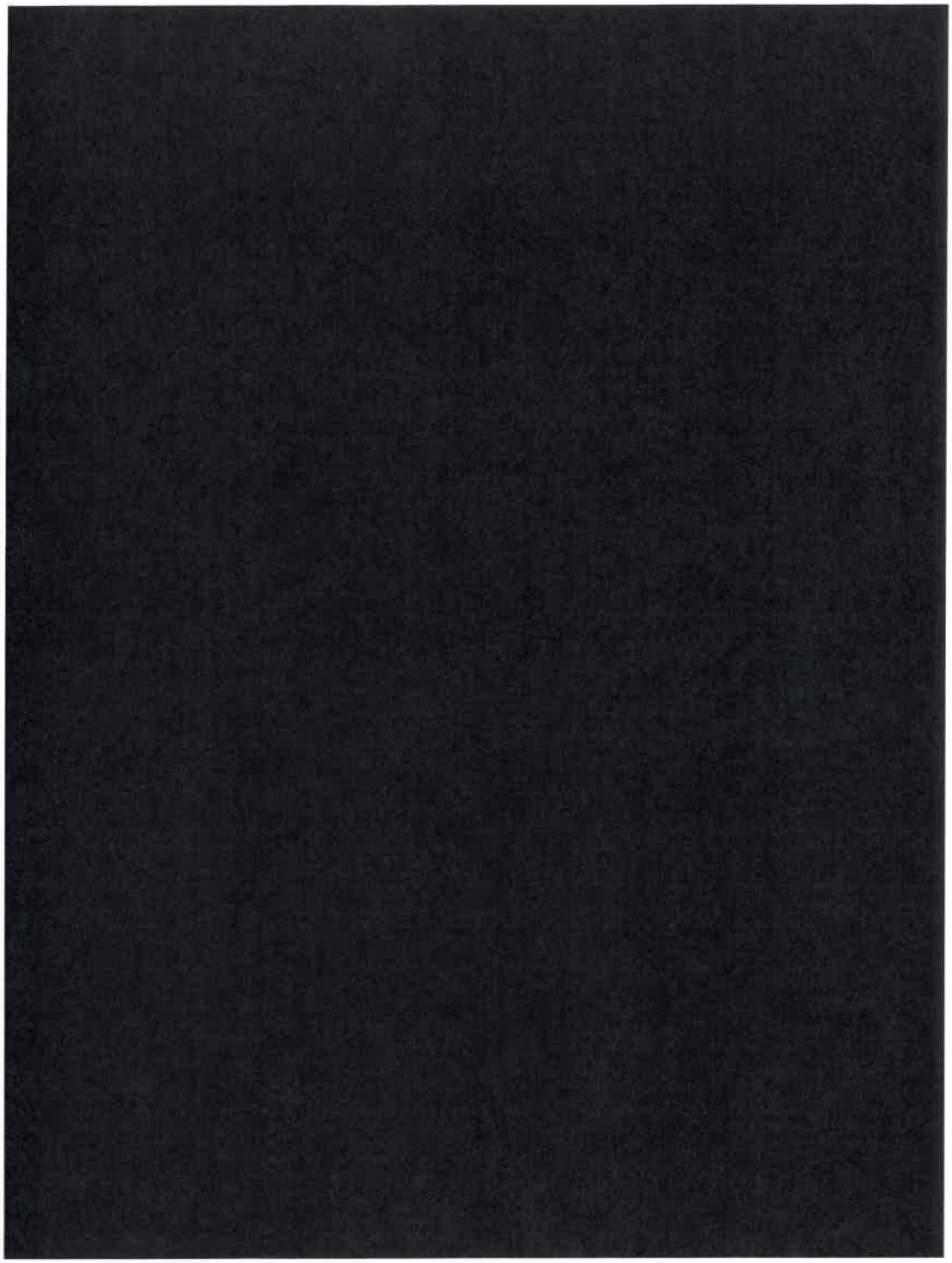

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

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:

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- **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 35.

Table 35. 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]	

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

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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

8.4.2 Health state utility values used in the health economic model

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 36.

Table 36. 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]		Denmark [66]	EV-301 trial **[18]**
Pre-progression (V subgroup; n=65), mean utility (SE)*				
Pre-progression, EV (ITT) vs. DPV				
Pre-progression (EV – ITT; n=270), mean utility (SE)*	[redacted]		Denmark [66]	EV-301 trial **[18]**
Pre-progression (DPV; n=251), mean utility (SE)*				

	HSUV (SE)	95% CI*	Tariff (value set) used	Source
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

8.5 Resource use and costs

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 2022 based on guidance from the Danish Medicines Council [75]. The detailed input and assumptions are described in the sections below.

8.5.1 Treatment Costs

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 37. The proposed list price for a 20 mg and a 30 mg vial of EV are [redacted] respectively. This translates to a monthly drug cost of [redacted] 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 (March 2022). Administration costs (Table 38) were obtained from DRG tariffs 2022. 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 2,038 DKK (Table 38).

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Table 39 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. Additional detail on the method of calculation for dose intensity is provided in Appendix L - Dose intensity.

Table 37. Drug acquisition costs

Drug	Dosing schedule*	Dose unit*	Standard package size	Alternative package size	AIP per standard vial, DKK	AIP per alternative vial, DKK	Source
EV	Days 1, 8, 15 of each 28-day cycle	1.25 mg/kg	30 mg	20 mg	[redacted]	[redacted]	Astellas, March 2022
V	Day 1 of each 21-day cycle	320 mg/m²	250 mg	50 mg	8,746.00	1,749.01	Medicinpriser.dk, March 2022[76]

The cost year is 2022 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 38. Administration costs for IV administered treatments (EV and V)

Delivery type(s)	Cost per administration*, 2022 DKK	Diagnosis/Procedure code	DRG Tariff (2022)
Outpatient visit – consultation	2,038	|DC679M|Kræft i urinblæren med metastaser|	|17MA98|MDC17 1-dagsgruppe, pat. mindst 7 år|[68]

The cost year is 2022 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

Table 39. Dose intensity and utilization weights

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

In the EV-301 study, [redacted] 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]. Given the comparable prevalence of subsequent treatment use between EV and comparators, costs of these treatments were not accounted for in the model.

8.5.2 Medical Costs

The medical 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 40. Specifically, outpatient costs were obtained from Tariff 17MA98. Costs per bed day for hospitalization visits were based on a long-term DRG (2022) 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, only outpatient, emergency and inpatient visits have been included. Since there is no Danish source available that provides pre-progression and post-progression resource use, the US study was considered the best source available. The unit cost available for hospitalization are in the per day format. To calculate the days of hospitalization per month, the average length of stay reported for various DRG codes associated with UC in the UK NHS were reviewed. This estimate of 3 days of LOS was used to convert frequency reported as hospitalizations per month by Flannery et al [77] to hospitalization days per month for the model use. The UK source was used in lieu of the publicly available Danish data.

Monthly resource use and costs by health state are summarized in Table 41. 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 2022 DKK.

Table 40. Unit medical costs

Medical care	Unit cost, DKK/period	Period	Diagnosis/ Procedure code	Sources and key assumptions
Hospital-based physician visits	2,038	per visit	|DC679M|Kræft i urinblæren med metastaser|	|17MA98|MDC17 1-dagsgruppe, pat. mindst 7 år|[68]
ED visits	2,038	per visit	|DC679M|Kræft i urinblæren med metastaser|	|17MA98|MDC17 1-dagsgruppe, pat. mindst 7 år|[68]
Hospitalization days	2,185	per day		Longterm tariff [68]. Length of stay estimate for Denmark was unavailable. A weighted average of excess bed days and length of stay was calculated based on HRG codes associated with bladder cancer patients in the UK reported by NHS trusts and NHS foundation trusts, which was estimated to be 3 days [78].

The cost year is 2022 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

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Table 41. 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
Hospitalization	0.14	0.36	Flannery 2018 [77] reports number of hospitalizations per patient per month which was multiplied by the LOS to obtain the number of days of hospitalization in a month. Length of stay estimates for Denmark were unavailable. A weighted average of excess bed days and length of stay was therefore calculated based on HRG codes associated with bladder cancer patients in the UK reported by NHS trusts and NHS foundation trusts, which was estimated to be 3 days [78].

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

8.5.3 Adverse Event Costs

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, Table 28. 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 (see Table 60 and Table 62). 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 38,408 DDK. 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. The clinical expert advising the DMC suggested at the dialogue meeting that fatigue would not be treated if it was the only AE presenting. It was also assumed 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 2022 by combining diagnosis and procedure codes, Table 42 [68]. The diagnosis code seemed to be the primary driver when combining this diagnosis code with different procedure codes, always resulting in the DRG tariff of DKK 2,038. As this was assumed to not reflect the actual cost of all the procedures included in the analysis, it was decided that the procedure codes should be the primary driver of the DRG tariff. Thus, the procedure/condition was chosen as both the diagnosis and procedure in the interactive DRG system to derive the appropriate DRG tariff. E.g., when assigning the DRG tariff for the AE "Febrile neutropenia", the combination of diagnosis code "DC679M - Kræft i urinblære med metastaser" and procedure code "DD709A-Neutropeni og agranulocytose forårsaget af lægemiddel" results in the DRG tariff of DKK 2,038, whereas choosing "DD709A-

Neutropeni og agranulocytose forårsaget af lægemiddel" as both the diagnosis and procedure code, leads to a DRG tariff of DKK 38,408.

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 [redacted] for patients assigned to EV compared with [redacted] for patients assigned to V.

Table 42. AE unit costs

Grade 3/4 AEs ≥ 5%	Unit cost, 2022 DKK	Diagnosis/Procedure code	Sources – 2022 DRG Tariffs
Anaemia	3,176	|DD649|Anæmi UNS|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
Neutropenia	3,176	|DD709A|Neutropeni og agranulocytose forårsaget af lægemiddel|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
Febrile neutropenia	38,408	|DD709A|Neutropeni og agranulocytose forårsaget af lægemiddel|	|16MA03|Granulocytose forårsaget af lægemiddel|[68]
Rash maculo-papular	2,041	|DR219|Hududslæt UNS|	| 09MA98| MDC09 1-dagsgruppe, pat. mindst 7 år|[68]
Decreased appetite	1,954	|DR630|Appetitløshed|	|10MA98| MDC10 1-dagsgruppe, pat. Mindst 7 år|[68]
Hyperglycemia	4,460	|DR739|Hyperglykæmi UNS|	|23MA03|Symptomer of fund, u. kompl. Bidiag.|[68]
Neutrophil count decreased	3,176	|DD728|Anden forstyrrelse i hvide blodlegemer|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
White blood cell count decreased	3,176	|DD728|Anden forstyrrelse i hvide blodlegemer|	|16MA98|MDC16 1-dagsgruppe, pat. mindst 7 år.|[68]
Fatigue	0		DMC meeting
Constipation	6,756	| DK590| Forstoppelse|	|06MA11 |Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.|[68]
Asthenia	0		Assumed the same as fatigue†

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Grade 3/4 AEs ≥ 5%	Unit cost, 2022 DKK	Diagnosis/Procedure code	Sources – 2022 DRG Tariffs
General physical health deterioration	0		Assumed the same as fatigue†
Abdominal pain	6,756	|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 2022 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

8.5.4 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 43, and the time for medical visits and procedures used in the model is presented in Table 44. 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 43. Patient cost inputs

Unit cost input	Unit cost, 2022 DKK	Sources
Patient time cost per hour	182 per hour	Medicinrådet, 2020[79]
Patient transportation costs*	102 per visit	

The cost year is 2022 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 44. Patient time inputs

Unit cost input	Patient time (minutes)	Sources
Infusion, vinflunine	20	Medicinrådet, 2020 [79]
Infusion, EV	30	
Outpatient clinic visit	30	
Admission, per day	1,440	
Oncologist visit	30	

CT = computed tomography; EV = enfortumab vedotin

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8.5.5 Terminal Care 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.

For the scenario analysis a cost for ≥ 12 days admission and ≤ 24 days of palliative care was applied based on a tariff of 71,612 DKK |26MP48|Specialiseret Palliativ indsats, Øvrig|

8.6 Results

8.6.1 Base case overview

Table 45 below provides an overview of the base case model settings applied in the analysis.

Table 45. 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	Lifetime
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)	Patient-level data from EV-301 trial for EV (pre-selected for V): KM curve through month 15; and V subgroup: KM curve through month 14
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	Piecewise extrapolations of EV (pre-selected V) and V subgroup data from EV-301 trial.

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Feature	Description
	EV (pre-selected V): KM through month 15 followed by exponential V: KM through month 15 followed by Weibull

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

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

Table 46 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 lifetime horizon, treatment with EV was estimated to add [redacted] LYs compared to treatment with V (Total LY of EV vs V: [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]

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 componen [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] 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 visits to healthcare professionals).

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 [3].

Table 46. Base case results, EV vs V.

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

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

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

A pricing analysis around the base case was also conducted to assess the impact of diffident EV vial (30 mg) price points on the ICER per QALY. The results of this analysis are reported in Figure 23 and Table 47 below. The ICER per QALY was estimated to be zero or below at the EV vial price of [redacted]

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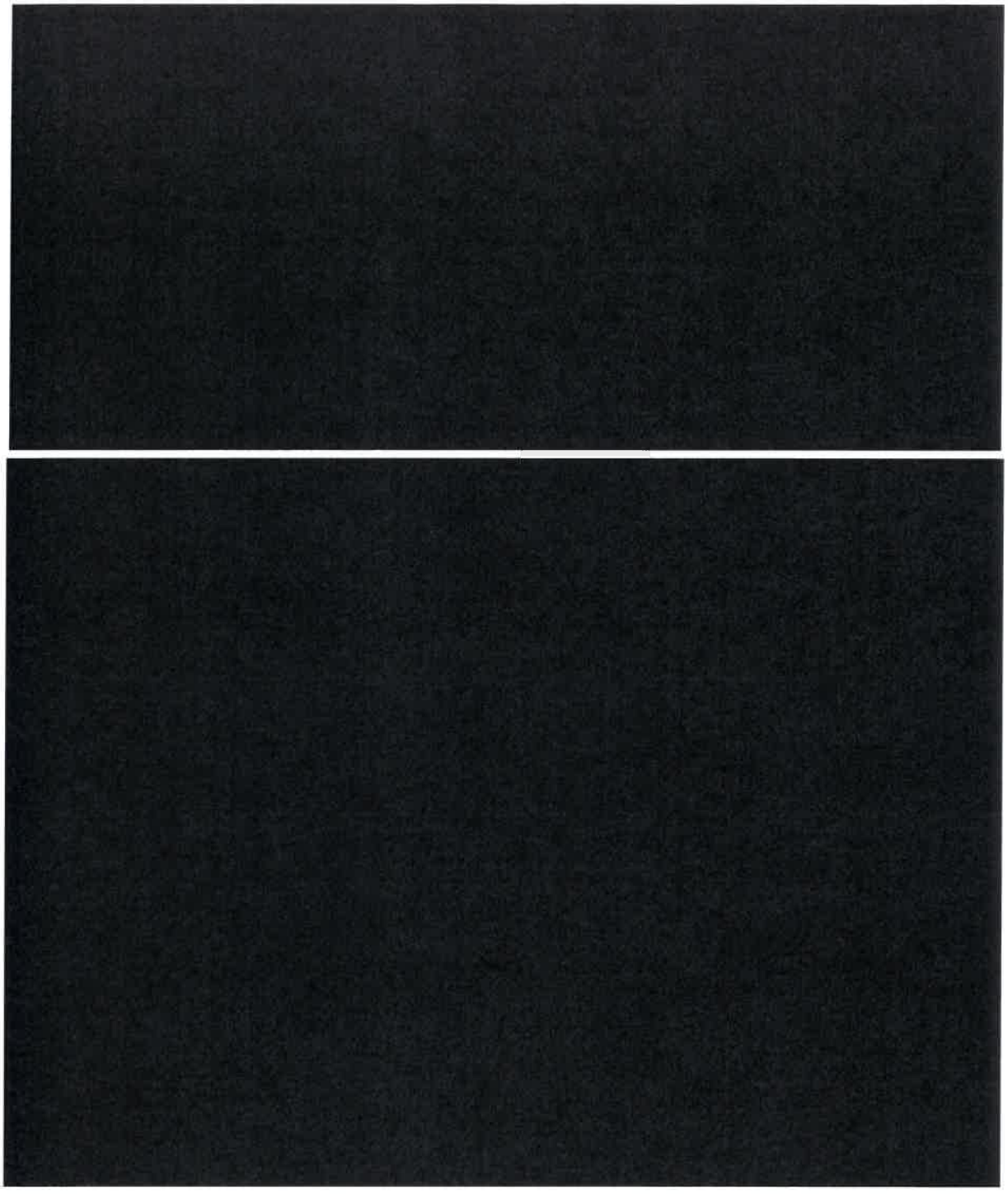

8.7 Sensitivity analyses

In addition to deterministic and probabilistic sensitivity analyses, additional scenario analyses will be presented in this section.

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8.7.1 Deterministic sensitivity analyses

A series of one-way sensitivity analyses (OWSAs) 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, Table 48, the ICER for EV vs. V ranged from [redacted] DKK to [redacted] DKK; key model drivers included pre-progression utility in the vinflunine subgroup, vinflunine drug cost, and pre-progression utility in the EV subgroup (Figure 24). 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 24.

Table 48. One-way sensitivity analyses results

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

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

AE = adverse event; BSA = body surface area; CI = confidence interval; EV = enfortumab vedotin; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; V = vinflunine

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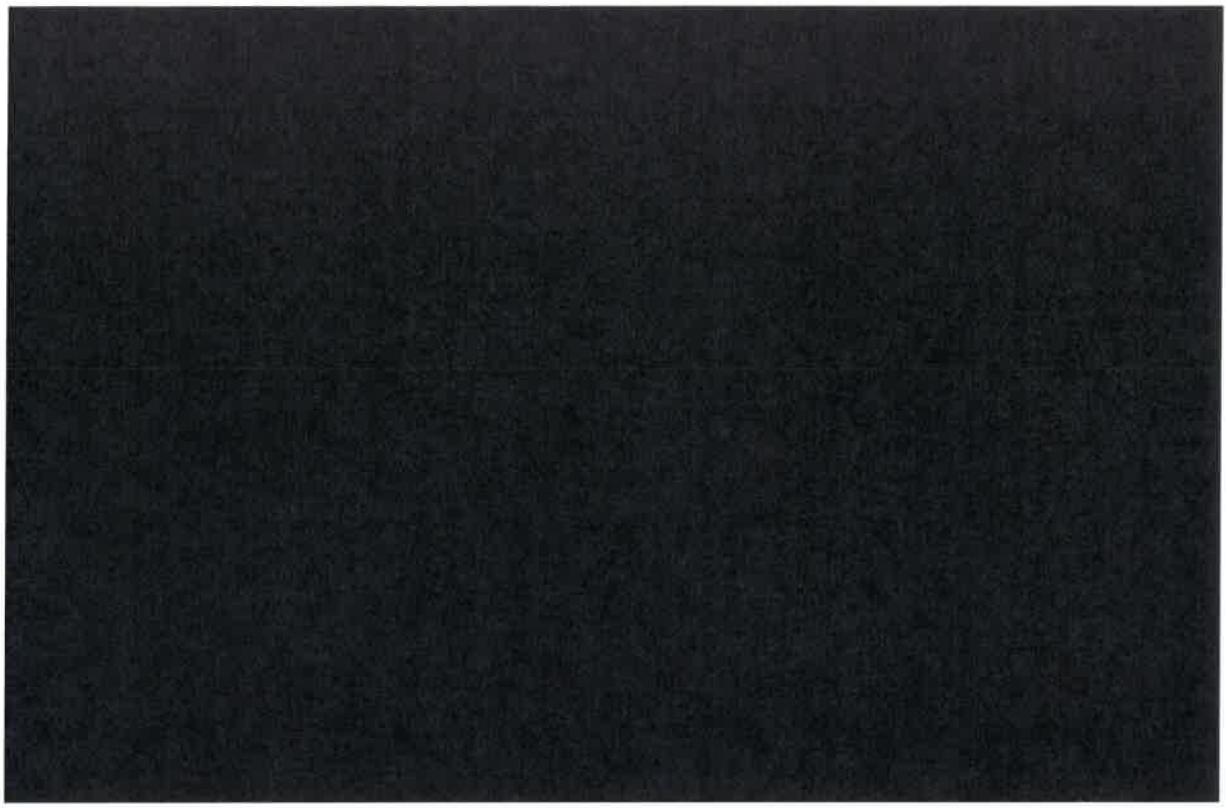

AE = adverse event; BSA = body surface area; CI = confidence interval; EV = enfortumab vedotin; ICER = incremental cost-effectiveness ratio; V = vinflunine

8.7.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was conducted in which multiple input parameters were varied simultaneously over 1,000 iterations, by sampling their values from uncertainty distributions. Averages of costs, life years and QALYs over the 1,000 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 Figure 25, Figure 26, and Table 49. The **probabilistic ICER** (DKK per QALY) was comparable with the base **case result, estimated at** 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** **DKK per QALY gained.** The data and assumptions underlying the probabilistic sensitivity analyses are shown in Table 65 in Appendix J.

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Table 49. Probabilistic outcomes vs. base-case outcomes

Outcomes	Values (95% CI)
Mean Probabilistic Outcomes over 1,000 iterations	
EV, total cost, DKK	[redacted]
V, total cost, DKK	
EV, total QALYs	
V, total QALYs	
Incremental cost, EV vs. V, DKK	
Incremental QALYs, EV vs. V	
Probabilistic ICER, cost per QALY, DKK	
Base Case Outcomes	
Base-case incremental cost, EV vs. V, DKK	[redacted]
Base-case incremental QALYs, EV vs. V	
Base-case ICER, cost per QALY, DKK	

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

[redacted]

QALY = quality-adjusted life years

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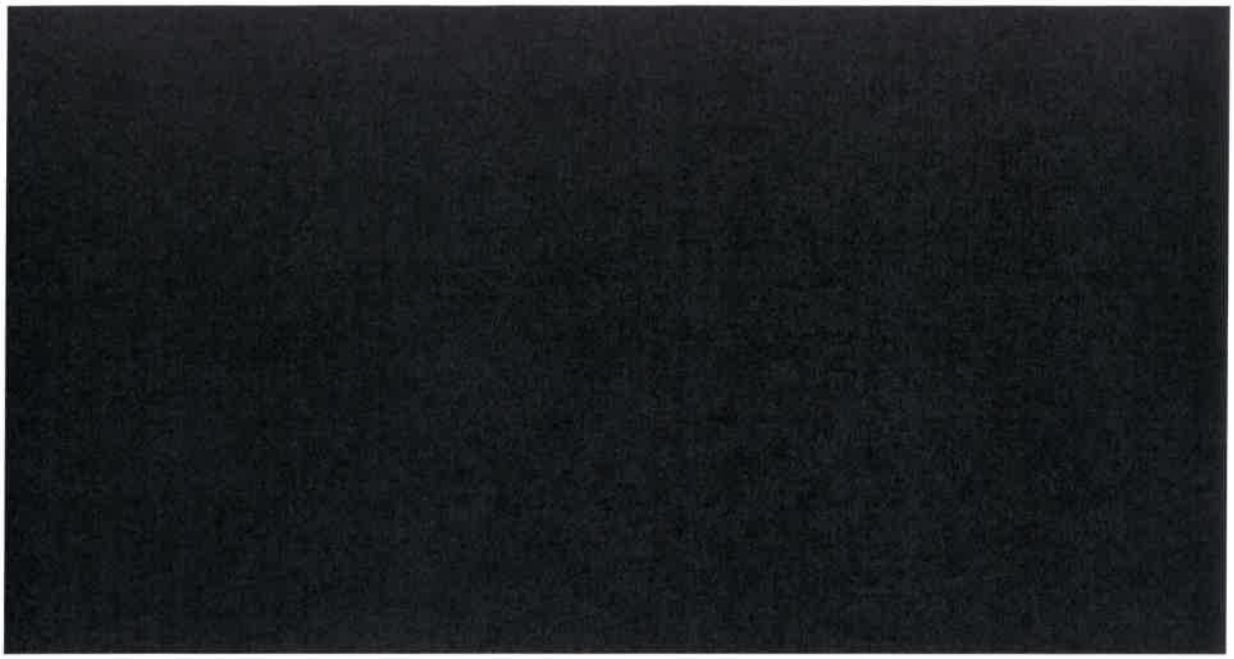

8.7.3 Scenario Analyses

Scenario analysis was performed to test the impact of change in key inputs and assumptions on the CE estimate. Table 50 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 disease management costs and resources similar to those used in the avelumab submission to DMC had the most impact on the base case CE estimates.

Table 50. Scenario Analyses

Parameter	Base Case	Scenario	ICER (cost/QALY), DKK
Time horizon	Lifetime	10 years	
Annual discount rates	3.5% for cost and health outcomes	0% 5%	

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Parameter	Base Case	Scenario	ICER (cost/QALY), DKK
OS	EV (pre-selected V): KM through month 15 followed by exponential; V: KM through month 15 followed by Weibull	Best fit OS curve for EV: Exponential; Best fit OS curve for V: Weibull	[redacted]
		Second best fit OS curve for EV: Weibull. Second best fit OS curve for V: Gompertz.	
PFS	EV (pre-selected V) and V: log-logistic extrapolations based on AIC-BIC criteria and visual inspection (KM vs model curve)	Second best fit PFS curve for EV: Log normal. Second best fit PFS curve for V: Log normal	
DOT	Patient-level data from EV-301 trial for EV (pre-selected for V): KM curve through month 15; and V subgroup: KM curve through month 14	Best fit DoT curve for EV: Exponential. Best fit DoT curve for V: Exponential	
		KM + Best fit DoT curve for EV: Exponential. Best fit DoT curve for V: Exponential	
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	
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	
Other costs	Medical cost, patient cost (leisure and travelling time spent in disease management-related visits and drug administration), and AE management costs	Disease management resource use reported in the avelumab submission for first-line maintenance	
		AE costs excluded	
	Terminal care costs are not included	Terminal care cost included: 71,612.00 DKK | 26MP48 | Specialiseret Palliativ indsats, Øvrig	
Comparator†	EV (preselected for V) vs. V subgroup	ITT as efficacy population and DPV as comparator (to reflect EV-301 trial)	

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Parameter	Base Case	Scenario	ICER (cost/QALY), DKK
		DPV price same as V price given D and P are not used in Denmark)	[redacted]
		ITT as efficacy population and DPV as comparator (to reflect EV-301 trial)	
		DP costs used for V in the DPV arm**	

* Disease management costs used in the avelumab submission are shown in Section 22.2.1.

† Inputs for the EV (ITT) and DPV populations from the EV-301 trial are shown in Section 22.2.2

** Calculated by assigning EV-301 reported utilization weight of 25.41% for vinflunine to D (38.11%) and P (36.48%) equally, bringing their utilization weights to 50.81% and 49.19% for D and P, respectively. This utilization weights were used to calculate drug and administration costs for the DPV arm.

AE = adverse event; AIC = Akaike information criterion; BIC = Bayesian information criterion EV = enfortumab vedotin; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier curve; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life years; V = vinflunine

8.8 Summary

A partitioned survival model was developed to assess the cost-effectiveness of EV vs chemotherapy (V) in patients with la/mUC previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor. 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.

In the base case, the disease course of the target population was estimated over a lifetime horizon (i.e., 33 years with the target cohort's baseline age at 67 years old). Both costs and outcomes were discounted at 3.5% annually. Efficacy (i.e., OS and PFS), duration of treatment (DoT), dose intensity, and utility by health state data were based on the subgroup analysis in EV-301 comparing EV with V. The OS extrapolations were piecewise fits for OS (Kaplan-Meier for 15 months followed by exponential for EV and Weibull for V) and single fit with log-logistic function for PFS for both EV and V. Treatment and administration costs while receiving EV (drug cost of [redacted] per month and administration cost of 6,646 DKK per month) or V (drug cost of [redacted] per month and administration cost of 2,954 DKK per month) are incurred based on the median DoT of approximately [redacted] months and [redacted] months for EV and V, respectively.

In the base case analysis, treatment with EV resulted in a gain of [redacted] quality-adjusted life-years (QALYs) over V (total [redacted] The treatment cost per patient (drug and administration cost) was estimated to [redacted] Total costs per patient were estimated to be [redacted] for treatment with EV and V, respectively. Total medical costs (in addition to the anti-cancer treatments) for EV and V were [redacted] respectively. The incremental cost-effectiveness ratio (ICER) was estimated to be [redacted] per QALY gained for EV vs V.

The results in the base case analysis were consistent with the majority of the univariate sensitivity analyses as well as most of the explored scenarios. The probabilistic ICER, estimated at [redacted] per QALY, was comparable to the base-case result. In deterministic sensitivity analyses (DSA), the ICER for EV vs V ranged from [redacted] The key model drivers were V drug cost, pre-progression utility in the V arm, and pre-progression utility in the EV arm.

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To summarize, the CEA estimates that treatment with EV results in an incremental cost of [redacted] per patient compared to treatment with V. These incremental costs are due to the higher medical costs incurred during EV treatment (driven by longer PFS and OS for patients treated with EV) as well as the higher treatment cost of EV. These incremental costs yielded a gain of [redacted] QALYs per patient for patients receiving EV due to the improved OS and maintained QoL during the pre-progression phase. EV presents a novel treatment option in a population with a high unmet need for safe and effective treatments. Treatment with EV increases time in the pre-progression state, improves OS, and is associated with higher quality of life (QOL).

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9. Budget impact analysis

The budget impact assessment follows the specifications from the DMC method guidelines [61]. The budget impact assessment is based on the global CE model as adapted for Denmark (Section 8), and uses the key parameters (e.g., extrapolated OS, PFS, and DoT curves, cost inputs, etc.) which were also used in the cost-effectiveness analysis.

Number of patients

In the budget impact assessment, it is assumed that the population for whom EV is indicated will be approximately [redacted] patients per year (Table 51), based on a range of [redacted] to [redacted] patients per year. Thus, an annual incidence of [redacted] patients and an assumed uptake of [redacted] among eligible patients in year 1, [redacted] uptake in year 2, and [redacted] uptake thereafter, were used in the budget impact analysis. This estimate is based on the following:

- EV as monotherapy is indicated for treatment of adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor [3]
- The DMC expert estimated that at least [redacted] 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 [redacted] patients per 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 [redacted] 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 vinflunine. 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 [redacted] patients.[9,10]

Table 51. 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
Number of patients treated with EV	[redacted]				
Number of patients treated with V					
Total estimated patient population					

EV = enfortumab vedotin; V = vinflunine

Table 52. Number of patients expected to be treated over the next five-year period - If EV is NOT introduced

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated with EV	[redacted]				

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Number of patients treated with V	[redacted]
Total estimated patient population	

EV = enfortumab vedotin; V = vinflunine

Expenditure per patient

Table 53. Costs per patient per year - if EV is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
EV, costs per patient, DKK	[redacted]				
Of which: Drug acquisition cost					
Of which: Administration cost					
Of which: Disease management cost: pre-progression					
Of which: Disease management cost: post-progression					
Of which: AE cost					
V, costs per patient, DKK					
Of which: Drug acquisition cost					
Of which: Administration cost					
Of which: Disease management cost: pre-progression					
Of which: Disease management cost: post-progression					
Of which: AE cost					

EV = enfortumab vedotin

Table 54. Costs per patient per year - if the EV is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
EV, costs per patient, DKK	[redacted]				
V, costs per patient, DKK					
Of which: Drug acquisition cost					
Of which: Administration cost					
Of which: Disease management cost: pre-progression					
Of which: Disease management cost: post-progression					
Of which: AE cost					

EV = enfortumab vedotin

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Budget impact

The budget impact analysis for years 1 to 5 with and without a recommendation for reimbursement of EV are shown below [redacted] Only costs that accrue to the hospital budget are considered. The following cost types are not considered in the budget impact analysis: patient costs, which do not accrue to the hospital budget. The costs in the analysis are not discounted. The total budget impact is [redacted] **in year 1 and increases to** [redacted] DKK in year 2. In subsequent years, the budget impact is [redacted] DKK (year 3), [redacted] DKK (year 4), and [redacted] DKK (year 5). The calculations are based on the assumption that all [redacted] **patients will start treatment on** day 1 of each year. The average annualized budget impact per patient over the 5-year time horizon was [redacted]

Table 55. Expected budget impact of recommending the EV over 5 years, undiscounted

	Year 1	Year 2	Year 3	Year 4	Year 5
EV is recommended (X)	[redacted]				
Of which: Drug acquisition cost					
Of which: Administration cost					
Of which: Disease management cost: pre-progression					
Of which: Disease management cost: post-progression					
Of which: AE cost					
Minus: EV is NOT recommended (Y)					
Of which: Drug acquisition cost					
Of which: Administration cost					
Of which: Disease management cost: pre-progression					
Of which: Disease management cost: post-progression					
Of which: AE cost					
Budget impact of the recommendation (X-Y)					
Budget impact per patient (annualized average over 5-year time horizon)					

EV = enfortumab Vedotin

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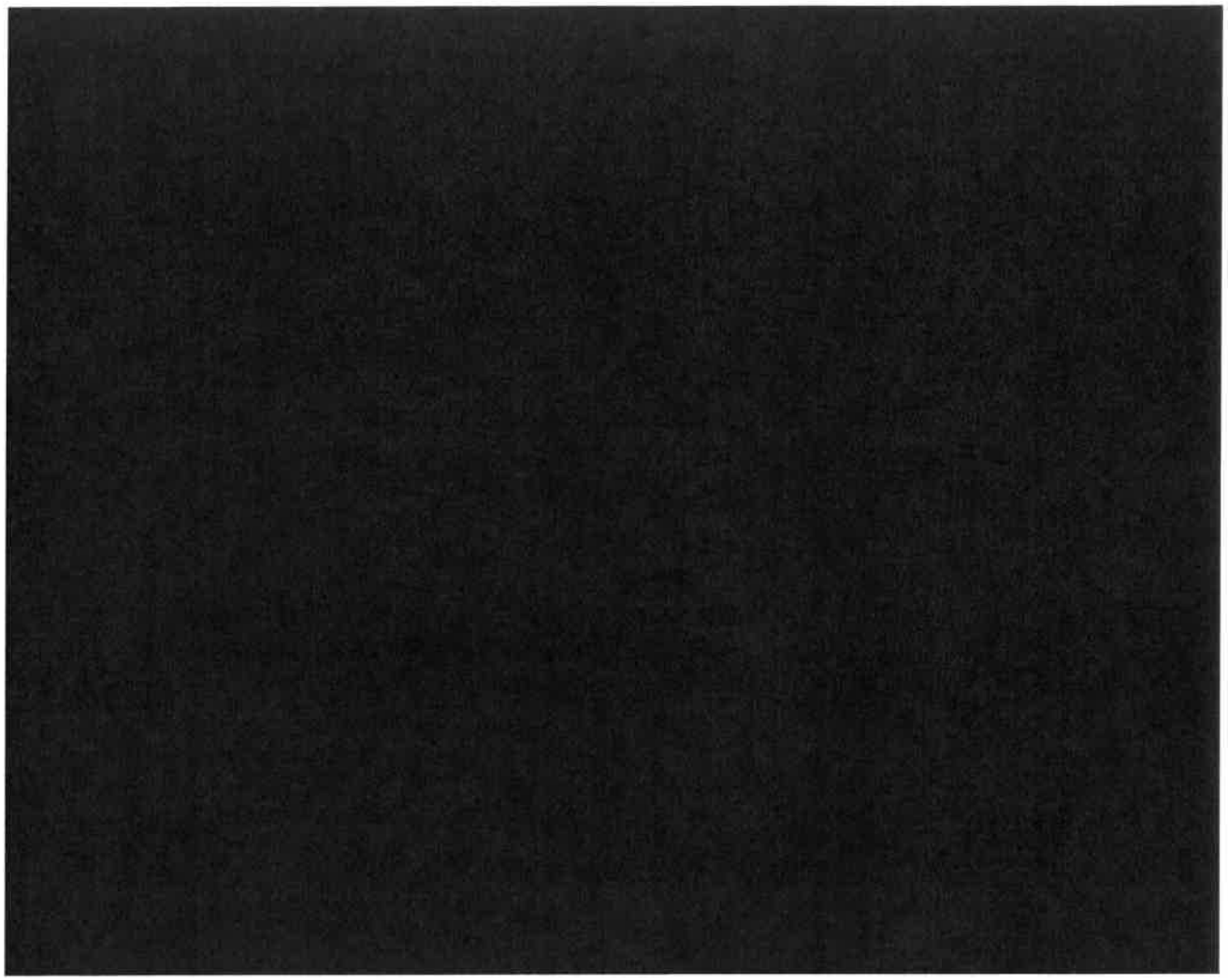

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10. Discussion on the submitted documentation

10.1 Quality assessment of EV-301

Overall, there was a low risk of bias and the trial was performed in accordance with Good Clinical Practice (GCP) guidelines with written informed consent obtained before trial entry. Disease and safety evaluation methods are consistent with other studies of la/mUC and outcome assessments were all conducted in accordance with trial validated methodology.

Baseline demographics and key disease characteristics between arms were well balanced, and treatment discontinuations were similar [15]. Of note, there was a slightly higher withdrawal rate before receiving study treatment in the chemotherapy arm because of withdrawal by patients (8.8% versus 5.0% in the EV arm), physician decision (7.2% versus 2.3%), and other (2.0% versus 0.3%) [31]; this is sometimes seen in open-label studies due to patients wishing to receive the intervention. The most common reason for treatment discontinuation was disease progression, which is accounted for within efficacy analyses.

Chemotherapy was selected by the investigator before randomization from a choice of docetaxel, paclitaxel, or vinflunine. As docetaxel and paclitaxel are not recommended for use in 2nd line in Denmark, a post hoc subgroup analysis of patients who were pre-selected to vinflunine is presented to align with Danish clinical practice.

10.2 Validation of efficacy data in model

EV-301 does not provide data spanning the full modeled time horizon of 33 years. Consequently, there is some uncertainty surrounding OS estimations. Extrapolation of the survival data from the vinflunine population of the EV-301 trial was necessary to project the outcomes beyond the trial observed period.

To assess the validity of the long-term survival extrapolation, comparisons were firstly made between the observed PFS from the vinflunine population of EV-301 trial against the predicted PFS curves based on CEA. The predicted curves fitted to the observed data reasonably well for the PFS, and the predicted medians were also close to the observed values. For OS, a piecewise fit of EV-301 observed KM curve until 15 months (time point at which patients at risk were the lowest) followed by a parametric extrapolation was used. An exponential fit was selected based on the visual inspection and AIC-BIC. Additionally, the extrapolated curves were measured against the EV-201 OS data for EV to justify the exponential distribution selection. As noted earlier, EV-201 has a longer follow-up data compared to EV-301 at the time of this analysis.

European-based retrospective analyses reported a median OS of 8.3 months in patients who received subsequent systemic treatments (e.g. gemcitabine-carboplatin, gemcitabine-cisplatin, and others) after progressing to a later line PD-1/PD-L1 inhibitor. These patients were also previously treated with platinum-based chemotherapy before receiving a PD-1/PD-L1 inhibitor. Similar results were reported with an estimated median OS of 7.6 months among US patients with la/mUC who were treated with taxane monotherapies following a PD-1/PD-L1 inhibitor. [80]

10.2.1 Internal validation

The model was subjected to rigorous internal verification as a quality assurance measure. Two separate researchers checked the model programming and mathematical calculations. Equations and parameters were assessed to ensure they were correctly cross-referenced against their sources and all modules of code were error-free and replicable. 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. Scenario analyses were performed to check if the model behaved as expected when stress-tested using extreme input values.

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10.2.2 External validation

A thorough quality assessment of the core CE 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 a clear separation between raw inputs, intermediate calculations, and the values obtained from the model traces. There was also 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 CE model was concluded to be well designed, appropriately implemented, and fit for the purpose of supporting the economic assessment of EV versus relevant alternative strategies.

10.3 Interpretation and conclusions of economic evidence

The CE of EV versus V was assessed using an economic model with robust design and thorough validation. The model shows that EV offers survival benefits to patients with la/mUC previously treated with platinum-based chemotherapy and PD-1/PD-L1 checkpoint inhibitor in terms of LYs and QALYs when compared to V. The results demonstrate that EV is a highly effective treatment associated with PFS and OS benefit for patients who have a high unmet need and poor prognosis. Treatment and administration costs while receiving EV (drug cost of [redacted] per month and administration cost of 6,646 DKK per month) or V (drug cost of [redacted] per month and administration cost of 2,954 DKK per month) are incurred based on the median DoT of approximately [redacted] months and [redacted] months for EV and V, respectively. There is no specified publicly available WTP threshold in Denmark. DSA and PSA suggest that the CE results are robust across plausible ranges.

Patients with la/mUC have poor prognosis and a high unmet need for safe and effective therapies. Considering our model estimations and given the clinically relevant survival benefit demonstrated through Phase III RCT EV-301, EV represents a life-extending treatment option for Danish patients with la/mUC. The budgetary impact of introducing EV was estimated at DKK [redacted] in year 5.

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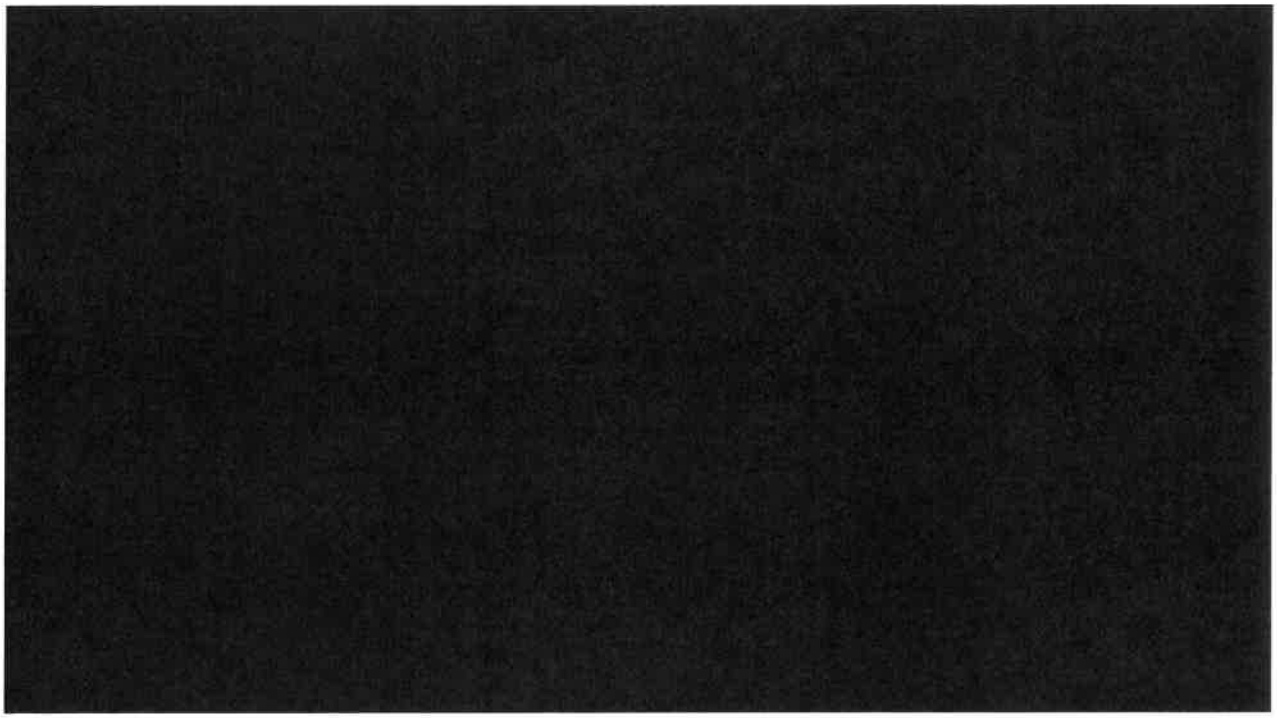
11. List of experts

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.

11.1 Nordic Clinical Experts – Validation of inputs

Jan Oldenburg - Norway

Clinical Oncologist, Akershus University Hospital



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12. References

1. Astellas Pharma A/S. Summary of Product Characteristics - Enfortumab Vedotin (Draft). 2021.

2. WHO Collaborating Centre for Drug Statistics Methodology. List of temporary ATC/DDDs and alterations [Internet]. 2021. Available from: https://www.whocc.no/atc_ddd_index/updates_included_in_the_atc_ddd_index/

3. Agency EM. Summary of opinion - Padcev. React Wkly. 2021;1877(1):152–152.

4. Witjes J a, Compérat E, Cowan NC, Santis M De, Gakis G, Lebrét T, et al. Guidelines on and Metastatic Bladder Cancer [Internet]. Guidelines. 2014. Available from: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Muscle-Invasive-and-Metastatic-Bladder-Cancer-2021V2.pdf

5. Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. Eur Urol [Internet]. 2018;74(6):784–95. Available from: https://www.sciencedirect.com/science/article/pii/S0302283818306511

6. American Cancer Society. What is Bladder Cancer? [Internet]. 2019. Available from: https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html

7. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester R, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma. Eur J Neurol [Internet]. 2018;73(1):111–22. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0302283817306656?via%3Dihub

8. NORDCAN. Denmark - Bladder and urinary tract [Internet]. 2019. Available from: https://gco.iarc.fr/media/nordcan/factsheets/91/en/countries/208/bladder_and_urinary_tract-280-denmark-208.pdf

9. Medicinrådet. Bilag til Medicinrådets anbefaling vedrørende avelumab til vedligeholdelsesbehandling af urotelialkræft [Internet]. 2021. Available from: https://medicinraadet.dk/media/bhthcx5r/bilagspakke_til_medicinrådets_anbefaling_vedr-_vedligeholdelses-behandling_af_urotelialkræft_adlegacy.pdf

10. Omland LH, Lindberg H, Carus A, Als AB, Jensen NV, Taarnhøj GA, et al. Real-world Treatment Patterns and Overall Survival in Locally Advanced and Metastatic Urothelial Tract Cancer Patients Treated with Chemotherapy in Denmark in the Preimmunotherapy Era: A Nationwide, Population-based Study. Eur Urol Open Sci. 2021;24:1–8.

11. Ullén A. Outside the box of immunotherapy – new hope for patients with advanced urothelial cancer. Acta Oncol (Madr). 2019;58(7):951–2.

12. Dansk BlæreCancer Gruppe. Behandling og opfølgning af muskelinvasiv blærekræft. 2020; Available from: https://www.dmcg.dk/siteassets/kliniske-retningslinjer---skabeloner-og-vejledninger/kliniske-retningslinjer-opdelt-pa-dmcg/blarecancer/dablaca_muskelinvasiv_1_1_admgodk111120.pdf

13. European Medicines Agency. Summary of Product Characteristics, Javlor [Internet]. 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/javlor-epar-product-information_en.pdf

14. Powles T, Bellmunt J, Comperat E, Santis M De, Huddart R, Loriot Y, et al. Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2021; Available from:

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https://doi.org/10.1016/j.annonc.2021.11.012

15. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee J-L, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med. 2021;384(12):1125–35.

16. Rosenberg JE, Donnell PHO, Balar A V, Mcgregor BA, Heath EI. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1 / Programmed Death Ligand 1 Therapy. J Clin Oncol. 2019;37.

17. U.S. Food & Drug Administration. FDA grants accelerated approval to enfortumab vedotin-ejfv for metastatic urothelial cancer [Internet]. 2019. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-enfortumab-vedotin-ejfv-metastatic-urothelial-cancer

18. Astellas Pharma A/S. A Post Hoc Analysis of Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer Enfortumab (EV-301). Data on File. 2021.

19. Rosenberg JE, Powles T, Sonpavde GP, Loriot Y, Duran I, Lee JL, et al. Analysis of hard-to-treat subgroups from EV-301: A phase III trial of enfortumab vedotin (EV) vs chemotherapy for previously treated advanced urothelial carcinoma. ESMO. 2021;698P.

20. Rosenberg JE, Powles T, Sonpavde GP, Loriot Y, Duran I, Lee J-L, et al. Poster Number 4516: Long-Term Outcomes in EV-301: 24-Months Findings From the Phase 3 Trial of Enfortumab Vedotin in Patients with Previously Treated Advanced Urothelial Carcinoma. ASCO. 2022.

21. Astellas Pharma A/S. EV-201 Cohort 1: Long-term Results of Enfortumab Vedotin Monotherapy for Locally Advanced or Metastatic Urothelial Cancer Previously Treated with Platinum and a PD-1 or PD-L1 Inhibitor (NCT03219333). (Clinical Study Report). Data on File. 2020;

22. Mamtani R, Rosenberg JE, Powles T, Sonpavde GP, Loriot Y, Duran I, et al. 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. ASCO 2021, Abstr No 4539.

23. Drakaki A, Kirby CJ, Van Der Heijden MS, Petrylak DP, Powles T, Chi KN, et al. Docetaxel with or without ramucirumab after immune checkpoint inhibition in platinum-refractory metastatic urothelial carcinoma (mUC): Prespecified subgroup analysis from the phase 3 RANGE trial. J Clin Oncol [Internet]. 2018 Feb 20;36(6_suppl):434. Available from: https://doi.org/10.1200/JCO.2018.36.6_suppl.434

24. Cancer Treatment Centers of America. Bladder cancer types [Internet]. 2021. Available from: https://www.cancercenter.com/cancer-types/bladder-cancer/types

25. Fleshner N, Herr H, Stewart A, Murphy G, Mettlin C, Menck H. The National Cancer Data Base report on bladder carcinoma. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1996;78(7):1505–15013.

26. Rouprêt M. Anatomical location of urothelial carcinomas of the urinary tract leads to perspectives of specific treatment. Futur Oncol. 2007;3(6):595–9.

27. Ghatalia P, Zibelman M, Geynisman D, Plimack E. Approved checkpoint inhibitors in bladder cancer: which drug should be used when? Ther Adv Med Oncol. 2018;10(10).

28. Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmström P-U, Choi W, et al. Bladder cancer. Lancet (London, England). 2016 Dec;388(10061):2796–810.

29. McCance KL, Huether SE, Brashers VL, Rote NS. Pathophysiology. 7th editio. 2014. 1348–1349 p.

30. Berdik C. Unlocking bladder cancer. Nature. 2017;551(7679):34–5.

31. Astellas Pharma A/S. An open-label, randomised phase 3 study to evaluate enfortumab vedotin vs chemotherapy in patients with previously treated locally advanced or metastatic urothelial cancer (EV-301). (Clinical Study Report). Data on File. 2021;

32. Freedman N, Silverman D, Hollenbeck A, Schatzkin A, Abnet C. Association between smoking and risk of bladder cancer among men and women. Jama. 2011;306(7):737–45.

33. Malats N, Real F. Epidemiology of bladder cancer. Hematol Oncol Clin North Am. 2015;29(2):177–89.

34. National Cancer Institute. SEER Cancer Stat Facts: Bladder Cancer [Internet]. 2019. Available from: https://seer.cancer.gov/statfacts/html/urinb.html

35. Lotan Y, Choueiri TK. Clinical presentation, diagnosis, and staging of bladder cancer [Internet]. 2021. Available from: https://somepomed.org/articulos/contents/mobipreview.htm?0/54/865?view=print

36. Cancer.Net. Bladder Cancer: Diagnosis [Internet]. 2020. Available from: https://www.cancer.net/cancer-types/bladder-cancer/diagnosis

37. Hafeez S, Huddart R. Advances in bladder cancer imaging. BMC Med. 2013 Apr;11:104.

38. Waldhoer T, Berger I, Haidinger G, Zielonke N, Madersbacher S. Sex Differences of ≥ pT1 Bladder Cancer Survival in Austria: A Descriptive, Long-Term, Nation-Wide Analysis Based on 27,773 Patients. Urol Int. 2015;94(4):383–9.

39. Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol Off J Am Soc Clin Oncol. 1999 Oct;17(10):3173–81.

40. Fairey AS, Kassouf W, Aprikian AG, Chin JL, Izawa JI, Fradet Y, et al. Age ≥ 80 years is independently associated with survival outcomes after radical cystectomy: results from the Canadian Bladder Cancer Network Database. Urol Oncol. 2012;30(6):825–32.

41. Rink M, Hansen J, Cha EK, Green DA, Babjuk M, Svatek RS, et al. Outcomes and prognostic factors in patients with a single lymph node metastasis at time of radical cystectomy. BJU Int [Internet]. 2013 Jan;111(1):74–84. Available from: https://bjui-journals.onlinelibrary.wiley.com/doi/epdf/10.1111/j.1464-410X.2012.11356.x

42. Balar A, Galsky M, Rosenberg J. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389(10064):67-76.

43. Bellmunt J, Fugeray R, Rosenberg J, Al. E. Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. Ann Oncol. 2013;24(6):1466–72.

44. Bellmunt J, DeWit R, Vaughn DJ, Fradet Y, Lee L, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376(11):1015–26.

45. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020;383(13):1218–30.

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46. Gómez De Liaño A, Duran I. The continuing role of chemotherapy in the management of advanced urothelial cancer. Ther Adv Urol. 2018 Dec;10(12):455–80.

47. European Medicines Agency. Assessment report for Docetaxel Accord [Internet]. 2012. Available from: ema.europa.eu/en/documents/assessment-report/docetaxel-accord-epar-public-assessment-report_en.pdf

48. European Medicines Agency. Assessment report Pazenir [Internet]. 2019. Available from: https://www.ema.europa.eu/en/documents/assessment-report/pazenir-epar-public-assessment-report_en.pdf

49. European Medicines Agency. CHMP Assessment report for Javlor - Vinflunine [Internet]. 2009. Available from: https://www.ema.europa.eu/en/documents/assessment-report/javlor-epar-public-assessment-report_en.pdf

50. Cancer WHOIA for R on. Cancer Today [Internet]. 2020. Available from: http://gco.iarc.fr/today

51. Hepp Z, Shah SN, Smoyer K, Vadagam P. Epidemiology and treatment patterns for locally advanced or metastatic urothelial carcinoma: a systematic literature review and gap analysis. J Manag Care Spec Pharm. 2021;27(2):240–55.

52. Bellmunt J et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009;27.

53. Dansk BlæreCancer Gruppe. Nationale kliniske retningsliner for behandling af blæretumorer i Danmark. Nationale kliniske retningslinier. 2016.

54. Swedish Key Expert. 2021.

55. medicin.dk. Javlor Vinflunin [Internet]. 2019. Available from: https://pro.medicin.dk/Medicin/Praeparater/4856

56. pro.medicin.dk. Docetaxel “Accord” [Internet]. 2020. Available from: https://pro.medicin.dk/Medicin/Praeparater/8285

57. pro.medicin.dk. Docetaxel “Kabi” [Internet]. 2020. Available from: https://pro.medicin.dk/Medicin/Praeparater/7695

58. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index - Paclitaxel [Internet]. 2020. Available from: https://www.whocc.no/atc_ddd_index/?code=L01CD01

59. pro.medicin.dk. Paclitaxel “Fresenius Kabi” [Internet]. 2021. Available from: https://pro.medicin.dk/Medicin/Praeparater/5984

60. pro.medicin.dk. Paclitaxel “Accord” [Internet]. 2021. Available from: https://pro.medicin.dk/Medicin/Praeparater/8583

61. Danish Medicines Council. The Danish Medicines Council methods guide for assessing new pharmaceuticals. 2021.

62. Balar AV, McGregor BA, Rosenberg JE, Van Der Heijden MS, Park SH, Lee J-L, et al. EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors. J Clin Oncol. 2021;39(6_suppl):394–394.

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63. Astellas Pharma A/S. Topline results_Data on File. 2022.

64. Astellas Pharma A/S. PRO Analysis of Data Collected in the EV-301 Study_ Data on File. 2021.

65. Finansministeriet. Dokumentationsnotat - den samfundsokonomiske diskonteringsrente [Internet]. 2021. Available from: https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf

66. Jensen CE, Sorensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Heal Econ Heal Policy [Internet]. 2021/02/03. 2021;19(4):579–91. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33527304

67. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19 : Partitioned Survival Analysis For Decision Modelling In Health Care : A Critical Review Report By The Decision Support Unit . 2017; Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf

68. Sundhedsdatastyrelsen. DRG-takster 2022 [Internet]. 2022. Available from: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022

69. Latimer N. NICE DSU Technical Support Document 14: Survival Analysis For Economic Evaluations Alongside Clinical Trials-Extrapolation With Patient-Level Data. Sheffield: Report By The Decision Support Unit. 2011; Available from: https://journals.sagepub.com/doi/pdf/10.1177/0272989X12472398

70. Jackson CH. flexsurv: A Platform for Parametric Survival Modeling in R. J Stat Softw [Internet]. 2016/05/12. 2016;70. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29593450

71. Denmark S. HISB8 Life Table (2 years tables) by sex, age and life table [Internet]. 2021. Available from: https://www.statbank.dk/HISB8

72. Gomez de Liano Lista A, van Dijk N, de Velasco Oria de Rueda G, Necchi A, Lavaud P, Morales-Barrera R, et al. Clinical outcome after progressing to frontline and second-line Anti-PD-1/PD-L1 in advanced urothelial cancer. Eur Urol [Internet]. 2019/11/09. 2020;77(2):269–76. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31699525

73. Hepp Z, Shah S, Tan K, Balakrishna S. Real-world outcomes in patients with locally advanced or metastatic urothelial carcinoma receiving taxane monotherapy following platinum and anti-PD-1/L1 therapy. J Clin Oncol [Internet]. 2020;458. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.6_suppl.458

74. Astellas Pharma A/S. Data on File.

75. Danish Medicines Council. The Danish Medicines Council methods guide for assessing new pharmaceuticals [Internet]. 2021. Available from: https://medicinraadet.dk/media/wq0dxny2/the_danish_medicines_council_methods_guide_for_assessing_new_pharmaceuticals_version_1-2_adlegacy.pdf

76. Lægemiddelstyrelsen. Medicinpriser [Internet]. 2022 [cited 2022 Feb 11]. Available from: https://medicinpriser.dk/Default.aspx

77. Flannery K, Cao X, He J, Zhong Y, Shah AY, Kamat AM. Survival Rates and Health Care Costs for Patients With Advanced Bladder Cancer Treated and Untreated With Chemotherapy. Clin Genitourin Cancer [Internet]. 2018/05/08. 2018;16(4):e909–17. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29735397

78. National Health Services. National Cost Collection for the NHS [Internet]. 2021. Available from: https://www.england.nhs.uk/national-cost-collection/#ncc1819

79. Medicinradet. Værdisætning af enhedsomkostninger [Internet]. 2022. Available from: https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf

80. Hepp Z, Shah SN, Liang S-Y, Tan K, Balakrishna S. Real-world outcomes in locally advanced or metastatic urothelial carcinoma following platinum and PD-1/L1 inhibitor therapy. Futur Oncol [Internet]. 2021; Available from: https://www.futuremedicine.com/doi/epub/10.2217/fon-2021-0573

81. ClinicalTrials.gov. A Study of Enfortumab Vedotin for Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer (EV-201) [Internet]. 2021. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03219333?view=results

82. Mueller HG, Wang JL. Hazard Rates Estimation Censoring with Varying Kernels and Bandawidths. Biometrics. 1994;50:61–76.

83. Hess K, Gentleman R. muhaz: Hazard Function Estimation in Survival Analysis. [Internet]. 2021. [cited 2022 May 25]. Available from: https://cran.r-project.org/web/packages/muhaz/muhaz.pdf

84. Astellas Pharma A/S. Dossier zur Nutzenbewertung gemäß § 35a SGB V - Behandlung des fortgeschrittenen oder metastasierten Urothelkarzinoms nach vorheriger platinhaltiger Chemotherapie sowie PD-(L) 1-Inhibitor_ Data on file. 2002.

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13. Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

Appendix A is not relevant for this assessment as the data included is based on a head-to-head study and thus no literature search was performed.

13.1 Unpublished data

[The quality of any unpublished data must be specifically addressed. Submission of a publication plan for unpublished data is encouraged].

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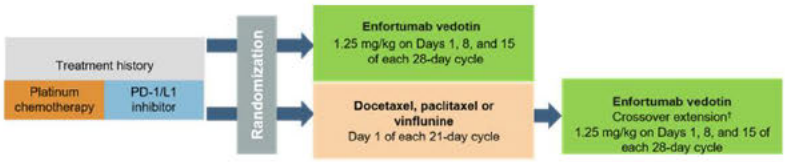
14. Appendix B - Main characteristics of included studies

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	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

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  - 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.

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Trial name: EV – 301	NCT number: NCT03474107 [15]
	• 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.

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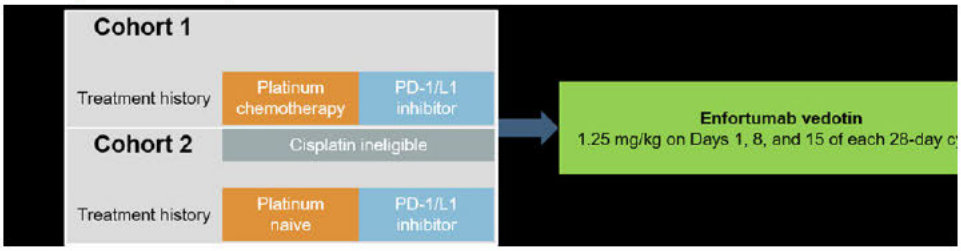
Trial name: EV – 301	NCT number: NCT03474107 [15]
Follow-up time	Patients had a follow-up visit 30 days (+ 7 days) after their last dose of drug for safety assessments. If a subject discontinued study drug prior to undocumented radiographic disease progression (i.e. PFS1), the subject was to enter the 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

Trial name: EV – 301	NCT number: NCT03474107 [15]
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]

Trial name: EV – 201	NCT number: NCT03219333 [16]
Objective	The objective was to demonstrate the efficacy and safety of Enfortumab Vedotin.
Publications – title, author, journal, year	**Cohort 1:** Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY, Galsky MD, Hahn NM, Gartner EM, Pinelli JM, Liang SY, Melhem-Bertrandt A, Petrylak DP. J Clin Oncol. 2019 Oct 10;37(29):2592-2600. **Cohort 2:** Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Yu, EY, Perylak, DP, O'Donnel, P H, Lee, JL, Stein, MN, Necci, A, Kojima, T, Harrison, MR, Park, SH, Quinn, AI, Heath, EI, Rosenberg, JE, Steinberg, J, Liang, SY, Trowbridge, J, Campbell, M, McGregor, B, Balar, AV Lancet Oncol. 2021 Jun;22(6):872-882.
Study type and design	Phase II singe arm, two cohort study. Cohort 1 enrolled patients who were previously treated with both platinum chemotherapy and an anti–PD1/L1 therapy, whereas Cohort 2 continues to enroll patients who were previously treated only with an anti–PD-1/L1 therapy. The primary completion date was October 27 2020. [81] EV-201 is a global, Phase II, single-arm, two-cohort, multicenter study that enrolled patients with la/mUC previously treated with a PD-1/L1 inhibitor therapy; patients enrolled in Cohort 1 had also previously received platinum-based chemotherapy treatment (41), while those recruited to Cohort 2 were platinum-naïve and cisplatin-ineligible (42). Treatment consisted of intravenous (IV) enfortumab vedotin 1.25 mg/kg (based on actual body weight with a maximum dose of 125 mg) over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, investigator decision, start of subsequent anticancer therapy, pregnancy, or study termination by the study sponsor. The results presented below are based on: • Cohort 1 as of 1 March 2019 (median follow-up of 10.2 months [range, 0.5–16.5]), with OS and safety data updated on 15 March 2020 (median follow-up of 22.3 months [range: 0.5–27.3]), and OS data updated on 8 September 2020 (median follow-up of 28.4 months [range, 0.5–32.6])[c] • Cohort 2 as of 8 September 2020 (median follow-up 13.4 months [range, 0.3–29.3] A study schematic is presented below. 
Sample size (n)	Cohort 1: 128 Cohort 2: 91

Trial name: EV – 201	NCT number: NCT03219333 [16]
Main inclusion and exclusion criteria	**Inclusion Criteria**: • Histologically documented urothelial carcinoma (squamous differentiation or mixed cell types allowed). • Metastatic disease or locally advanced disease that is not resectable. • Must have received prior treatment with a CPI in the locally advanced or metastatic urothelial cancer setting. A CPI is defined as a programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. Patients who received CPI therapy in the neoadjuvant/adjuvant setting and had recurrent or progressive disease either during therapy or within 3 months of therapy completion are eligible. • Must either have prior treatment with platinum-containing chemotherapy (Cohort 1) or be platinum-naïve and ineligible for treatment with cisplatin at time of enrollment (Cohort 2). • Must have had progression or recurrence of urothelial cancer during or following receipt of most recent therapy. • Tumor tissue samples must be available for submission to the sponsor prior to study treatment. • Must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1). • An Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤1 for Cohort 1 or ≤2 for Cohort 2. **Exclusion Criteria:** • Ongoing sensory or motor neuropathy Grade ≥2. • Active central nervous system (CNS) metastases. • Immunotherapy related myocarditis, colitis, uveitis, or pneumonitis. • Prior enrollment in an enfortumab vedotin study or prior treatment with other monomethyl auristatin E (MMAE)-based antibody-drug conjugates (ADCs). • Uncontrolled tumor-related pain or impending spinal cord compression.
Intervention	Cohort 1: Enfortumab vedotin 1.25 mg/kg monotherapy administered as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle Cohort 2: Enfortumab vedotin 1.25 mg/kg monotherapy administered as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle
Comparator(s)	*Not applicable*
Follow-up time	Median follow-up for cohort 1 was 28.4 months (0.49-32.62) Median follow-up for cohort 2 was 13.4 months (0.33-29.27)
Is the study used in the health economic model?	Yes

Trial name: EV – 201	NCT number: NCT03219333 [16]
Primary, secondary, and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was ORR assessed by assessed per RECIST version 1.1 by BICR. Secondary endpoints included DoR and DCR assessed by BICR and investigator. **Other endpoints:** PFS assessed by BICR and investigator, OS, safety, and tolerability of enfortumab vedotin.
Method of analysis	The Clopper-Pearson method was used to calculate the ORR and its 2-sided 95% CI. For time to event endpoints, the median survival time was estimated using the KM method; the associated 95% CI was calculated based on the complementary log-log transformation.
Subgroup analyses	Pre-planned subgroups included age group, sex, geographic region, ECOG performance status score, liver metastasis presence, preselected chemotherapy group, primary site of tumor, previous systemic therapies, and response to previous CPI status.
Other relevant information	

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15. Appendix C - Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety					
	EV-301		EV-301		EV-201
	EV (N = 301)	Chemotherapy (N = 307)	EV (N = 73)	Vinflunine (N = 78)	Cohort 1 (n=125)
Median age (range)	68 (34–85)	68 (30–88)	[redacted]		69 (40-84)
Male, n (%)	238 (79.1)	232 (75.6)			88 (70)
Geographic region, n (%)					
Western Europe	126 (41.9)	129 (42.0)			0
The US	43 (14.3)	44 (14.3)			117 (94)
Rest of the World	132 (43.9)	134 (43.6)			8(6)
Tobacco use, n (%)					
Former user	167 (55.5)	164 (53.4)			82 (66)
Current user	29 (9.6)	31 (10.1)			
Never used	91 (30.2)	102 (33.2)			43 (34)
Unknown					NR
NR	14 (4.7)	10 (3.3)			NR
History of diabetes or hyperglycaemic, n (%)	56 (18.6)	58 (18.9)			NR
ECOG PS, n (%)					
0	120 (39.9)	124 (40.4)			40(32)
1	181 (60.1)	183 (59.6)			85 (68)
Bellmunt risk score, n (%)					
0–1	201 (66.8)	208 (67.8)			72 (57.6)
≥2	90 (29.9)	96 (1.3)			52/124 (42)
NR	10 (3.3)	3 (1.0)			1 missing (0.8)
Origin site of primary disease, n (%)					
Upper urinary tract	98 (32.6)	107 (34.9)			44 (35)
Bladder or other site	203 (67.4)	200 (65.1)			81 (65)
Histologic type at initial diagnosis, n (%)					
Urothelial or transitional cell carcinoma	229 (76.1)	230/305 (75.4)			84 (67)
UC, mixed types	45 (15.0)	42/305 (13.8)			15 (12)

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety					
	EV-301		EV-301		EV-201
	EV (N = 301)	Chemotherapy (N = 307)	EV (N = 73)	Vinflunine (N = 78)	Cohort 1 (n=125)
Other	27 (9.0)	33/305 (10.8)			26 (21)
Site of metastasis, n (%)					
Lymph node only	34 (11.3)	28/306 (9.2)			13 (10)
Visceral site	234 (77.7)	250/306 (81.7)			112 (90)
Liver	93 (30.9)	95/307 (30.9)			50 (40)
Bone	NR	NR			51 (41)
Lung	NR	NR			53(42)
Previous systemic therapies, n (%)					
1–2	262 (87.0)	270 (87.9)			62 (49.6)
≥3	39 (13.0)	37 (12.1)			63 (50.4)
Best response among patients who previously received CPI treatment, n (%)					
Response	61 (20.3)	50 (16.3)			25 (20)
No response	207 (68.8)	215 (70.0)			100 (80)
Median time since diagnosis of metastatic or locally advanced disease (range)	14.8 (0.2–114.1)	13.2 (0.3–118.4)			15.4 (1.85)
Prior radiation therapy, n (%)	96 (31.9)	103 (33.6)			NR
Prior PD-1/L-1, n (%)					
Nivolumab	21 (7.0)	13 (4.2)			18 (14)
Pembrolizumab	146 (48.5)	144 (46.9)			59 (47)
Atezolizumab	86 (28.6)	89 (29.0)			62 (50)
Avelumab	16 (5.3)	13 (4.2)			1 (1)
Durvalumab	35 (11.6)	56 (18.2)			6 (5)
Other	11 (3.7)	11 (3.6)			NR
Type of prior platinum-based treatment, n (%)					
Cisplatin-based only	193 (64.1)	190 (61.9)			92 (74)
Carboplatin-based only	74 (24.6)	85 (27.7)			43 (34)
Both	34 (11.3)	31 (10.1)			NR

Sources: [15,16,18]

15.1 Comparability of patients across studies

Patient demographics and clinical characteristics in EV-201 were broadly similar to those in the EV-301, although fewer patients in the EV-201 study were male (70% vs 79%) and more patients had an ECOG score of 1 (68% vs 60%), a Bellmunt risk score of ≥1 (58% vs 67%) and visceral metastases (90% vs 78%). [16]

It was not possible to externally validate the difference between the populations with a Danish clinical expert since the comparison between the two populations is not specifically related to Danish clinical practice. Instead, a UK clinical expert was consulted. The expert suggested that EV-201 patients may exhibit better performance than EV-301 patients due to the amount of pre-selection and pre-treatment (i.e., survivorship bias), but that EV-201 data are still supportive of a higher tail than the EV-301 trial.

15.2 Comparability of the study populations with Danish patients eligible for treatment

Since epidemiological data on the UC population in Denmark is limited, the comparison was based on a recently published study from Denmark on real-world treatment patterns and overall survival in la/mUC treated with chemotherapy in Denmark in the pre-immunotherapy Era [10]. The EV-301 study population is comparable to the Danish population with respect to age and gender [10,15]. However, in Danish clinical practice, there are more patients with poor performance status compared to Ev-301. The difference is caused by the inclusion criteria in the EV-301 of an ECOG PS 0-1. This means that the results are not transferable to patients with a ECOG PS ≥ 2 [9].

16. Appendix D - Efficacy and safety results per study

16.1 Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Overall Survival	The time from randomization to the date of death from any cause.	N/A	Clinical relevance was investigated with the use of the stratified log-rank test. Minimal clinically important difference [9] Median OS: 3 months OS rate: 5%-points in 12 months
Progression-free survival	The time from the date of randomization until the date of radiological disease progression, or until death due to any cause.	Investigator assessed. Evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.	Clinical relevance was investigated with the use of the stratified log-rank test. Minimal clinically important difference [9] Median PFS: 3 months PFS rate: 10 %-points in 12 months
Overall Response Rate	The proportion of participants with a complete or partial objective response.	Investigator assessed. Evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.	Clinical relevance was investigated with the use of a stratified Cochran-Mantel-Haenszel test.
Disease Control Rate	The proportion of participants with a complete or partial objective response or a stable disease (at least 7 weeks).	Investigator assessed. Evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.	Clinical relevance was investigated with the use of a stratified Cochran-Mantel-Haenszel test.

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Outcome measure	Definition	Validity	Clinical relevance
Duration of Response	The time from the date of the first response CR/PR (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.	Investigator assessed. Evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.	Clinical relevance was investigated with the use of the KM method.
Complete response		Investigator assessed. Evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.	
Partial response		Investigator assessed. Evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.	
Progressive disease	The time from the start of study treatment to first documented PD as determined by BICR or death due to any cause.	Investigator assessed. Evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.	
Quality of Life	Definition is not provided.	Patient-reported outcome. QoL was assessed using European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) and EQ-5D-5L.	Minimal clinically important difference [9] EORTC-QLQ-C30: 10 points in 12 months Q-5D: 0.1 points in 12 months

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Outcome measure	Definition	Validity	Clinical relevance
Safety assessed by Adverse Events	Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-Emergent Adverse Event (TEAE) is defined as an adverse event observed or worsened after starting administration of the study drug. The number and percentage of participants with treatment-emergent AEs, Serious Adverse Events (SAEs), AEs leading to withdrawal of treatment, and AEs related to study drug will be summarized by system organ class, preferred term, and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be listed. A study drug-related TEAE is defined as any TEAE with a causal relationship of YES by the investigator.	Investigator assessed. Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.	Minimal clinically important difference [9] Grade 3-4: 10 %-points in 12 months

16.2 Results per study

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Table A3a Results of EV-301 (NCT03474107) -ITT											
				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 (data cut 2020)	*Enfortumab Vedotin*	*134/301*	*12.88 months (10.58–15.21)*	*3.91*	*N/A*	*N/A*	*HR: 0.70*	*0.56-0.89*	*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	*167/307*	*8.97 months (8.05–10.74)*								
Median overall-survival (data cut 2021)	*Enfortumab Vedotin*	*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.*	[20]
	Chemo-therapy	*237/307*	*8.94 months (8.25–10.25)*								
Median progression-free survival (data cut 2020)	*Enfortumab Vedotin*	*201/301*	*5.55 months (5.32-5.82)*	*1.84*	*N/A*	*N/A*	*HR: 0.62*	*0.51-0.75*	*<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	*231/307*	*3.71 months (3.52-3.94),*								
Median progressi	*Enfortumab Vedotin*	*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*	[20]

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Table A3a Results of EV-301 (NCT03474107) -ITT											
				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		
on-free survival (data cut 2021)	*Chemo-therapy*	*248/ 307*	*3.71 months (3.52-3.94),*							*with the use of KM method and comparisons between groups were conducted with the use of the stratified log-rank test.*	
Overall response rate	*Enfortumab Vedotin*	*117/ 288*	*40.6% (34.9-46.5)*	*22.7*	*15.41-29.68**	*<0.001**				*ORR was compared with the use of a stratified CMH-test.*	[15,19]
	Chemo-therapy	*53/ 296*	*17.9% (13.7-22.8)*								
Disease control rate	*Enfortumab Vedotin*	*207/ 288*	*71.9% (66.3-77.0)*	*18.5*	*10.68-25.99**	*<0.001**				*Disease control rate was compared with the use of a stratified CMH-test.*	[15]
	Chemo-therapy	*158/ 296*	*53.4% (47.5-59.2)*								
Median Duration of response	*Enfortumab Vedotin*	*63/ 117*	*7.39 months (5.59-9.46)*	*0.72*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*The duration of response was analyzed with the use of the KM method.*	[15]
	Chemo-therapy	*29/ 53*	*8.11 months (5.65-9.56)*								
Complete response	*Enfortumab Vedotin*	*14/ 288*	*4.9%*	*2.2*	*-1.00-5.61**	*0.164**	*RR: 1.80***	*0.77-4.22***	*0.178***	*CMH- test*	[15]
	Chemo-therapy	*8/ 296*	*2.7%*								

Table A3a Results of EV-301 (NCT03474107) -ITT											
				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, EORTC QLQ-C30 (baseline)	*Enfortumab Vedotin*	[redacted]		*0.75*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[64]
	Chemo-therapy										
Quality of life, EORTC QLQ-C30 (12 weeks)	*Enfortumab Vedotin*			*3.42*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[64]
	Chemo-therapy										
Quality of life, EORTC QLQ-C30 (12 weeks)	*Enfortumab Vedotin*			*2.17 (SE: 1.86)*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Mixed model repeated measures*	[64]
	Chemo-therapy										
Quality of life, EORTC QLQ-C30 (End of	*Enfortumab Vedotin*			*2.22*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[64]
	Chemo-therapy										

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Table A3a Results of EV-301 (NCT03474107) -ITT											
				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		
treatment)		[redacted]									
Quality of life, EQ-5D-5L (baseline)	*Enfortumab Vedotin*			*-0.15*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[64]
	Chemo-therapy										
Quality of life, EQ-5D-5L (12 weeks)	*Enfortumab Vedotin*			*2.82*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[64]
	Chemo-therapy										
Quality of life, EQ-5D-5L (12 weeks)	*Enfortumab Vedotin*			*1.77 (SE: 1.79)*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Mixed model repeated measures*	[64]
	Chemo-therapy										
Quality of life, EQ-5D-5L (end of treatment)	*Enfortumab Vedotin*			*2.39*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Descriptive statistics were used.*	[64]
	Chemo-therapy										

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Table A3a Results of EV-301 (NCT03474107) -ITT											
				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	*Enfortumab Vedotin*	*290/296*	*98.0%*	*1*	*-1.22-3.41**	*0.320**	*RR: 0.99***	*0.97-1.01***	*0.325***	*Descriptive statistics were used.*	[15]
	Chemo-therapy	*288/291*	*99.0%*								
[redacted]											
Serious TEAEs	*Enfortumab Vedotin*	*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.*	[15]
	Chemo-therapy	*128/291*	*44.0%*								
[redacted]											
TEAEs Grade ≥3	*Enfortumab Vedotin*	*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.*	[15]
	Chemo-therapy	*193/291*	*66.3%*								

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Table A3a Results of EV-301 (NCT03474107) -ITT											
				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		
[redacted]											
TEAEs leading to dose reduction	*Enfortumab Vedotin*	*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.*	[15]
	Chemo-therapy	*81/ 291*	*27.8%*								
[redacted]											
TEAEs leading to dose interruption	*Enfortumab Vedotin*	*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.*	[15]
	Chemo-therapy	*85/ 291*	*29.2%*								
[redacted]											

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Table A3a Results of EV-301 (NCT03474107) -ITT											
				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		
[redacted]											
TEAEs leading to treatment withdrawal	*Enfortumab Vedotin*	*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.*	[15]
	Chemo-therapy	*51/ 291*	*17.5%*								
[redacted]											
TEAEs leading to death	*Enfortumab Vedotin*	*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.*	[15]
	Chemo-therapy	*16/ 291*	*5.5%*								
[redacted]											

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Table A3a Results of EV-301 (NCT03474107) -ITT											
				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		
[redacted]											
TEAEs leading to death, excluding disease progression	*Enfortumab Vedotin*	*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.*	[15]
	Chemo-therapy	11/ 291	3.8%								
[redacted]											

* 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:

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

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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		
[redacted]											

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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		
[redacted]											

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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		
[redacted]											

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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		
[redacted]											

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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		
[redacted]											

* 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:

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

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* 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:

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

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Table A3c Results of EV-301 (NCT03474107) – Hard-to-treat 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 (Age ≥65 years)	*Enfortumab Vedotin*	*85/193*	*14.32 months*	*4.86 months*			*HR: 0.745*	*0.558-0.995*		*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.*	[18]
	Chemo-therapy	*101/196*	*9.46 months*								
Median OS (Presence of liver metastasis)	*Enfortumab Vedotin*	*53/93*	*9.63 months*	*3.68 months*			*HR: 0.660*	*0.456-0.957*			[18]
	Chemo-therapy	*63/95*	*5.95 months*								
Median OS (Primary upper tract disease)	*Enfortumab Vedotin*	*44/98*	*12.62 months*	*1.71 months*			*HR: 0.848*	*0.567-1.269*			[18]
	Chemo-therapy	*52/107*	*10.91 months*								
Median OS (Nonresponse to prior PD-1/L1 inhibitor)	*Enfortumab Vedotin*	*100/207*	*11.63 months*	*2.46 months*			*HR: 0.757*	*0.580-0.988*			[18]
	Chemo-therapy	*120/215*	*9.17 months*								

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Table A3c Results of EV-301 (NCT03474107) – Hard-to-treat 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 PFS (Age ≥65 years)	*Enfortumab Vedotin*	*126/193*	*5.65 months*	*1.87 months*			*HR: 0.616*	*0.485-0.781*		PFS 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.	[18]
	Chemo-therapy	*151/196*	*3.78 months*								
Median PFS (Presence of liver metastasis)	*Enfortumab Vedotin*	*71/93*	*4.14 months*	*1.51 months*			*HR: 0.597*	*0.428-0.833*			[18]
	Chemo-therapy	*75/95*	*2.63 months*								
Median PFS (Primary upper tract disease)	*Enfortumab Vedotin*	*63/98*	*5.62 months*	*1.84 months*			*HR: 0.716*	*0.511-1.003*			[18]
	Chemo-therapy	*74/107*	*3.78 months*								
Median PFS (Nonresponse to prior PD-1/L1 inhibitor)	*Enfortumab Vedotin*	*146/207*	*5.42 months*	*1.77 months*			*HR: 0.697*	*0.556-0.873*			[18]
	Chemo-therapy	*160/215*	*3.65 months*								

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Table A3c Results of EV-301 (NCT03474107) – Hard-to-treat 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**		
ORR (Age ≥65 years)	*Enfortumab Vedotin*	*75/184*	*40.8% (33.59-48.23*	*20.9%*	*10.75-30.61*	*<0.001**	*RR: 2.05***	*1.47-2.86***	*<0.001***	Overall response rate was compared with the use of a stratified Cochran–Mantel–Haenszel test.	[18]
	Chemo-therapy	*38/191*	*19.9% (14.48-26.27)*		*11.65-29.71**						
ORR (Presence of liver metastasis)	*Enfortumab Vedotin*	*33/93*	*35.5% (25.83-46.09)*	*24.7%*	*9.96-38.70*	*<0.001**	*RR: 3.30***	*1.73-6.30***	*<0.001***		[18]
	Chemo-therapy	*10/93*	*10.8% (5.28-18.89)*		*12.73-35.91**						
ORR (Primary upper tract disease)	*Enfortumab Vedotin*	*43/98*	*43.9% (33.87-54.27)*	*24.8%* *24.9**	*11.07-37.80*	*<0.001**	*RR: 2.30***	*1.46-3.63***	*<0.001***		[18]
	Chemo-therapy	*20/105*	*19.0% (12.04-27.87)*		*12.19-36.64**						

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Table A3c Results of EV-301 (NCT03474107) – Hard-to-treat 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**		
ORR (Nonresponse to prior PD-1/L1 inhibitor)	*Enfortumab Vedotin*	*79/199*	*39.7% (32.85-46.86)*	*22.3%*	*12.67-31.68*	*<0.001**	*RR: 2.28***	*1.62-3.22***	*<0.001***	Overall response rate was compared with the use of a stratified Cochran–Mantel–Haenszel test.	[18]
	Chemo-therapy	*36/207*	*17.4% (12.49-23.25)*		*13.59-30.60**						
Overall TRAE (Age ≥65 years)	*Enfortumab Vedotin*	*177/190*	*93.2%*	*1.2%*	*-4.26-6.73**	*0.656**	*RR: 1.01***	*0.96-1.07***	*0.673***	*Descriptive statistics were used.*	[18]
	Chemo-therapy	*173/188*	*92.0%*								
Overall TRAE (Presence of liver metastasis)	*Enfortumab Vedotin*	*81/90*	*90.0%*	*0.9%*	*-8.40-12.67**	*0.843**	*RR: 1.01***	*0.91-1.12***	*0.848***		[18]
	Chemo-therapy	*82/92*	*89.1%*								
Overall TRAE (Primary upper tract disease)	*Enfortumab Vedotin*	*91/96*	*94.8%*	*0.7%*	*-6.45-7.72**	*0.830**	*RR: 1.01***	*0.94-1.08***	*0.836***		[18]
	Chemo-therapy	*96/102*	*94.1%*								

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Table A3c Results of EV-301 (NCT03474107) – Hard-to-treat 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**		
Overall TRAE (Nonresponse to prior PD-1/L1 inhibitor)	*Enfortumab Vedotin*	*190/ 202*	*94.1%*	*4.0%*	*-1.36-9.50**	*0.137**	*RR: 1.04***	*0.99-1.11***	*0.142***	*Descriptive statistics were used.*	[18]
	Chemo-therapy	*182/ 202*	*90.1%*								
TRAEs Grade ≥3 (Age ≥65 years)	*Enfortumab Vedotin*	*108/ 190*	*56.8%*	*3.1%*	*-6.86-12.98**	*0.545**	*RR: 1.06***	*0.88-1.27***	*0.542***		[18]
	Chemo-therapy	*101/ 188*	*53.7%*								
TRAEs Grade ≥3 (Presence of liver metastasis)	*Enfortumab Vedotin*	*43/90*	*47.8%*	*6.5%*	*-7.80-20.45**	*0.379**	*RR: 1.16***	*0.84-1.60***	*0.381***		[18]
	Chemo-therapy	*38/92*	*41.3%*								
TRAEs Grade ≥3 (Primary upper tract disease)	*Enfortumab Vedotin*	*57/96*	*59.4%*	*8.4%*	*-5.39-21.72**	*0.236**	*RR: 1.16***	*0.91-1.50***	*0.236***		[18]
	Chemo-therapy	*52/ 102*	*51.0%*								

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Table A3c Results of EV-301 (NCT03474107) – Hard-to-treat 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**		
TRAEs Grade ≥3 (Nonresponse to prior PD-1/L1 inhibitor)	*Enfortumab Vedotin*	*100/ 202*	*49.5%*	*1.0%*	*-8.67-10.64**	*0.841**	*RR: 1.02***	*0.84-1.25***	*0.842***		[18]
	Chemo-therapy	*98/ 202*	*48.5%*								

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Table A3d Results of EV-201 - (NCT03219333)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]											
Median PFS per BICR (Data cut March 2019)	*Cohort 1*	*81/125*	*5.8 months (4.93-7.46)*								[16]
[redacted]											
ORR per blinded independent central review (Data cut March 2019)	*Cohort 1*	*55/125*	*44% (35.1-53.2)*								[16]

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Table A3d Results of EV-201 - (NCT03219333)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median time to response (Data cut March 2019)	*Cohort 1*	*/125*	*1.84 months (range,1.2-9.2)*								[16]
Median duration of response (Data cut March 2019)	*Cohort 1*	*/125*	*7.6 months (4.93-7.46)*								[16]
Any adverse event (Data cut March 2019)	*Cohort 1*	*125/125*	*100%*								[16]
Treatment-related adverse events (Data cut March 2019)	*Cohort 1*	*117/125*	*94%*								[16]
Grade ≥3 treatment-related adverse events (Data cut March 2019)	*Cohort 1*	*68/125*	*54%*								[16]
Treatment related serious adverse events (Data cut March 2019)		*24/125*	*19%*								[16]
Treatment- related adverse events resulting in treatment		*15/125*	*12%*								[16]

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Table A3d Results of EV-201 - (NCT03219333)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
discontinuation (Data cut March 2019)											
The treatment-related adverse event leading to death (Data cut March 2019)*		*0/125*	*0%*								[16]

* There were no treatment-related deaths during the 30-day safety reporting period. One death as a result of interstitial lung disease that occurred outside the safety reporting period was reported as treatment-related.

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17. Appendix E - Safety data for intervention and comparator(s)

Table 56. Summary of TEAEs – EV-301[15]

TEAEs (data cut 2020)	Enfortumab vedotin (N=296) n (%)	Chemotherapy (N=291) n (%)
Overall	290 (98.0)	288 (99.0)
Serious adverse events	138 (46.6)	128 (44.0)
Grade ≥3 severity	210 (70.9)	193 (66.3)
Leading to dose reduction	101 (34.1)	81 (27.8)
Leading to dose interruption	180 (60.8)	85 (29.2)
Leading to treatment withdrawal	51 (17.2)	51 (17.5)
Leading to death	21 (7.1)	16 (5.5)
Leading to death, excluding disease progression	11 (3.7)	11 (3.8)
Drug-related Grade ≥3 severity		
Death	130 (43.9)	161 (55.3)
TEAEs (data cut 2021)	**Enfortumab vedotin (N=296) n (%)**	**Chemotherapy (N=291) n (%)**

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Overall	[redacted]	
Serious adverse events		
Grade ≥3 severity		
Leading to dose reduction		
Leading to dose interruption		
Leading to treatment withdrawal		
Leading to death		
Leading to death, excluding disease progression		
Drug-related Grade ≥3 severity		
Death		
Adverse event occurring in ≥ 20% of patients in either treatment arm		
Alopecia	139 (47.0)	110 (37.8)
Decreased appetite	121 (40.9)	78 (26.8)
Fatigue	107 (36.1)	78 (26.8)
Diarrhea	103 (34.8)	66 (22.7)
Peripheral sensory neuropathy	102 (34.5)	66 (22.7)

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Pruritis	102 (34.5)	20 (6.9)
Nausea	89 (30.1)	74 (25.4)
Constipation	82 (27.7)	73 (25.1)
Dysgeusia	74 (25.0)	23 (7.9)
Pyrexia	65 (22.0)	41 (14.1)
Anemia	59 (19.9)	87 (29.9)

Table 57. Summary of TRAEs – EV-301 [15]

TRAEs	Enfortumab vedotin (N=296) n (%)	Chemotherapy (N=291) n (%)
Any grade[†]	**278 (93.9)**	**267 (91.8)**
Alopecia	134 (45.3)	106 (36.4)
Peripheral sensory neuropathy[§]	100 (33.8)	62 (21.3)
Pruritus	95 (32.1)	13 (4.5)
Fatigue	92 (31.1)	66 (22.7)
Decreased appetite	91 (30.7)	68 (23.4)
Diarrhea	72 (24.3)	48 (16.5)
Dysgeusia	72 (24.3)	21 (7.2)

Nausea	67 (22.6)	63 (21.6)
Rash maculopapular	48 (16.2)	5 (1.7)
Rash	45 (15.2)	11 (3.8)
Dry skin	42 (14.2)	2 (0.7)
Constipation	37 (12.5)	48 (16.5)
Weight decreased	35 (11.8)	11 (3.8)
Anemia	34 (11.5)	59 (20.3)
Asthenia	31 (10.5)	32 (11.0)
Neutrophil count decreased	30 (10.1)	49 (16.8)
Vomiting	26 (8.8)	31 (10.7)
WBC decreased	16 (5.4)	31 (10.7)
≥Grade 3‡	**152 (51.4)**	**145 (49.8)**
Rash maculopapular	22 (7.4)	0 (0.0)
Fatigue	19 (6.4)	13 (4.5)
Neutrophil count decreased	18 (6.1)	39 (13.4)
Neutropenia	14 (4.7)	18 (6.2)
Hyperglycemia	11 (3.7)	0 (0.0)

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Diarrhea	10 (3.4)	5 (1.7)
Peripheral sensory neuropathy§	9 (3.0)	6 (2.1)
Drug eruption	8 (2.7)	1 (0.3)
Lipase increased	6 (2.0)	3 (1.0)
Asthenia	4 (1.4)	7 (2.4)
Lymphocyte count decreased	4 (1.4)	12 (4.1)
Febrile neutropenia	2 (0.7)	16 (5.5)
WBC decreased	4 (1.4)	20 (6.9)

Abbreviations: AE, adverse event; SAF, Safety Analysis Set; TRAE, treatment-related adverse event; WBC, white blood cell.

† Occurring in ≥10% of patients in either treatment arm; ‡ Occurring in ≥2% of patients in either treatment arm; § A total of 113 patients (enfortumab vedotin, n=55; chemotherapy, n=58) had pre-existing peripheral neuropathy.

Source: Astellas/Seagen, 2020. (Astellas Pharma US Inc. IS. An open-label, randomized phase 3 study to evaluate enfortumab vedotin vs chemotherapy in subjects with previously treated locally advanced or metastatic urothelial cancer (EV-301): Clinical Study Report. . Data on file. 2021.)

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Table 58. TRAE of Special Interest* by Grade – EV-301 [15]

	Enfortumab vedotin (N=296)						Chemotherapy (N=291)					
Event, n (%)	**Any**	**1**	**2**	**3**	**4**	**5**	**Any**	**1**	**2**	**3**	**4**	**5**
Skin reactions†	139 (47.0)	41 (13.9)	55 (18.6)	42 (14.2)	1 (0.3)	0	46 (15.8)	30 (10.3)	14 (4.8)	2 (0.7)	0	0
Rash	130 (43.9)	41 (13.9)	46 (15.5)	42 (14.2)	1 (0.3)	0	28 (9.6)	21 (7.2)	6 (2.1)	1 (0.3)	0	0
Severe cutaneous adverse reaction‡	60 (20.3)	20 (6.8)	25 (8.4)	14 (4.7)	1 (0.3)	0	22 (7.6)	12 (4.1)	8 (2.7)	2 (0.7)	0	0
Peripheral neuropathy	137 (46.3)	44 (14.9)	78 (26.4)	15 (5.1)	0	0	89 (30.6)	45 (15.5)	37 (12.7)	7 (2.4)	0	0
Sensory events§	130 (43.9)	43 (14.5)	76 (25.7)	11 (3.7)	0	0	86 (29.6)	44 (15.1)	35 (12.0)	7 (2.4)	0	0
Motor events	22 (7.4)	5 (1.7)	12 (4.1)	5 (1.7)	0	0	7 (2.4)	5 (1.7)	2 (0.7)	0	0	0
Ocular disorders	55 (18.6)	40 (13.5)	13 (4.4)	2 (0.7)	0	0	14 (4.8)	11 (3.8)	2 (0.7)	1 (0.3)	0	0
Dry eye	47 (15.9)	34 (11.5)	11 (3.7)	2 (0.7)	0	0	9 (3.1)	6 (2.1)	2 (0.7)	1 (0.3)	0	0

Blurred vision	12 (4.1)	10 (3.4)	2 (0.7)	0	0	0	6 (2.1)	5 (1.7)	0	1 (0.3)	0	0
Corneal disorders	2 (0.7)	2 (0.7)	0	0	0	0	0	0	0	0	0	0
Infusion-related reactions	26 (8.8)	11 (3.7)	11 (3.7)	4 (1.4)	0	0	13 (4.5)	6 (2.1)	7 (2.4)	0	0	0
Systemic events	23 (7.8)	10 (3.4)	9 (3.0)	4 (1.4)	0	0	9 (3.1)	4 (1.4)	5 (1.7)	0	0	0
Local events	3 (1.0)	1 (0.3)	2 (0.7)	0	0	0	6 (2.1)	4 (1.4)	2 (0.7)	0	0	0
Infusion site reactions	2 (0.7)	0	2 (0.7)	0	0	0	4 (1.3)	3 (1.0)	1 (0.3)	0	0	0
Extravasation site reactions	3 (1.0)	1 (0.3)	2 (0.7)	0	0	0	4 (1.4)	2 (0.7)	2 (0.7)	0	0	0
Hyperglycemia	19 (6.4)	3 (1.0)	4 (1.4)	11 (3.7)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0

*Events represent listings by Preferred Term and may include Sponsor Specific Query/Customized Medical Queries (SSQ/CMQ) or Standard MedDRA Queries.

‖Indicates rash or severe cutaneous adverse reactions.

‡Composite Standard MedDRA Query High Level Term of severe cutaneous adverse reactions including: stomatitis, drug eruption, conjunctivitis, dermatitis bullous, skin exfoliation, blister, erythema multiforme, exfoliative rash, fixed eruption, mouth ulceration, pemphigus, and toxic skin eruption.

§Represents "Any peripheral neuropathy sensory events (SSQ/CMQ)" including: peripheral sensory neuropathy, neuropathy peripheral, paraesthesia, polyneuropathy, hypoaesthesia, neurotoxicity, dysaesthesia, gait disturbance, burning sensation, neuralgia, and sensory loss.

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Table 59. Time to Onset of Treatment-Related Adverse Events of Special Interest – EV-301.

Event	Enfortumab vedotin (N=296)		Chemotherapy (N=291)	
	n	Median (range), months	n	Median (range), months
Skin reactions	139	0.427 (0.03, 12.68)	46	0.657 (0.07, 9.56)
Peripheral neuropathy*	137	2.694 (0.03, 11.99)	89	0.821 (0.03, 9.07)
Corneal disorders	2	4.337 (1.91, 6.77)	0	NA
Dry eye	47	1.906 (0.30, 9.66)	9	2.464 (0.03, 5.09)
Blurred vision	12	2.448 (0.07, 5.09)	6	0.871 (0.03, 4.14)
Infusion-related reactions	26	0.509 (0.03, 9.40)	13	0.033 (0.03, 3.19)
Hyperglycemia	19	0.559 (0.26, 5.78)	1	1.413 (1.41, 1.41)

*The time to first onset of grade ≥2 peripheral neuropathy was median (range) of 4.435 (0.36, 12.02) months and 1.725 (0.07, 9.89) months for enfortumab vedotin and chemotherapy groups, respectively.
NA denotes not applicable.

Table 60. NCI-CTCAE Grade ≥3 or Higher Treatment-emergent Adverse Events Reported for 2% of Subjects in Either Treatment Arm (SAF).

Preferred Term (MeDRA v23.0)	Overall Incidence, n (%)			
	Enfortumab Vedotin (n=296)		Chemotherapy	
	All Causality	Treatment-related	All Causality	Treatment-related
Overall	210 (70.9)	152 (51.4)	193 (66.3)	145 (49.8)
Rash maculopapular	[redacted]	22 (7.4)	[redacted]	0
Hyperglycaemia	[redacted]	11 (3.7)	[redacted]	0

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Neutrophil count decreased	[redacted]	18 (6.1)	[redacted]	39 (13.4)
Fatigue		19 (6.4)		13 (4.5)
Anaemia		[redacted]		[redacted]
Decreased appetite				
Neutropenia		14 (4.7)		18 (6.2)
Diarrhoea		10 (3.4)		5 (1.7)
Peripheral sensory neuropathy		9 (3.0)		6 (2.1)
Urinary tract infection bacterial		2 (0.7)		0
Drug eruption		8 (2.7)		1 (0.3)
Lipase increased		6 (2.0)		3 (1.0)
Asthenia		4 (1.4)		7 (2.4)
Lymphocyte count decreased		4 (1.4)		12 (4.1)
Febrile neutropenia		2 (0.7)		16 (5.5)
White blood cell count decreased		4 (1.4)		20 (6.9)
Constipation		[redacted]		[redacted]
General physical health deterioration				
Abdominal pain				

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Table 61. Summary of TEAE in vinflunine subgroup – EV-301 – Post hoc analysis.

	Enfortumab Vedotin (N = 71)	Vinflunine (N = 75)	RR	HR, (95% CI)	P-value
[redacted]					

Source: [18]

Table 62. Overview of TEAEs occurring in patients preselected for vinflunine.

TEAEs (data cut 2020)	Enfortumab vedotin (N=71) n (%)	Vinflunine (N=75) n (%)
TEAEs occurring in ≥ 10% of patients in either treatment arm		
[redacted]		

[redacted]

TEAEs of Grade ≥3 occurring in 2% of patients in either treatment arm

[redacted]

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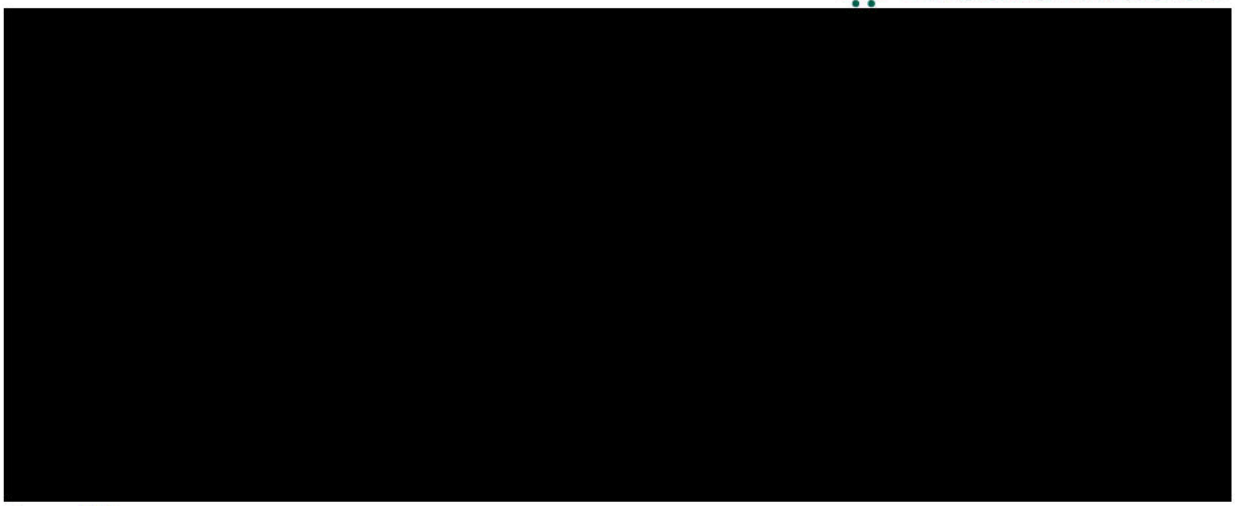

Source: [18]

Table 63. Treatment-related adverse events occurring in ≥20% (preferred term) - EV-201.

TRAEs	Any grade	≥Grade 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Rash maculopapular	27 (22)	5 (4)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0

Source: [16]

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18. Appendix F - Comparative analysis of efficacy and safety

This assessment does not include comparative analyses of efficacy and safety. In accordance with section 7.1.2 in the DMC application template, the comparative analysis was omitted as a single RCT provides head-to-head evidence of EV and taxane chemotherapy

Table A4 Meta-analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the included studies were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the included studies were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the resulting HR to an assumed 1-year survival rate of 64.33% in the comparator group.	
Example: HRQoL		−4.5	−8.97 to −0.03	0.05	NA	NA	NA	HRQoL results for the included studies were synthesized using the standardized mean difference (SMD). The estimated meta-analytical SMD of −0.3 (95% CI −2.99 to −0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale. *Fill in the name of an appropriate, measure of HRQoL.	
Insert outcome 4									

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19. Appendix G – Extrapolation and Hazard Plots

19.1 OS

The HR of OS between V vs EV (pre-selected V subgroup) was [redacted] suggesting more favourable survival for patients treated with EV. The PH assumption between EV (V subgroup) and V arms holds as validated through the reasonably proportional log cumulative hazard functions between the EV (V subgroup) and V arms (Figure 28b) and the non-significant test results of the Schoenfeld residuals tests (Figure 29b).

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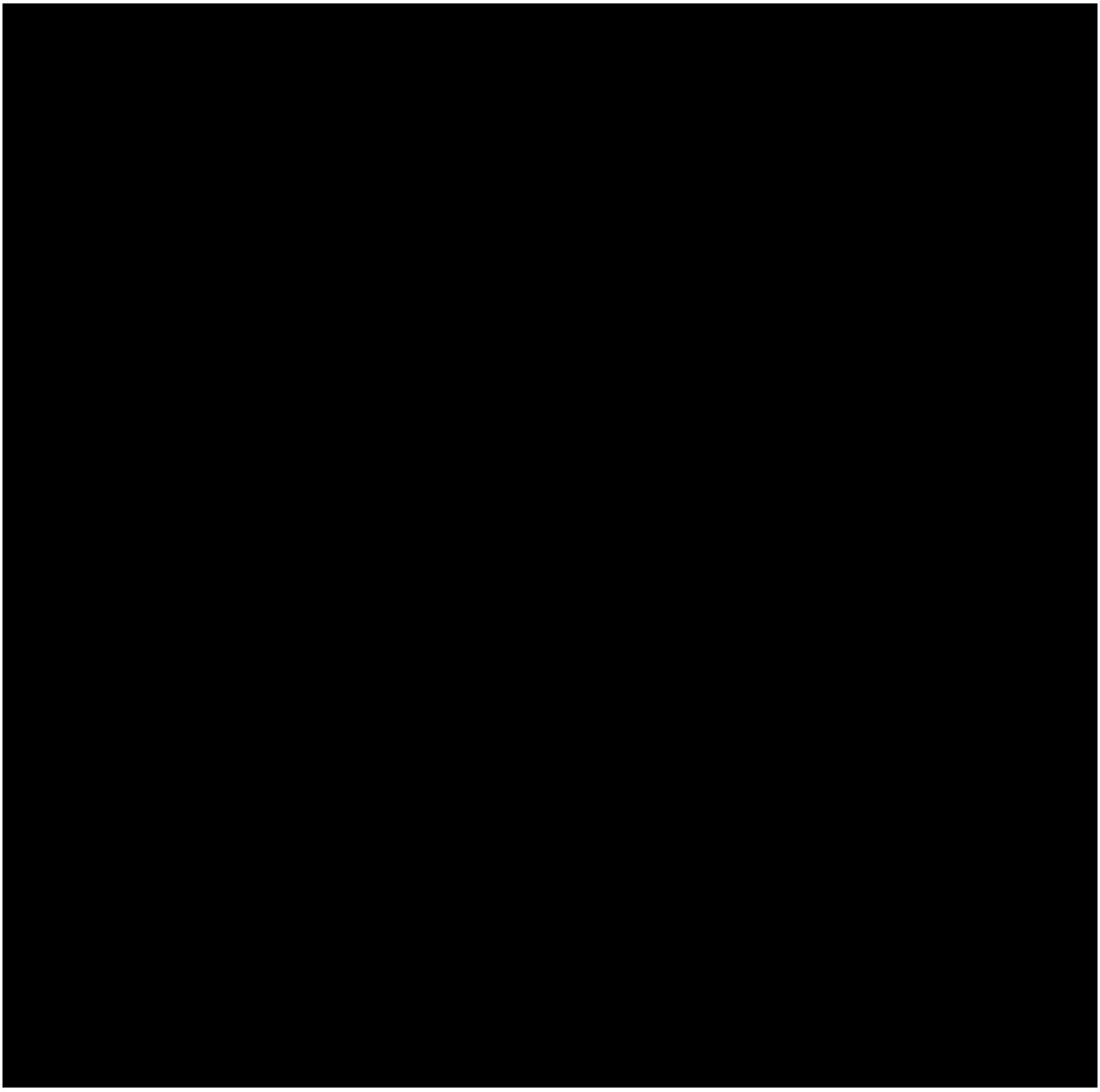

19.2 PFS

The HR of PFS between V vs EV (V subgroup) was [redacted] suggesting more favourable PFS for patients treated with EV. The PH assumption was satisfied between the EV (V subgroup) and V arms based on the log cumulative hazard functions (Figure 30b) and Schoenfeld residual test results (Figure 31b).

Figure 30. Log cumulative hazard plots for PFS

(a) EV (ITT) vs. DPV **(b) EV (pre-selected V subgroup) vs. V**

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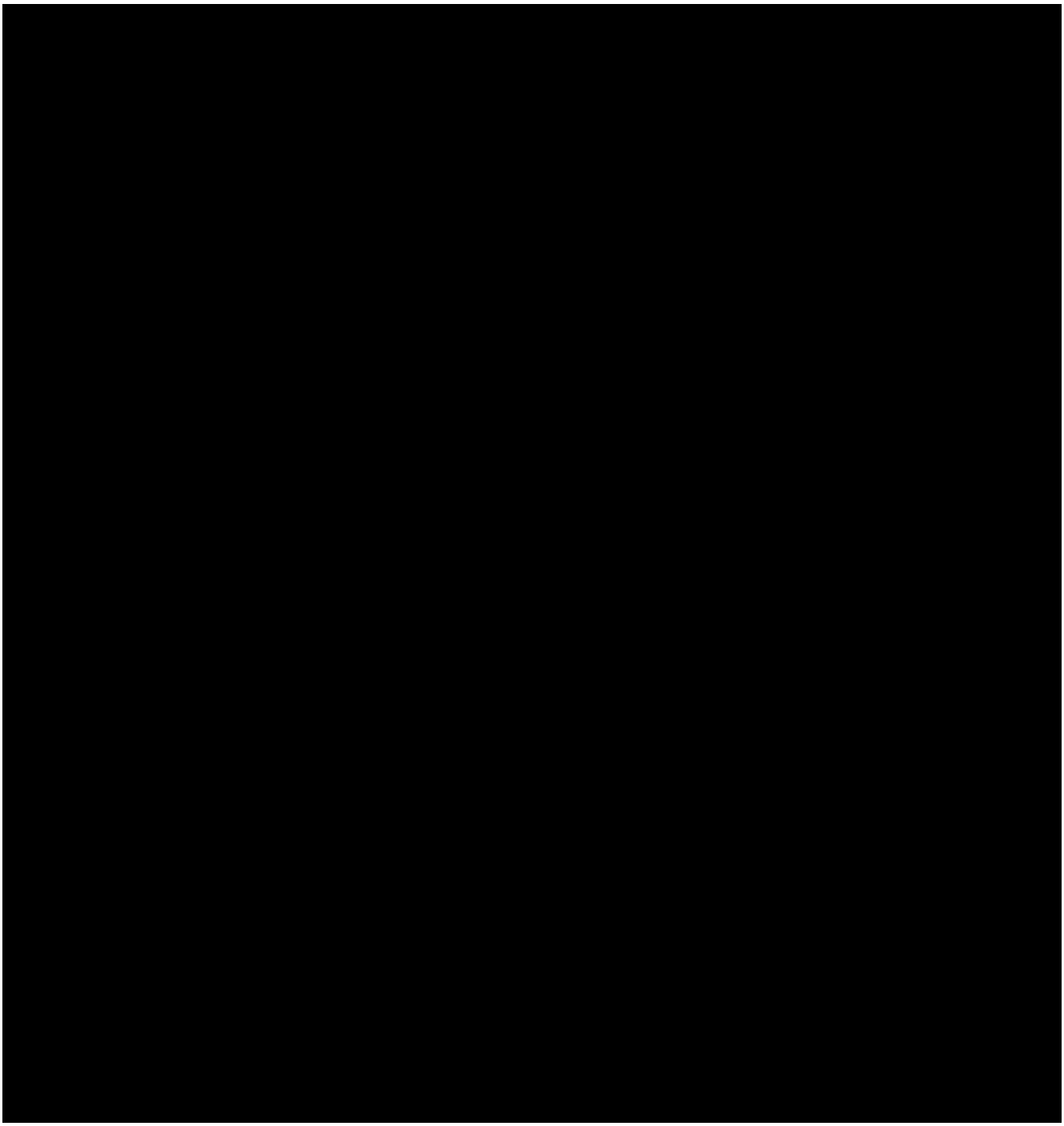

19.3 Smoothed and Unsmoothed Hazard Plots

The smoothed hazards were estimated using the muhaz function from the muhaz package which applied kernel-based methods developed by Mueller and Wang[82]. The predicted hazard curves were drawn from the parametric survival models estimated using flexsurvreg package in R [70]. The unsmoothed hazards based on observed data were plotted using the pehaz function from the muhaz package in R [83]. The pehaz function divided time domain into bins of

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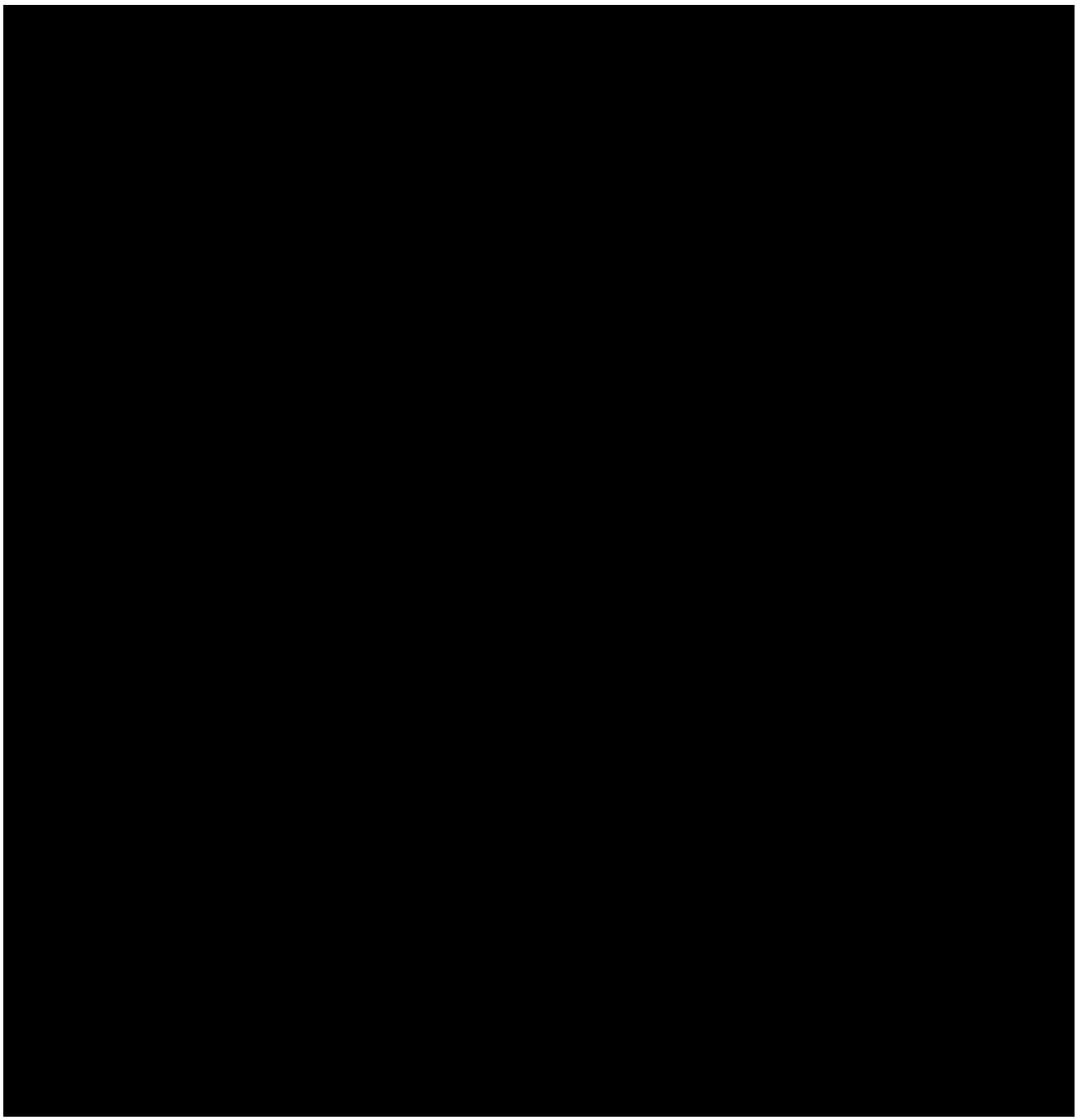
equal widths based on follow-up time length and number of uncensored observations per the Mueller approach. Hazards were then estimated in each bin as the number of events in that bin divided by the time length per bin.



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20. Appendix H - HRQoL completion rate

20.1 EQ-5D-5L

20.1.1 **Completion rates**

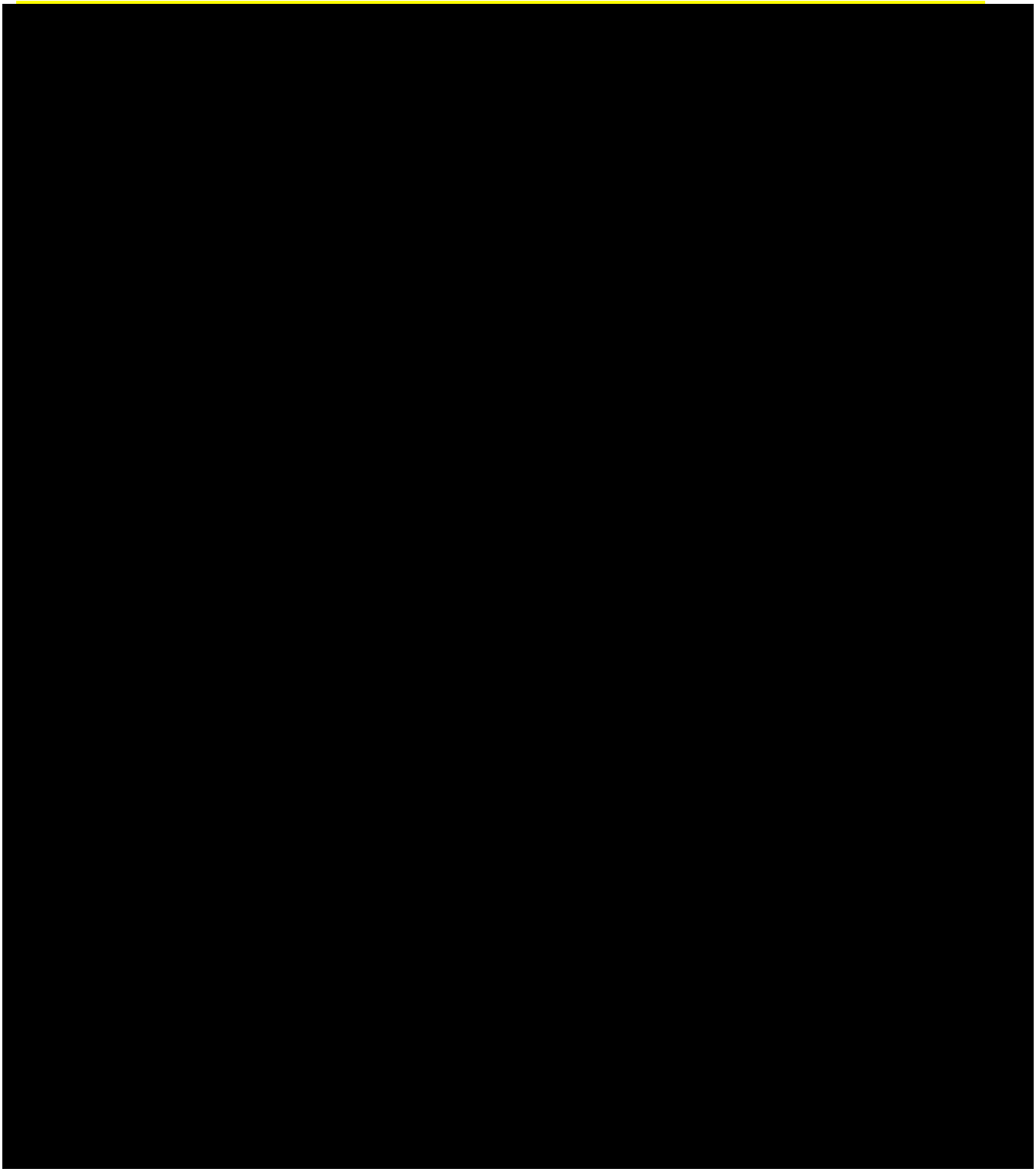

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Table 64. Response rate for the EQ-5D VAS (mFAS) - 1st data cut-off from 07/15/2020

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

Source: [84]

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

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21. Appendix I - Mapping of HRQoL data

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 (reference a).

EQ-5D-5L data were obtained from all randomized patients in the EV-301 trial.

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.

- EV denotes all EV-treated patients;
- EV (subgroup DP) denotes EV-treated patients whose pre-selected chemotherapy was Docetaxel or Paclitaxel;
- EV (subgroup D) denotes EV-treated patients whose pre-selected chemotherapy was Docetaxel;
- EV (subgroup P) denotes EV-treated patients whose pre-selected chemotherapy was Paclitaxel;
- EV (subgroup V) denotes EV-treated patients whose pre-selected chemotherapy was Vinflunine;
- DPV denotes patients receiving Docetaxel, Paclitaxel, or Vinflunine;
- DP denotes patients receiving Docetaxel or Paclitaxel;
- D denotes patients receiving Docetaxel;
- P denotes patients receiving Paclitaxel;
- V denotes patients receiving Vinflunine.

SOURCE: Jensen, Cathrine Elgaard, et al. "The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data." Applied Health Economics and Health Policy (2021): 1-13.

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22. Appendix J - Probabilistic sensitivity analyses

22.1 Probabilistic Sensitivity Analyses

The parameters varied in the probabilistic sensitivity analysis are presented in Table 65.

Table 65. Probabilistic sensitivity analysis parameters

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

AE = adverse event; BSA = body surface area; DoT = duration of treatment; EV = enfortumab vedotin; HR = hazard ratio; ITT = intention-to treat; OS = overall survival; PFS= progression-free survival; SE = standard error; V = vinflunine

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22.2 Scenario Analyses

22.2.1 Disease Management Frequencies Used in Avelumab Submission

One of the scenario analyses used disease management frequencies (under medical costs) from the avelumab submission as a first-line maintenance treatment in patients with urothelial cancer.[9] The DMC preferred scenario assumed 0.33 visits per month for both oncologist and a CT-scan for patients on or off the active treatment. To estimate the impact of these frequencies on current model results, we assumed a similar frequency of resource under the pre- and post-progression health states. Similarly, corresponding frequencies were used to calculate associated patient costs. These inputs are presented in Table 66Table 66.[9]

Table 66. Medical resource frequencies (avelumab submission), unit cost, and patient time

Medical care	Frequency per month, pre-progression	Frequency per month, post-progression	Unit cost, DKK/period	Period	Sources and key assumptions
Hospital-based physician visits	0.33	0.33	1,906	per visit	DRG Takster 2021 | Tariff 11MA98 - (MDC11 1-dagsgruppe - Nyre- og urinvejssygdomme) (Avelumab)
CT scan	0.33	0.33	2,007	per visit	DRG Takster 2021 | Tariff 30PR06 – (CT-scanning, kompliceret) (Avelumab)

	Patient time (minutes)	Source
CT, abdominal/pelvic	15	Medicinradet, 2020 [79]
Blood test	5	

The cost year is 2021 for all costs.

CT = computed tomography

22.2.2 EV (ITT) and DPV populations from EV-301 trial

One of the scenario analyses used the EV (ITT) and DPV populations from the EV-301 trial. Relevant inputs are presented in Table 67 and Table 68.

Table 67. Clinical and cost input data used in the scenario

Name of estimates	Results from study	Input value used in the model	How is the input value obtained/estimated*
Clinical inputs			
OS **EV (ITT), median (95% CI), months** **DPV, median (95% CI), months** **EV (ITT) vs. DPV, HR (95% CI)**	 12.88 (10.58, 15.21) 8.97 (8.05, 10.74) 0.70 (0.56, 0.89) p=0.001	Piecewise extrapolations of EV (ITT) and DPV data from EV-301 trial	EV (ITT) and DPV: KM through month 15 followed by Weibull†

Name of estimates	Results from study	Input value used in the model	How is the input value obtained/estimated*
PFS		Parametric extrapolation for EV (ITT) and DPV data from EV-301 trial	EV (ITT) and DPV: log-logistic extrapolations based on AIC-BIC criteria and visual inspection (KM vs model curve)‡
EV (ITT), median (95% CI), months	5.55 (5.32, 5.82)		
DPV, median (95% CI), months	3.71 (3.52, 3.94)		
EV (ITT) vs. DPV, HR (95% CI)	0.62 (0.51, 0.75) p<0.001		
DoT, EV (ITT), months (median)	4.99	Patient-level data from EV-301 trial for EV (ITT): KM curve through month 20; and DPV subgroup: KM curve through month 15	Patient-level data from EV-301 trial**
DoT, DPV, months (median)	3.45		
Pre-progression (EV – ITT), mean utility (SE)*	[redacted]		Utility scores were estimated based on EQ-5D-5L data from the EV-301 trial and the Danish EQ-5D-5L value set.[66]
Pre-progression (DPV), mean utility (SE)*			
Post-progression (Full ITT), mean EQ-5D utility (SE)*			
Cost inputs, DKK			
D, Acquisition (per cycle)	[redacted]		
P, Acquisition (per cycle)			
V, Acquisition (per cycle)			
D, Administration (per cycle)			
P, Administration (per cycle)			
V, Administration (per cycle)			
Adverse reaction costs, DPV			
Monthly DPV related patient cost			
Cost inputs for scenario where cost of DPV = cost of V			
DPV, Acquisition (per cycle)			
DPV, Administration (per cycle)			
Adverse reaction costs, DPV			
Monthly DPV related patient cost			

* Calculations: If intermediate outcome measures were linked to final outcomes, describe them here (for example, if a change in a surrogate outcome was linked to a final clinical outcome). Explain how the relationship was estimated, what sources of evidence were used, how the sources of evidence were identified (e.g., systematic literature review) and what other evidence exists. Details must be provided in a separate appendix with reference here.

AE = adverse event; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CI = 95% confidence interval; DoT = duration of treatment; DMC = Danish Medicines Council; DPV = docetaxel, paclitaxel, or vinflunine; EQ-5D = EuroQOL-5 dimensions; EV = enfortumab vedotin; HR = hazard ratio; ITT = intention-to treat; KM = Kaplan Meier; NC = not calculable; OS = overall survival; PFS= progression-free survival; SE = standard error; V = vinflunine

Table 68. Adverse reaction outcomes*

Grade 3 or 4 AEs	Clinical documentation		Used in the model (numerical value)	
	EV (ITT; n=296), n (%)	DPV (n=291), n (%)	EV (ITT; n=296), n (%)	DPV (n=291), n (%)
Anemia	[redacted]			
Neutropenia				
Febrile neutropenia				
Rash maculo-papular				
Decreased appetite				
Hyperglycemia				
Neutrophil count decreased				
White blood cell count decreased				
Fatigue				
Constipation				
Asthenia				
General physical health deterioration				
Abdominal pain				

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

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

SOURCES: Powles 2021, Astellas Pharma [15,31]

22.2.2.1 OS

In the EV (ITT) vs. DPV scenario, OS inputs for EV (ITT; n = 301) and DPV (n = 307) were derived using individual patient data from the phase 3 EV-301 study. For EV (ITT) and DPV, standard parametric models were used to fit an OS curve and extrapolate OS estimates. For the DPV arm, the model allows for independent parametric survival models or the application of a HR to the EV OS data (see Appendix G). For both treatment arms, estimated OS rates over time were capped by the age-gender adjusted national mortality rates in Denmark (based on Danish life tables).

The selected OS extrapolation approach for the EV (ITT) and DPV arms was a piecewise approach based on the KM curve until month [redacted] followed by a parametric function with Weibull distribution. These approaches were selected based on AIC/BIC statistics (Table 69) and visual fit inspection (Figure 39). The piecewise approach was chosen because, for both treatments, the remaining sample sizes after month 15 were too small to be representative of the survival trajectories of their respective groups.

Statistical goodness of fit and visual validation for the parametric curves are summarized in Table 69 and Figure 39.

Table 69. Statistical goodness of fit for OS extrapolation of EV (ITT) and DPV arms

Distribution	EV (ITT)		DPV	
	AIC	BIC	AIC	BIC
Exponential	[redacted]			

Distribution	EV (ITT)		DPV	
	AIC	BIC	AIC	BIC
Weibull	[redacted]			
Log-Logistic				
Log-Normal				
Gompertz				
Generalized Gamma				

AIC = Akaike information criterion; BIC = Bayesian information criterion; DPV = docetaxel, paclitaxel, or vinflunine; EV = enfortumab vedotin; ITT = intention to treat; OS = overall survival

Grey shaded cells: distribution with the best fit

[redacted]

22.2.2.2 PFS

In the EV (ITT) vs. DPV scenario, PFS inputs for EV (ITT; n = 301) and DPV (n = 307) were derived using individual patient data from the phase 3 EV-301 study. For EV (ITT) and DPV, standard parametric models were used to fit an PFS curve and extrapolate PFS estimates. For the DPV arm, the model allows for independent parametric survival models or the application of a HR to the EV PFS data (see Appendix G). For both treatment arms, estimated PFS rates over time were capped by the age-gender adjusted national mortality rates in Denmark (based on Danish life tables).

The selected PFS extrapolation approach for the EV (pre-selected V subgroup) arm and the V arm was a parametric function with log-logistic distribution. This approach was selected based on AIC/BIC statistics (Table 70) and visual fit inspection (Figure 40).

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Statistical goodness of fit and visual validation figures for the parametric curves fitted for all arms are summarized in Table 70 and Figure 40.

Table 70. Statistical goodness of fit for PFS extrapolation of EV (ITT) and DPV arms

Distribution	EV (ITT)		DPV	
	AIC	BIC	AIC	BIC
Exponential	[redacted]			
Weibull				
Log-Logistic				
Log-Normal				
Gompertz				
Generalized Gamma				

AIC = Akaike information criterion; BIC = Bayesian information criterion; DPV = docetaxel, paclitaxel, or vinflunine; EV = enfortumab vedotin; ITT = intention to treat; OS = overall survival

[redacted]

22.2.2.3 DoT

In the EV (ITT) vs. DPV scenario, DoT for the EV (ITT) and DPV arms were based on the KM curve from the EV-301 trial data (through [redacted] months for the EV subgroup and [redacted] months for the DPV subgroup). Parametric functions considered for DoT extrapolation included exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions, which were evaluated based on AIC/BIC (Table 71) and visual inspection (Figure 41). However, as the

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number at risk dropped to 0 in both EV (ITT) and DPV arms, indicating a complete data set, no extrapolation was necessary. Percentage of patients who received treatment out of the randomized patients for the relevant patient subgroups were used as the adjustment factors for each treatment arm (Table 72).

Table 71. Statistical goodness of fit for DoT extrapolation of EV (ITT) and DPV arms

Distribution	EV (ITT)		DPV	
	AIC	BIC	AIC	BIC
Exponential	[redacted]			
Weibull				
Log-Logistic				
Log-Normal				
Gompertz				
Generalized Gamma				

AIC = Akaike information criterion; BIC = Bayes an information criterion; DOT = duration of treatment; DPV = docetaxel, paclitaxel, or vinflunine; EV = enfortumab vedotin; ITT = intention to treat
Grey shaded cells: distribution with the best fit.

Table 72. Percentage of randomized patients receiving study treatment in EV-301

Treatment arm	Number of patients received treatment	Number of randomized patients	Percentage*
EV (ITT)	[redacted]	301	[redacted]
DPV		307	

*Percentage of patients who received treatment out of the randomized patients were used as adjustment factors to include untreated patients in the DoT curves used in the core EV model.
DOT = duration of treatment; DPV = docetaxel, paclitaxel, or vinflunine; EV = enfortumab vedotin; ITT = intention to treat

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

23.1 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 42. The OS was longer in the EV arm compared with the chemotherapy arm, consistent with median OS for the overall population. [19]

In the subgroup age ≥65 years (Figure 42.A), 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. [19]

In the subgroup with presence of liver metastasis (Figure 42.B), 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. [19]

In the population with primary upper tract disease (Figure 42.C), 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. [19]

In the population with nonresponse to prior PD-1/L1 inhibitor (Figure 42.D), 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. [19]

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Figure 42. Kaplan-Meier estimates of OS by subgroups - hard-to-treat.

Source: [19]

23.2 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 43.

In the subgroup age ≥65 years (Figure 43.A), 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. [19]

In the subgroup with presence of liver metastasis (Figure 43.B), 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. [19]

In the population with primary upper tract disease (Figure 43.C), 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. [19]

In the population with nonresponse to prior PD-1/L1 inhibitor (Figure 43.D), 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. [19]

Figure 43. Kaplan-Meier estimates of PFS by subgroups - hard-to-treat.

Source: [19]

23.3 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. [19]

23.4 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 safety population. [19]

The TRAEs of Grade 3 or higher that occurred in at least 5% of patients included decreased appetite (7.0%), hyperglycemia (8.5%), and malignant neoplasm progression (7.0%) in the EV arm and neutropenia (14.7%), asthenia (8.0%), anemia (6.7%), general physical health deterioration (6.7%), constipation (8.0%), febrile neutropenia (8.0%), neutrophil count decrease (6.7%), and abdominal pain (6.7%) in the vinflunine arm. [19]

In the subgroup age ≥65 years the TRAEs of Grade 3 or higher that occurred in at least 5% of the patients included maculopapular rash (7.4%), fatigue (7.9%), and decreased neutrophil count (7.4%) in the EV arm and fatigue (6.4%), decreased neutrophil count (13.8%), neutropenia (8.0%), anemia (8.0%), decreased white blood cell count (7.4%) and febrile neutropenia (5.9%). [19]

In the subgroup with presence of liver metastasis the TRAEs of Grade 3 or higher that occurred in at least 5% of the patients included maculopapular rash (8.9%), fatigue (5.6%), decreased neutrophil count (5.6%), and neutropenia (5.6%) in the EV arm and fatigue (5.4%), decreased neutrophil count (7.6%), and febrile neutropenia (6.5%). [19]

In the subgroup with primary upper tract disease the TRAEs of Grade 3 or higher that occurred in at least 5% of the patients included maculopapular rash (10.4%), fatigue (9.4%), decreased neutrophil count (9.4%), neutropenia (6.3%) and anemia (6.3%) in the EV arm and decreased neutrophil count (17.6%), neutropenia (6.9%), decreased white blood cell count (8.8%) and febrile neutropenia (6.9%). [19]

In the subgroup with nonresponse to prior PD-1/L1 inhibitor the TRAEs of Grade 3 or higher that occurred in at least 5% of the patients included maculopapular rash (9.4%), fatigue (5.0%), and decreased neutrophil count (5.0%), in the EV arm and decreased neutrophil count (13.4%), neutropenia (5.0%), anemia (5.9%), decreased white blood cell count (7.4%) and febrile neutropenia (5.0%). [19]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

24. Appendix L - Dose intensity

The dose intensity was calculated using the following equation:

$$Dose\ intensity = \frac{(Total\ drug\ administered / B)}{Duration\ of\ Exposure / cycle\ length)}$$

Where B*= body wight (EV) or B*= body surface area (DPV). The unit for EV is mg/kg/cycle and for DPV is mg/m²/cycle.

The relative dose intensity is

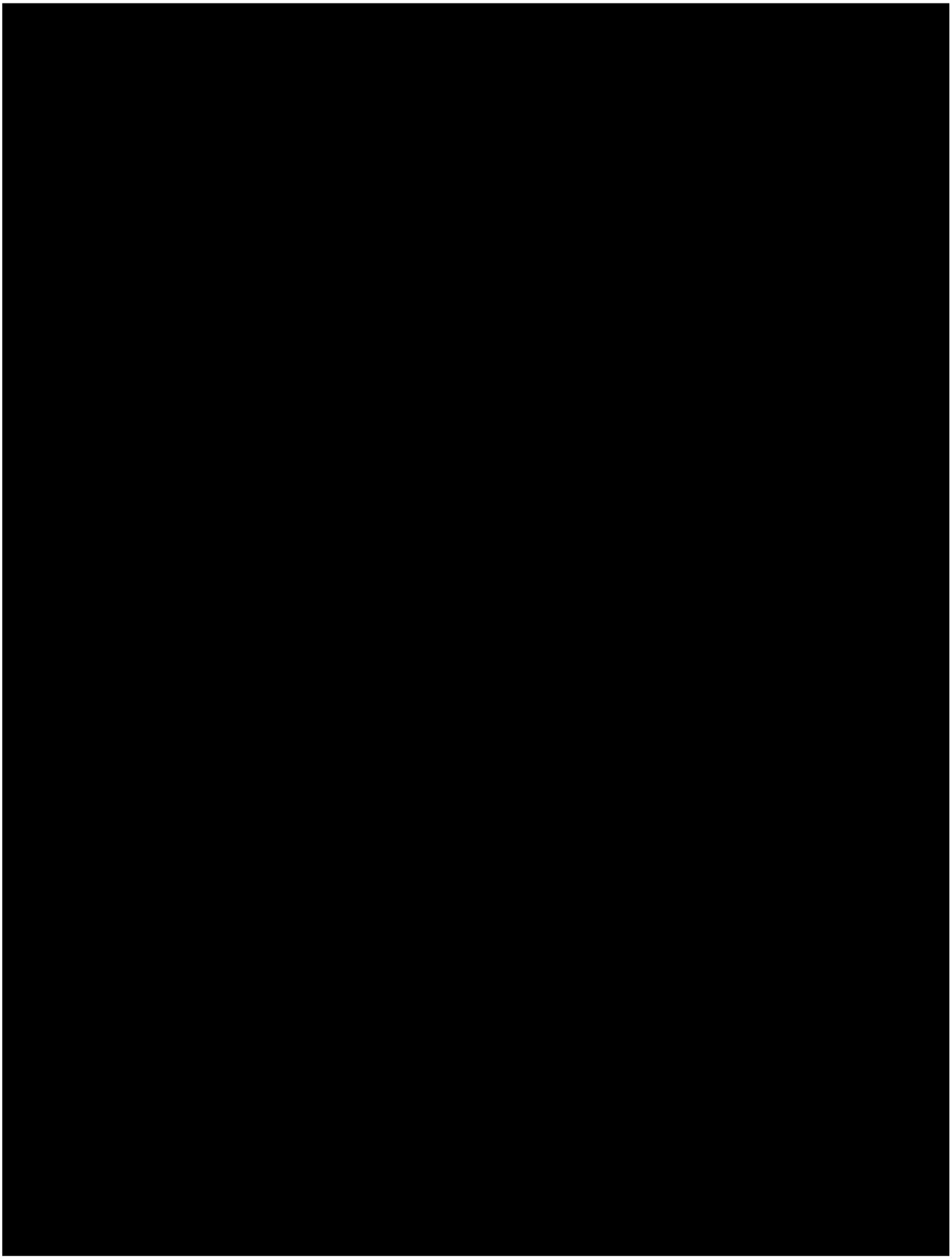
$$Relative\ dose\ intensity = \frac{Dose\ intensity}{Planned\ dose\ intensity} * 100$$

Where planned dose intensity = Initial dose of the drug multiplied by planned number of dosing days per cycle. Unit for Enfortumab vedotin is mg/kg/cycle and for Chemotherapy is mg/m^2/cycle.

Detailed study drug exposure and treatment compliance data are provided in T[redacted]

[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



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