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

For public – confidential data redacted

Technology appraisal committee C 11 March 2025

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Company: Astellas

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on metastatic urothelial cancer

Urothelial cancer is the most common type of bladder cancer

Background	Urothelial cancer (UC) affects cells which form the inner lining of the bladder, urethra, ureter, or renal pelvis
	Accounts for approximately 90% of bladder cancers
Epidemiology and prognosis	Around 16,500 new bladder cancers were diagnosed in England in 2020; more common in men than women
	1-year overall survival for people with metastatic disease is 30%
Classification	Unresectable or locally advanced: UC that has spread to nearby or pelvic lymph nodes or walls of the pelvis or abdomen
	Metastatic: UC that has spread outside of the pelvis
Symptoms	Blood in urine most common symptom

UC, urothelial cancer

Patient perspectives

Unmet need for new treatments with less side effects than chemotherapy

Submissions from Action Bladder Cancer UK, Fight Bladder Cancer and patient expert

- Urgent need for new treatments that improve outcomes and quality of life for people with metastatic urothelial cancer
- Current treatments such as chemotherapy have limited effectiveness and poor side effects profile
- EV+P demonstrated benefits in survival and side effects in clinical trials
- EV+P represents advancement in treatment pathway, but access to treatment is a challenge

"I had chemotherapy and that made me really ill, so they had to stop it. Then I was told they couldn't do much more."

"We've heard so much about trials and new treatments, but they feel out of reach. We don't know what's available to us"

EV, enfortumab vedotin; P, pembrolizumab

Clinical perspectives

Treatments that provide durable control of urothelial cancer are needed

Submissions from clinical experts

- Intent of current treatment is palliative
- Unmet need for treatments that provide longer term disease control without compromising quality of life
- Currently, first-line treatment is chemotherapy with avelumab maintenance. Atezolizumab is available following progression
- People unable to have chemotherapy have poorer outcomes and need alternative treatment options
- EV+P improved overall survival in clinical trial, it is expected to be given as first-line treatment – a step change

"Improvement of overall survival seen in [EV+P clinical trial] is unprecedented"

"…ongoing efforts to help better understand and deliver toxicity management for EV+P…"… "Toxicity profile was manageable"

EV, enfortumab vedotin; P, pembrolizumab

Equality considerations

- Incidence of bladder cancer is higher for people who are most socioeconomically deprived
- People who live in rural areas may have difficulty visiting hospitals for treatment
- There may be differences in bladder cancer outcomes based on people's age and sex
- Proportion of black people in the EV+P clinical trial is an underrepresentation
- Nearly a quarter of people in the EV+P trial were above 75 years old
- Treatment may not be available equally across the UK
- Women are often diagnosed at a more advanced stage than men
- People with metastatic urothelial cancer are often older, the severity modifier may not fully capture the unmet need for this group

NICE Can these equality issues be addressed in a technology appraisal?

EV, enfortumab vedotin; P, pembrolizumab

Description of treatment pathway

Eligibility for cisplatin is based on Galsky criteria

People for whom cisplatin is unsuitable meet at least one of the following criteria:

- Eastern Cooperative Oncology Group performance status of 2
- Kidney function (creatinine clearance less than 60 mL/min)
- Grade ≥ 2 hearing loss (moderate)
- Grade ≥ 2 neuropathy (moderate)
- New York Heart Association Class III heart failure

Company:

- Most people (90%) are eligible for platinum-based treatments

EAG:

- Clinical expert suggests 2/3 of platinum-eligible patients treated with cisplatin in practice

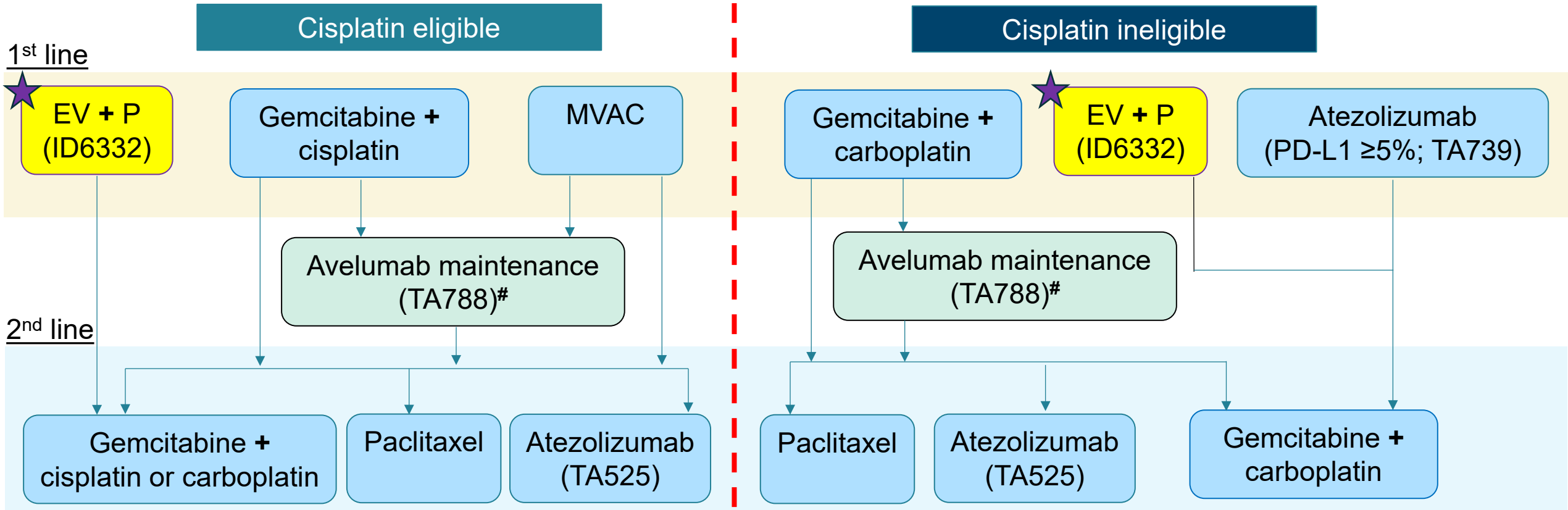
People eligible for cisplatin in EV-302

	EV+P (N=442)	PBC+Gem (N=444)
Eligible, n (%)	240 (54.3)	242 (54.5)
Ineligible, n (%)	202 (45.7)	202 (45.5)

Does cisplatin eligibility in EV-302 represent NHS clinical practice?

EV, enfortumab vedotin; P, pembrolizumab

Treatment pathway



#following response to platinum-based treatment

EV, enfortumab vedotin; P, pembrolizumab; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin

Company:

- EV+P expected to displace first-line platinum-based treatment
- Atezolizumab only used in 3% of people eligible for platinum treatments

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- Does the treatment pathway represent NHS clinical practice?
- Would platinum-based treatments be displaced by EV+P at first-line?
- Are MVAC and atezolizumab considered comparators?

Technology (Padcev® with Keytruda®, Astellas)

Marketing authorisation	• Enfortumab vedotin in combination with pembrolizumab is indicated 'for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy' • MHRA licence granted in October 2024 via International Recognition Route
Mechanism of action	• Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) that binds to Nectin-4 on urothelial cells leading to cancer cell disruption and death • Pembrolizumab (P) is a programmed cell death protein 1 (PD-1) inhibitor which enhances the antitumour activity of immune (T) cells
Administration	Given intravenously • EV: 1.25 mg/kg (maximum 125mg) on Days 1 and 8 of a 21-day cycle • P: 200 mg every 3 weeks or 400 mg every 6 weeks • P given in trial for maximum of 35 x 3-weekly cycles (~2 years)

Price	List price
	• EV: 20 mg vial £578; 30 mg vial £867
	  • Cost per average treatment course ([redacted])*
	• P: 100mg/4ml £2,630
	  • Cost per average treatment course ([redacted])*
	A patient access scheme is applicable for EV + P and some comparators

*From company's budget impact model, takes average treatment duration and relative dose intensity into account

Key issues

Issue	ICER impact
Which model should be used to estimate avelumab time on treatment?	Small
Should a 1.2 severity weighting be applied to the incremental QALYs?	Large

Other issues

Issue	ICER impact
What is the committee's preferred approach for modelling progression-free survival?	Small
What pre-progression utilities are most appropriate to apply?	Small
Is it appropriate to apply a treatment effect waning assumption for any of the treatments?	Large

Small: <£5000/QALY; Large: >£5000/QALY

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

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Key clinical trials

Clinical trial designs and outcomes

Company updated trial results with most recent data cut-off (August 2024; median follow up 29.1 months)

	EV-302 (N=886)
Design	Open-label, phase 3 randomised trial
Population	People aged ≥ 18 years with previously untreated locally advanced or metastatic urothelial cancer
Intervention	Enfortumab vedotin (EV) with pembrolizumab (P)
Comparator(s)	Platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine (PBC+Gem; avelumab maintenance therapy permitted for this group)
Treatment duration	**EV+P** (n=440): median [redacted] **PBC+Gem** (n=433): median [redacted]
Primary outcome	Progression-free survival and overall survival
Key secondary outcomes	HRQoL, adverse events, treatment discontinuation, pain progression
Locations	Global (including [redacted] people from UK)
Used in model?	Yes, updated data cutoff applied in model (August 2024)

See baseline characteristics

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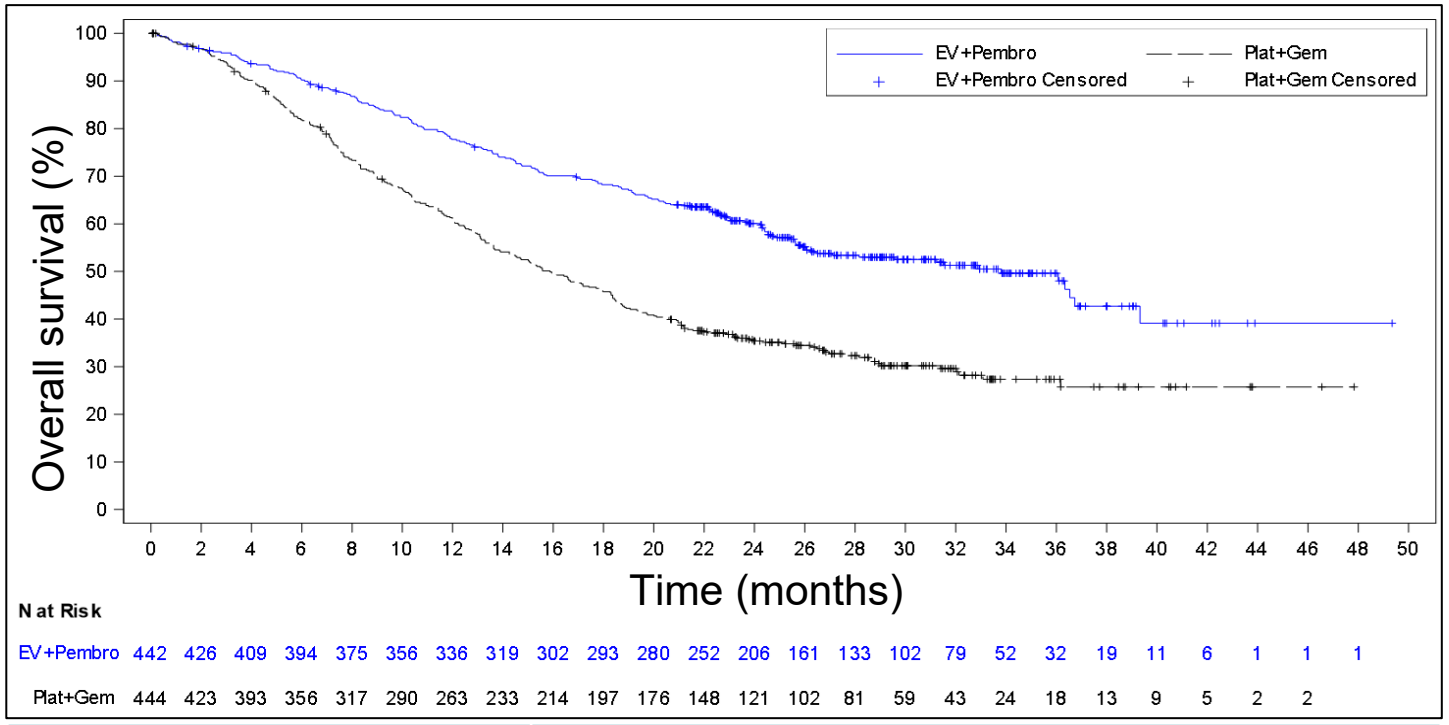
EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; HRQOL, health-related quality of life

Clinical trial results - overall survival (ITT)

EV+P improves overall survival when compared with PBC+Gem

OS Kaplan-Meier plot August 2024 data cut-off



	August 2024 data cut-off	
	EV+P	PBC+Gem
Median OS, months (95% CI)	33.8 (26.1 to 39.3)	15.9 (13.6 to 18.3)
Number of events (%)	203 (45.9)	297 (66.9)
HR (95% CI; P value)	0.513 (0.428 to 0.614; P<0.00001)	

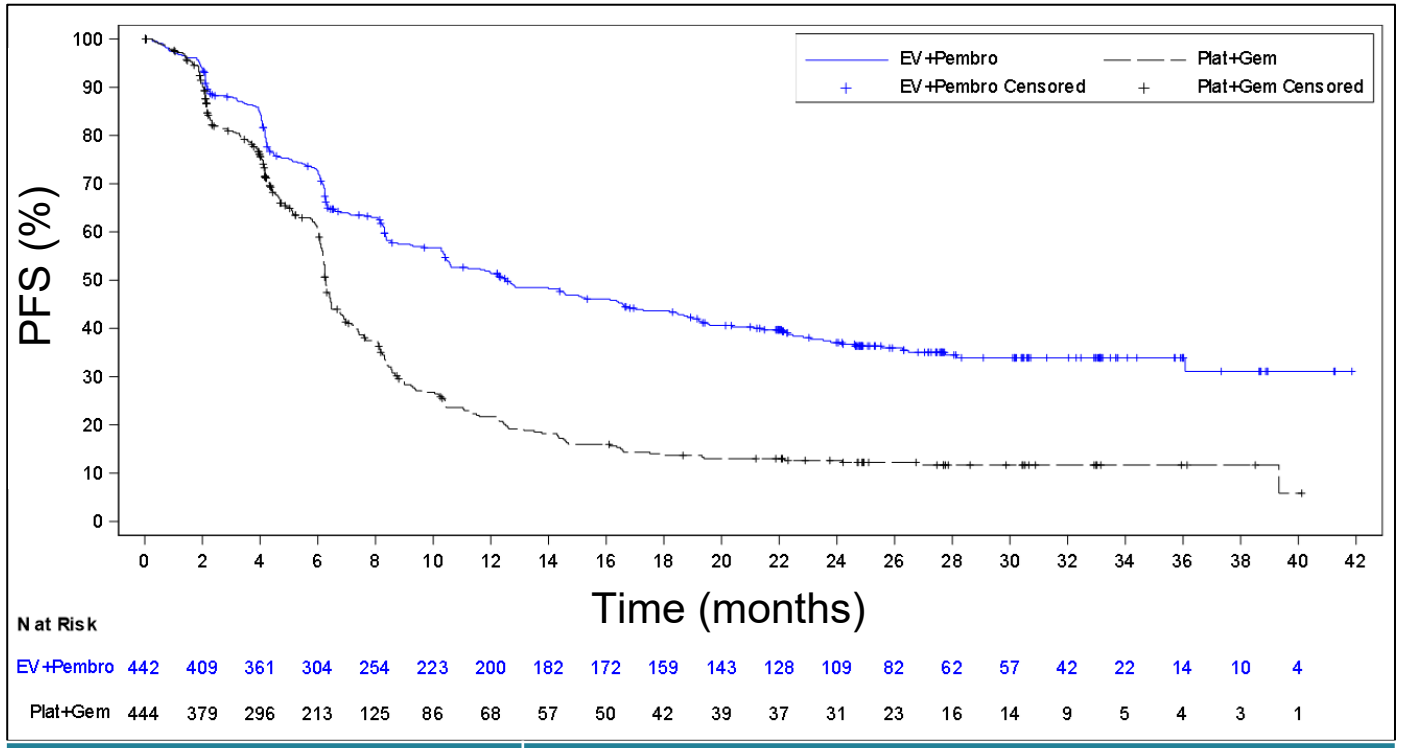
What is the impact of the OS results on the urothelial cancer treatment pathway?

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; OS, overall survival; NE, not estimated, NA, not available

Clinical trial results - progression-free survival (ITT)

EV+P improves progression-free survival when compared with PBC+Gem

PFS Kaplan-Meier plot August 2024 data cut-off



	August 2024 data cut-off	
	EV+P	PBC+Gem
Median PFS, months (95% CI)	12.5 (10.4 to 16.6)	6.3 (6.2 to 6.5)
Number of events (%)	262 (59.3)	317 (71.4)
HR (95% CI; P value)	0.481 (0.407 to 0.570; P<0.00001)	

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; PFS, progression-free survival ; NE, not estimated, NA, not available

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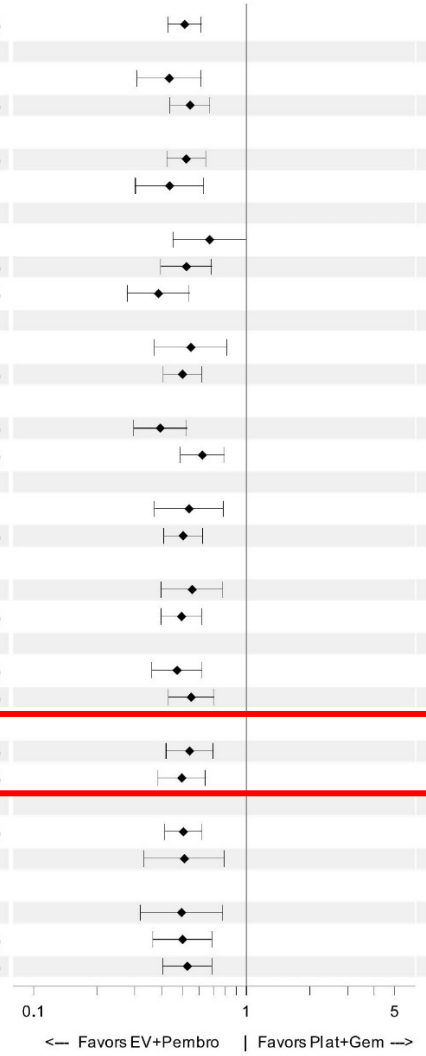
Clinical trial results – subgroup analysis

EV+P improves overall survival for both cisplatin-eligible and –ineligible subgroups

Subgroup analyses for overall survival August 2024 data cut-off

Subgroup	Median OS, months (Events/N) EV+Pembro	Plat+Gem	Hazard Ratio (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428,0.614)
Age			
<65 years	39.3 (59/144)	18.7 (87/135)	0.434 (0.307,0.614)
>=65 years	27.1 (144/298)	14.6 (210/309)	0.544 (0.439,0.674)
Race			
White	26.1 (158/308)	15.1 (207/290)	0.521 (0.422,0.644)
Other	36.3 (45/134)	19.1 (90/154)	0.436 (0.302,0.629)
Region			
North America	25.7 (57/103)	21.0 (54/85)	0.672 (0.451,1.000)
Europe	25.6 (90/172)	14.6 (140/197)	0.522 (0.397,0.687)
Rest of World	- (56/167)	15.5 (103/162)	0.386 (0.277,0.539)
Sex			
Female	25.4 (46/98)	14.6 (70/108)	0.549 (0.371,0.811)
Male	33.8 (157/344)	16.4 (227/336)	0.501 (0.407,0.617)
ECOG PS			
0	36.5 (77/223)	18.7 (136/215)	0.394 (0.296,0.524)
1-2	22.8 (126/219)	13.3 (160/227)	0.621 (0.490,0.787)
Primary disease site of origin			
Upper tract	36.5 (60/135)	18.3 (63/104)	0.538 (0.371,0.781)
Lower tract	32.9 (142/305)	15.6 (233/339)	0.504 (0.408,0.623)
Liver metastases			
Present	19.1 (68/100)	10.1 (82/99)	0.556 (0.399,0.776)
Absent	39.3 (135/342)	18.3 (215/345)	0.496 (0.400,0.615)
PD-L1 expression			
Low (CPS < 10)	31.2 (91/184)	15.1 (136/185)	0.472 (0.361,0.618)
High (CPS >= 10)	36.5 (111/254)	17.1 (158/254)	0.550 (0.431,0.703)
Cisplatin eligibility			
Eligible	36.7 (101/244)	18.7 (143/234)	0.541 (0.419,0.699)
Ineligible	25.6 (102/198)	12.7 (154/210)	0.498 (0.386,0.642)
Metastatic disease site			
Visceral metastases	25.7 (163/318)	13.5 (235/318)	0.505 (0.412,0.619)
Lymph node only	- (34/103)	24.4 (54/104)	0.512 (0.332,0.789)
Renal function			
Normal	39.3 (33/84)	18.6 (61/95)	0.496 (0.318,0.773)
Mild	36.5 (69/165)	18.4 (101/162)	0.502 (0.365,0.689)
Moderate/Severe	25.6 (101/193)	13.3 (135/187)	0.528 (0.405,0.689)



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

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Base case results based on ITT population, but company also presented results for cisplatin-eligible and –ineligible subgroups

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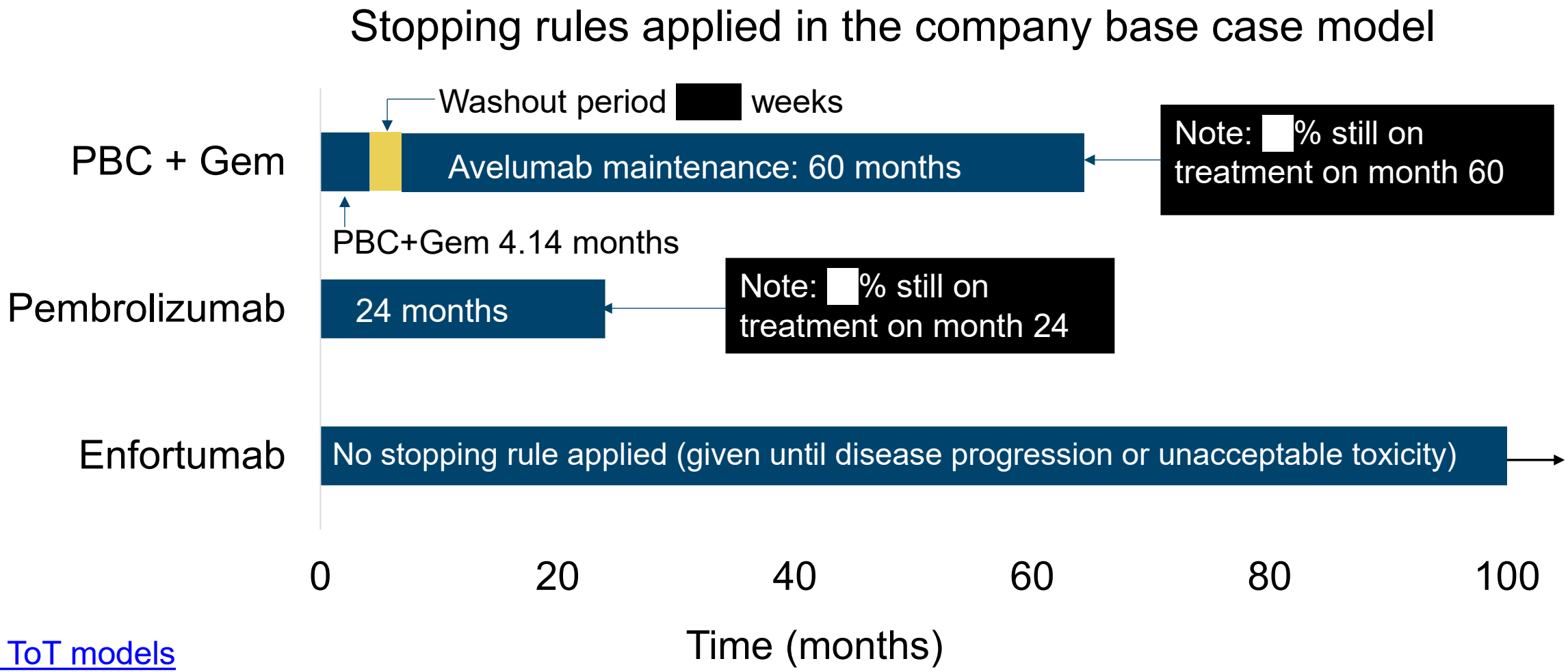
Time on treatment assumptions in the economic model



[See ToT models]

- Are these stopping rules relevant to clinical practice?
- How would treatment effect be impacted when P is stopped at month 24 but EV continues?

PBC, platinum-based chemotherapy; Gem, gemcitabine

ICER impact: Small

Key issues: Time on maintenance treatment (1/2)

Unclear which model should be used to estimate time on maintenance treatment

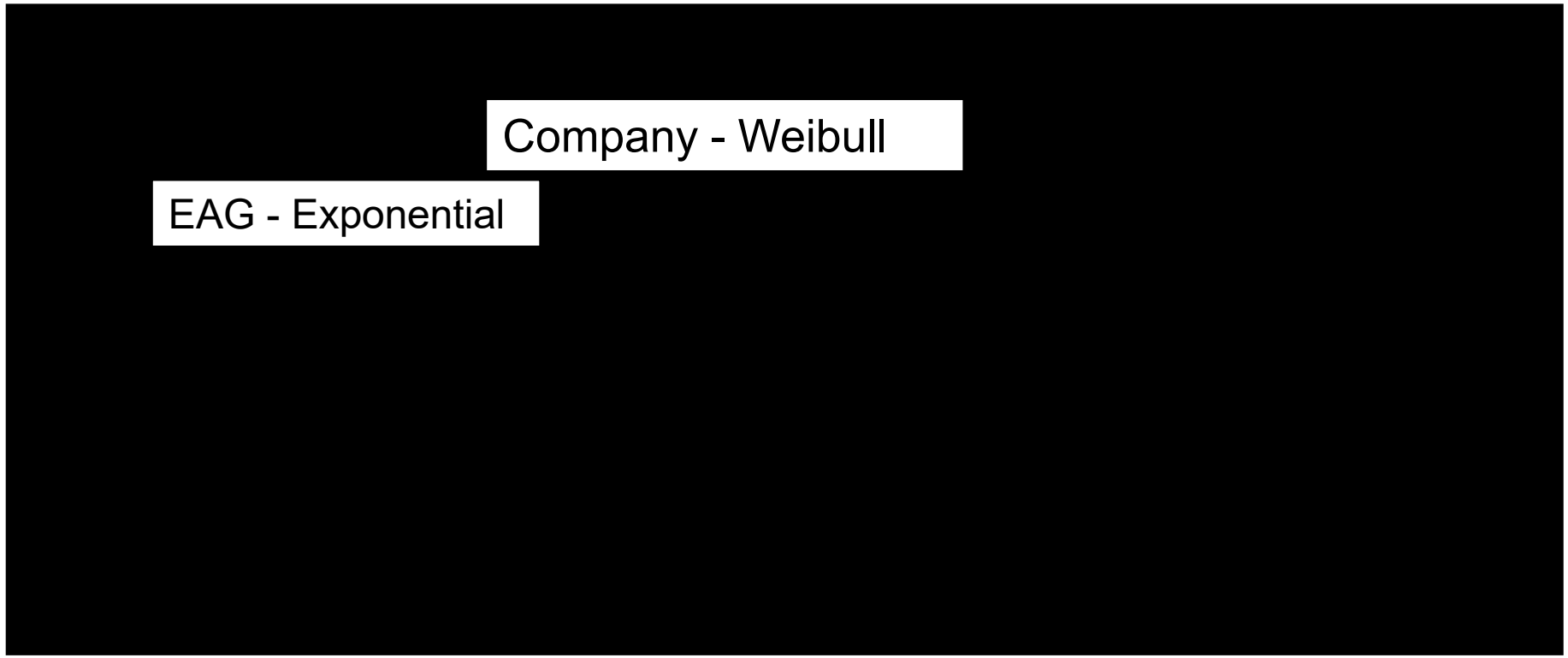
Background

- 30% of people in EV-302 had avelumab maintenance after a response to PBC+Gem
- Time on avelumab maintenance treatment modelled by EAG and company using different parametric curves

Company

- Applied 60 months stopping rule for avelumab
- Weibull curve prediction of people on treatment at year 5 aligns with TA788 (avelumab)

Time on treatment extrapolation – avelumab maintenance (ITT)



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See ToT models

ICER impact: Small

Key issues: Time on maintenance treatment (2/2)

Unclear which model should be used to estimate time on maintenance treatment

EAG comments

- Clinical expert noted avelumab maintenance usually given for less than a year in the UK, EV-302 trial may not be reflective of UK practice
- Exponential curve selected because it results in the lowest mean time on treatment ([redacted] months)

Modelled mean time on treatment

Treatment	Mean (months)	Proportion on treatment			
		Y1	Y2	Y3	Y5
Company (Weibull) - SOC: Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG (exponential) - SOC: Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Which model should be applied to estimate avelumab time on treatment?
- Should the proportion on avelumab maintenance treatment be set to 0% after 1 year?

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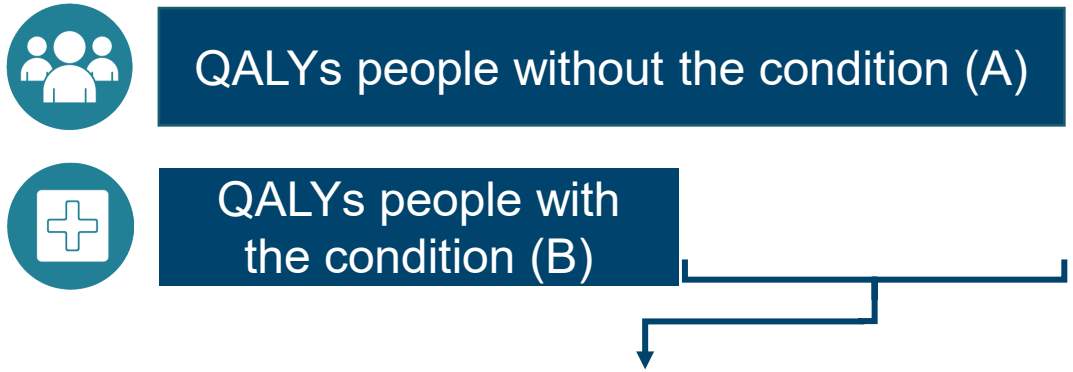
EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; SOC, standard of care; Y, year

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

QALY, quality-adjusted life year

Key issue: Severity (1/3)

Company and EAG base cases do not meet severity weighting

Background

- Company and EAG base case below the threshold for applying a severity weighting
- In EV-302 trial people could have subsequent treatments not considered standard care in the NHS
  → Could impact OS, also leads to uncertainty in severity calculation

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	**Absolute QALY shortfall (has to be ≥12)**	**Proportional QALY shortfall (has to be ≥0.85)**
Company base case	9.80	1.62	8.18	0.83
EAG base case	9.49	1.55	7.94	0.84

OS, overall survival; QALY, quality-adjusted life year

See inputs for severity

ICER impact: Large

Key issue: Severity (2/3)

Unclear if trial treatments which are not recommended in the NHS impacted OS

Company

- OS for PBC+Gem higher than in NHS practice due to subsequent treatments

Second (and beyond) subsequent treatment in EV-302

	EV+P (N=442)	PBC+Gem (N=444)
EV monotherapy n(%)	[redacted]	[redacted]
Erdafitinib n(%)	[redacted]	[redacted]
Sacituzumab govitecan n(%)	[redacted]	[redacted]

- Not possible to adjust for treatment effect with trial data, due to limited data
- Using published or NHS OS data for PBC+Gem would be flawed, would not reflect recent NICE recommendation for avelumab maintenance (May 2022)
  →2–3-year follow-up of avelumab data needed to compare PBC+Gem arm with EV-302
- 5 of the 7 OS curves tested suggests a severity weighting should be applied

EAG comments

- Adjustment to OS curves to remove treatment effect of non-standard treatments would better reflect NHS clinical practice
- Company response regarding limited data reasonable
- Avelumab used for longer period in model compared with NHS practice, this likely further overestimates OS for PBC+Gem

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; OS, overall survival

Key issue: Severity (3/3)

ICER impact: Large

*rounded up

Most OS curves suggest a severity weighting, but the base case curve does not

Scenario	Total QALYs: general population	Total QALYs: urothelial cancer with SOC	QALY shortfall	QALY weight
PBC OS log-logistic	9.80	PBC:1.62	Absolute shortfall: 8.18 Proportional shortfall: 0.83	1
PBC OS Exponential		PBC:1.34	Absolute shortfall: 8.46 Proportional shortfall: 0.86	**1.2**
PBC OS Weibull		PBC:1.28	Absolute shortfall: 8.53 Proportional shortfall: 0.87	**1.2**
PBC OS Gompertz		PBC:1.40	Absolute shortfall: 8.41 Proportional shortfall: 0.86	**1.2**
PBC OS Gamma		PBC:1.28	Absolute shortfall: 8.52 Proportional shortfall: 0.87	**1.2**
PBC OS Generalised gamma		PBC:1.49	Absolute shortfall: 8.32 Proportional shortfall: 0.85*	**1.2**
PBC OS Log-normal		PBC:1.63	Absolute shortfall: 8.17 Proportional shortfall: 0.83	1

EAG and company base case

Should a x1.2 severity weighting be applied?

Company: G. Gamma similar to base case and clinical expert OS estimates

OS estimates

EAG: using G. Gamma reasonable, but should be applied to both arms. Has a greater effect on the EV + P arm increasing the ICER

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EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; OS, overall survival; QALY, quality-adjusted life year

Overall survival extrapolations

Model	AIC	BIC	Timepoint		
			2 years	5 years	10 years
EV+P					
Average (range) of company expert estimates			58% (50-60%)	32% (20-45%)	16% (5-35%)
Log-logistic	1969.96	1978.14	60%	31%	16%
Generalised gamma	1972.23	1984.50	60%	28%	8%
PBC+Gem					
Average (range) of company expert estimates			35% (30-45%)	11% (5-20%)	6% (0-10%)
Log-logistic	2484.83	2493.02	36%	13%	5%
Generalised gamma	2491.04	2503.33	37%	12%	3%

Summary of cost-effectiveness results

All ICERs are reported in PART 2 slides because they contain comparator PAS

Summary of base case results

- **Without severity weight**: the company and EAG base case ICERs are >£30,000/QALY
- **With severity weight x1.2**: the company and EAG base case ICERs are >£30,000/QALY

Results of scenario analyses for the following parameters will be discussed:

- OS extrapolation
- PFS extrapolation
- ToT extrapolation
- Utility values
- Treatment waning

PAS, patient access scheme; ICER, incremental cost-effectiveness ratio, OS, overall survival; PFS, progression-free survival, ToT, time on treatment

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Managed access

Company did not submit proposal for managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

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Summary of company and EAG base case assumptions

Base case results based on ITT population, but company also presented results for cisplatin-eligible and –ineligible subgroups

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Discounting	3.5% after first year	3.5% from start of model
OS extrapolation	Log-logistic	
PFS extrapolation	**EV+P:** Spline fit with 2 knots **PBC+Gem:** Spline fit with 3 knots	**EV+P:** Log-logistic **PBC+Gem:** Log-logistic
Pre-progression utilities	Treatment dependent for **EV+P** [redacted] and **PBC+Gem** [redacted]	**EV+P:** treatment independent [redacted] **PBC+Gem:** treatment dependent for first 6 months [redacted] then treatment independent afterwards [redacted]
Avelumab time on treatment	Weibull model, mean treatment time: [redacted]	Exponential model, mean treatment time: [redacted]
Severity weighting	1 (Proportional shortfall = 0.83)	1 (Proportional shortfall = 0.84)
Treatment waning	Not applied	Not applied. Provided scenarios

OS, overall survival; PFS, progression-free survival; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

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

Supplementary appendix

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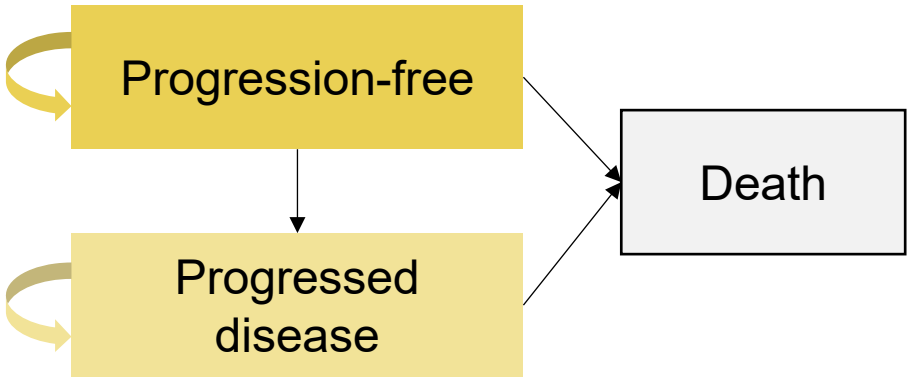
Company's model overview

Partitioned survival model

Model structure



Parameter	Input
Time horizon	Lifetime (maximum 30 years, people enter aged 67.9 years)
Discounting	3.5% for costs and QALYs (after 1st year)
Cycle length	1 week
Population	First-line adult patients with unresectable or metastatic urothelial cancer who are eligible for chemotherapy
Intervention	EV+P
Comparator	PBC+Gem
Utility values	EQ-5D-5L mapped to EQ-5D-3L
Subsequent treatments	PBC+Gem , atezolizumab and paclitaxel

QALY, quality-adjusted life years; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

How company incorporated evidence into model

EAG: 2022/2023 NHS Reference Cost now available

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	EV-302 trial
Intervention efficacy	OS and PFS from EV-302 trial
Comparator efficacy	OS and PFS from EV-302 trial
Relative dose-intensities	EV-302 trial, previous NICE TAs
Subsequent treatment	Based on EV-302; EV monotherapy excluded and reweighted; pembrolizumab replaced by atezolizumab
Utilities	EQ-5D-5L from EV-302 trial mapped to EQ-5D-3L
Costs	BNF, MIMs
Resource use	NHS Reference Costs 2021/22, PSSRU 2023, Round et al. (2015), TA788

OS, overall survival; PFS, progression-free survival; BNF, British National Formulary; PSSRU, Personal Social Services Research Unit; MIMS, Monthly Index of Medical Specialities; EQ-5D, European Quality of Life-5 Dimensions; 5L, 5 levels; 3L, 3 levels

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People with untreated unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy	As per scope	Definition of unresectable and advanced disease may differ among clinicians
Intervention	EV+P	As per scope	No comment
Comparators	**Cisplatin eligible:** • Gemcitabine plus cisplatin • Methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF]) **Cisplatin ineligible:** • Gemcitabine plus carboplatin • Atezolizumab (PDL-1 ≥5%)	MVAC only used as 1L for 2% of people so excluded. Atezolizumab used in 3% of people who are platinum-eligible	Reasonable to exclude MVAC Agree with excluding atezolizumab as a comparator.
Outcomes	OS, PFS, RR	As per scope	No comment

OS, overall survival; PFS, progression-free survival; RR, response rates; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin

EV-302 baseline characteristics

EAG: trial generally representative of relevant population

Baseline characteristics for intervention and comparator

Characteristic	EV + P (N=442)	PBC+Gem (N=444)
Median age (range), yr	69.0 (37-87)	69.0 (22-91)
Age ≥ 75 years, n (%)	102 (23.1)	108 (24.3)
Male, n (%)	344 (77.8)	336 (75.7)
ECOG status		
ECOG status 0, n (%)	223 (50.5)	215 (48.4)
ECOG status 1, n (%)	204 (46.2)	216 (48.6)
Disease status at randomization, n (%)		
Locally advanced	21 (4.8)	24 (5.4)
Metastatic	421 (95.2)	420 (94.6)
Cisplatin eligibility status, n (%)		
Eligible	240 (54.3)	242 (54.5)
Ineligible	202 (45.7)	202 (45.5)
PD-L1 expression, n/total n (%)		
High, CPS ≥10	254/438 (58.0)	254/439 (57.9)
Low, CPS <10	184/438 (42.0)	185/439 (42.1)

NICE

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; ECOG, Eastern Cooperative Oncology Group; PDL-1, programme death ligand 1; CPS, combined positive score

Adverse events

EAG clinical expert: EV+P would require additional ophthalmology management

Treatment-emergent adverse events of special interest for EV+P August 2024 data cut-off

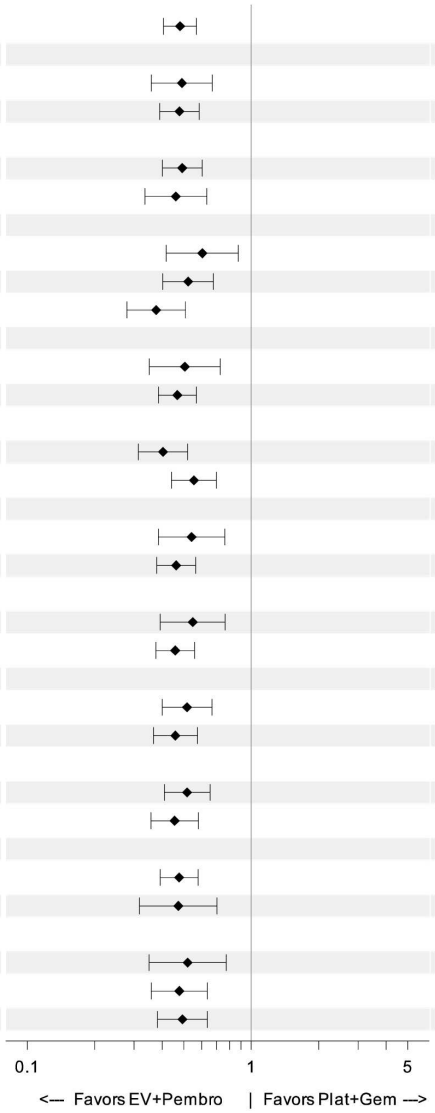
Adverse event	EV+P (N=440)	EV+P (N=440)	PBC+Gem (N=433)	PBC+Gem (N=433)
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Peripheral Neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Skin reactions	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
SCAR	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Ocular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]
Corneal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reactions	[redacted]	[redacted]	[redacted]	[redacted]

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

Subgroup analysis

PFS results for subgroups in EV-302 (data cut-off: 8 August 2024)

Subgroup	Median PFS, months (Events/N) EV+Pembro	Plat+Gem	Hazard Ratio (95% CI)
Overall	12.5 (262/442)	6.3 (317/444)	0.481 (0.407,0.570)
Age			
<65 years	14.6 (87/144)	6.4 (90/135)	0.490 (0.358,0.670)
>=65 years	12.3 (175/298)	6.2 (227/309)	0.478 (0.390,0.585)
Race			
White	10.5 (191/308)	6.2 (214/290)	0.492 (0.401,0.604)
Other	19.2 (71/134)	6.5 (103/154)	0.461 (0.335,0.633)
Region			
North America	10.3 (72/103)	6.3 (57/85)	0.605 (0.418,0.876)
Europe	10.4 (102/172)	6.3 (149/197)	0.523 (0.403,0.678)
Rest of World	19.3 (88/167)	6.2 (111/162)	0.376 (0.279,0.508)
Sex			
Female	10.4 (59/98)	6.1 (75/108)	0.505 (0.351,0.727)
Male	14.0 (203/344)	6.3 (242/336)	0.468 (0.385,0.569)
ECOG PS			
0	17.3 (121/223)	6.7 (151/215)	0.404 (0.314,0.520)
1-2	9.3 (141/219)	6.1 (166/227)	0.555 (0.440,0.699)
Primary disease site of origin			
Upper tract	12.3 (81/135)	6.2 (70/104)	0.542 (0.384,0.763)
Lower tract	12.8 (179/305)	6.3 (246/339)	0.462 (0.379,0.564)
Liver metastases			
Present	8.1 (74/100)	6.0 (80/99)	0.548 (0.392,0.766)
Absent	16.4 (188/342)	6.4 (237/345)	0.458 (0.376,0.557)
PD-L1 expression			
Low (CPS < 10)	10.5 (122/184)	6.3 (131/185)	0.517 (0.400,0.667)
High (CPS >= 10)	16.4 (138/254)	6.2 (182/254)	0.459 (0.365,0.576)
Cisplatin eligibility			
Eligible	15.0 (140/244)	6.5 (155/234)	0.518 (0.409,0.655)
Ineligible	10.6 (122/198)	6.1 (162/210)	0.455 (0.357,0.580)
Metastatic disease site			
Visceral metastases	10.4 (203/318)	6.2 (242/318)	0.477 (0.393,0.579)
Lymph node only	22.1 (50/103)	8.3 (60/104)	0.473 (0.317,0.704)
Renal function			
Normal	18.7 (47/84)	6.7 (64/95)	0.520 (0.350,0.774)
Mild	12.7 (91/165)	6.3 (118/162)	0.477 (0.358,0.636)
Moderate/Severe	10.5 (124/193)	6.2 (135/187)	0.493 (0.381,0.637)

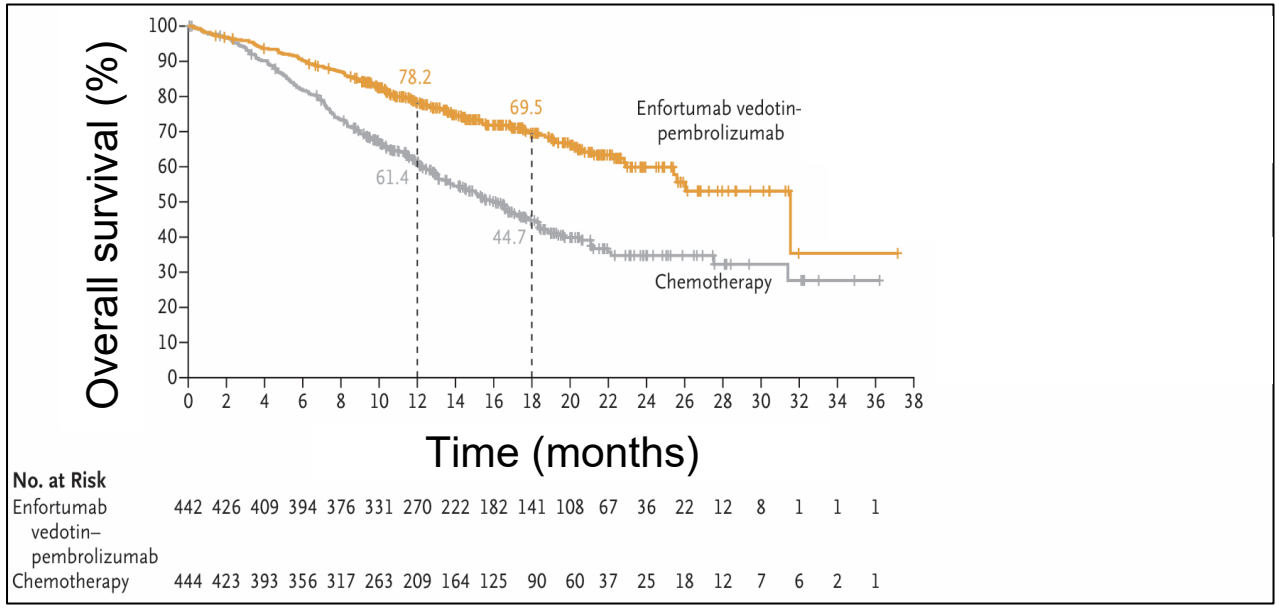


CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1

Clinical trial results - overall survival (ITT)

EV+P improves overall survival when compared with PBC+Gem

OS Kaplan-Meier plot August 2023 data cut-off



	August 2023 data cut-off	
	EV+P	PBC+Gem
Median OS, months (95% CI)	31.5 (25.4 to NE)	16.1 (13.9 to 18.3)
Number of events (%)	133 (NA)	226 (NA)
HR (95% CI; P value)	0.47 (0.38 to 0.58; P<0.001)	

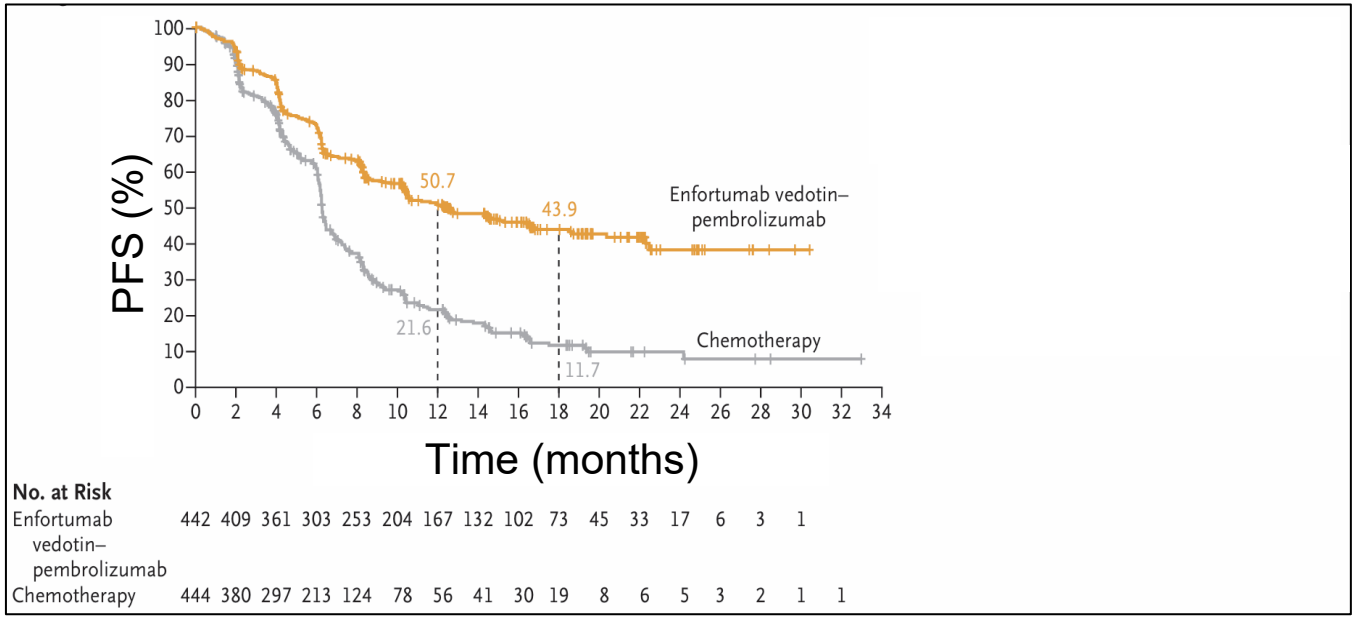
NICE

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; OS, overall survival; NE, not estimated, NA, not available

Clinical trial results - progression-free survival (ITT)

EV+P improves progression-free survival when compared with PBC+Gem

PFS Kaplan-Meier plot August 2023 data cut-off



	August 2023 data cut-off	
	EV+P	PBC+Gem
Median PFS, months (95% CI)	12.5 (10.4 to 16.6)	6.3 (6.2 to 6.5)
Number of events (%)	223 (NA)	307 (NA)
HR (95% CI; P value)	0.45 (0.38 to 0.54; P<0.001)	

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine; PFS, progression-free survival ; NE, not estimated, NA, not available

Issue: Progression-free survival extrapolation (1/3)

Company used spline models for extrapolating PFS

Background

- Company and EAG both applied independently fitted models for PFS extrapolation
- Disagree on choice of model to apply

Company

- Standard parametric curves do not capture changing hazard over time for EV+P and PBC+Gem
- Spline models best for capturing changing shape of curves over time, used in base case

Progression-free survival estimates (ITT)

*EV+P: hazard 2 knots; PBC+Gem: odds 3 knots

	EV+P			PBC+Gem		
Timepoint	2 years	5 years	10 years	2 years	5 years	10 years
Company expert estimate [Average (range)]	39% (36-50%)	25% (15-30%)	18% (7-25%)	9.5% (6-10%)	5% (3-7%)	3.5% (2-7%)
Company base case (spline fit)*	37.7%	25.6%	15.8%	11.5%	9.3%	5.0%
EAG base case (log-logistic)	35.2%	15.8%	7.7%	8.2%	1.6%	0.5%

PFS, progression-free survival; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

ICER impact: Small

Issue: Progression-free survival extrapolation (2/3)

EAG prefers a parametric model for extrapolating PFS

EAG comments

- Agree that initial observed hazards increase up to about 6 months then gradually fall
  →But log-logistic used for EAG base case also follows similar pattern
- With company's spline model, PFS crosses OS at about 8 years for EV+P
  - Company applied constraint in model to fix this
- EAG prefers parametric log-logistic models for both EV+P and PBC+Gem
  - Notes company use a different spline fit for each arm

See PFS hazard plots

Relationship between OS, PFS and ToT for EV+P

What is the committee's preferred approach for modelling PFS?

PFS, progression-free survival; OS, overall survival; ToT, time on treatment, EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

ICER impact: Small

Issue: Progression-free survival extrapolation (3/3)

Company and EAG PFS extrapolations

[redacted]

[redacted]

PFS, progression-free survival; KM, Kaplan-Meier; EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

Issue: Pre-progression utilities (1/2)

Company and EAG applied different pre-progression utilities

Background

- Treatment-dependent and independent utility values from EV-302 available
- Company and EAG disagree on which values to apply for pre-progression health state

Company

- Applied treatment-dependent utility value because treatment arm was a statistically significant covariate

EAG comments

- Adverse events expected for both EV+P and PBC+Gem, which affect utility values
- Lower utilities initially expected for PBC+Gem while on treatment (for about 4.5 months)
- But utilities expected to improve over 2-3 months and to be equal with EV+P arm
- Data shows no significant difference in utility values for both arms after 5 – 8 months
- EAG base case uses treatment-dependent utility values for the first 6 months for PBC+Gem then treatment-independent values for both PBC+Gem and EV+P after that

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

ICER impact: Small

Issue: Pre-progression utilities (2/2)

Company and EAG applied different pre-progression utilities

Health state	Treatment	EV-302 ITT Mean (SE)	Company base case	EAG base case
Pre-progression	**Treatment dependent**			
	EV+P	[redacted]	[redacted]	[redacted]
	PBC+Gem	[redacted]	[redacted]	[redacted] for first 6 months; [redacted] for remaining time in pre-progression
	Treatment-independent			
		[redacted]		
Post-progression	**Treatment-independent**			
		[redacted]	[redacted]	[redacted]

NICE

Should the utility values be based on treatment arm? What are the committee's preferred pre-progression utility values?

ITT, intention-to-treat; SE, standard error

ICER impact: Large

Issue: Treatment effect waning

Unclear if a treatment effect waning assumption should be applied

Background

- Treatment waning was not applied for the company or EAG base case
- There is no stopping rule for EV, but P has a 2-year stopping rule

Company

- Some people expected to remain on long-term EV treatment
- Base case applied independently fitted model, this should include any treatment effect waning

EAG comments

See treatment effect waning assumptions in recent NICE appraisals

- Independently fitted models that converge suggests waning accounted for
  →OS hazards for EV+P and PBC+Gem gradually converge
- Unclear if stopping pembrolizumab leads to treatment effect waning
- Explored scenarios assuming waning starts:
  I. when pembrolizumab treatment stops (at two years), and ends after five years
  II. when pembrolizumab treatment stops (at two years), and ends after seven years
  III. two years after pembrolizumab treatment stops (at four years), and ends after seven years
- Scenarios may over-estimate treatment waning effect because EV treatment would not be stopped

NICE Is it appropriate to apply a treatment effect waning assumption for any of the treatments?

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine

Relevant waning assumptions in recent NICE appraisals

Appraisal	Waning assumption
Pembrolizumab with axitinib, renal cell carcinoma (TA650)	• Not enough evidence to assume a life-time effect of pembrolizumab; treatment benefit waning should be applied. • Waning effect applied 5 years after starting pembrolizumab.
Lenvatinib with pembrolizumab renal cell carcinoma (TA858)	• Waning effect plausible, but uncertain. • Noted pembrolizumab limited to 2 years, but lenvatinib could continue after that time point. Uncertainty in the long-term treatment effect of pembrolizumab, but not possible to plausibly separate out any potential waning of treatment effect.
Pembrolizumab with lenvatinib endometrial cancer (TA904)	• Waning plausible, but uncertain. Preferred scenarios where treatment waning occurred 5-7 years after starting pembrolizumab treatment.
Pembrolizumab with trastuzumab gastric or gastro-oesophageal junction adenocarcinoma (TA983)	• Waning not discussed.

ICER impact: Small

ToT curves used in company base case (1/2)

Pembrolizumab costs set to £0 from 24 months – does not align with trial

Background

- In EV-302, pembrolizumab 200 mg IV given on day 1 of each 3-week cycle, to a maximum of 35 cycles

Company: People may have missed doses so maximum number of cycles later than 24 months.
Pembrolizumab ToT KM curve is complete so base case uses KM curve

NICE tech team: Company and EAG models set pembrolizumab costs to £0 from 24 months (approx. [redacted] remain on treatment). Scenarios are provided with pembrolizumab costs applied for full ToT KM

Should the model include pembrolizumab treatment costs beyond 24 months? Would a stopping rule apply for pembrolizumab in NHS practice? If so, what?

NICE

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

ToT curves used in company base case (2/2)

Summary of ToT curves used in company base case

Treatment	ITT	Cisplatin-eligible	Cisplatin-ineligible
EV	Log-logistic	Lognormal	Lognormal
Pembrolizumab[a]	K-M curve	K-M curve	K-M curve
PBC+Gem[b]	K-M curve	K-M curve	K-M curve
Avelumab[c]	Weibull	Weibull	Weibull

[a] K-M curve was complete, treatment stopping rule at 2 years
[b] K-M curve was complete; treatment stopping rule at 4.14 months (i.e. maximum of six three-week cycles of therapy)
[c] Treatment stopping rule at 60 months

ToT, time on treatment; KM, Kaplan-Meier

Values used to estimate QALY shortfall

Factor	Value
Sex distribution	77% male, 23% female
Starting age	67.9 years

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

OS hazards with parametric models for EV+P (ITT)

[redacted]

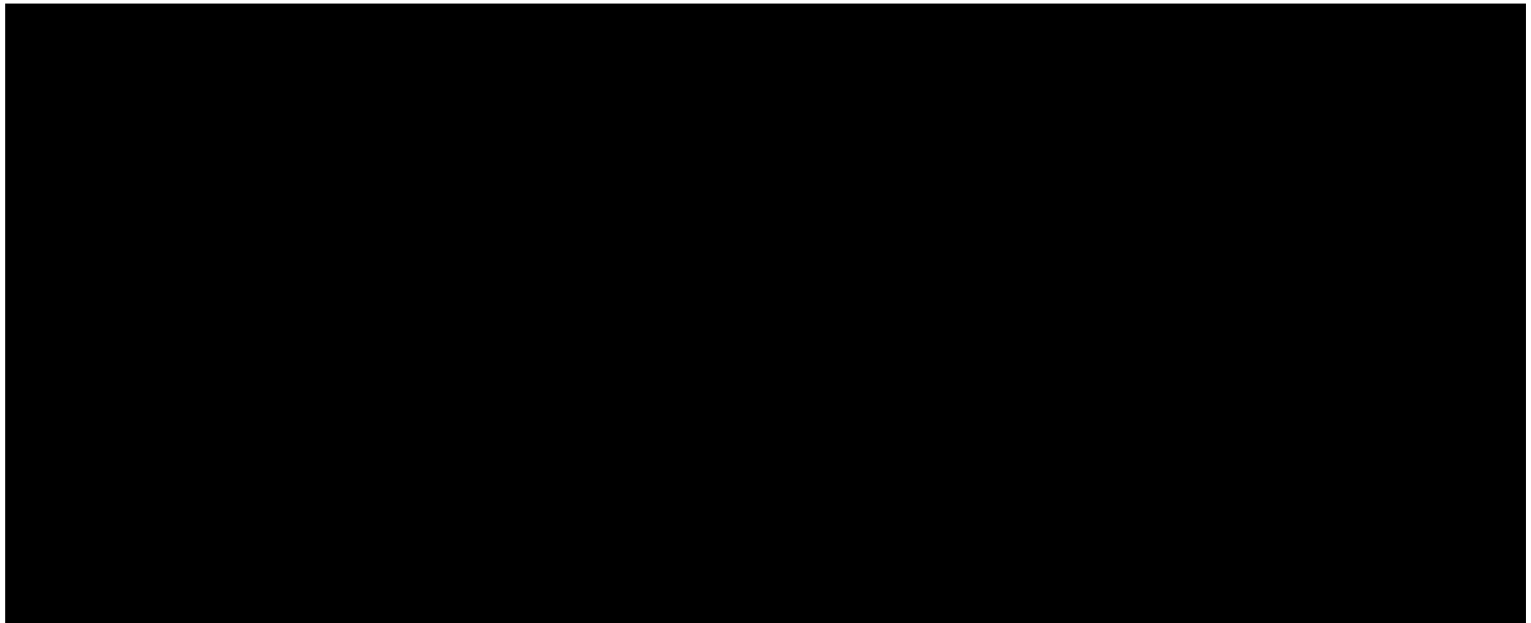
OS hazards with parametric models for PBC+Gem (ITT)

[redacted]

OS, overall survival; ITT, intention-to-treat

PFS hazards with parametric models for EV+P (ITT)

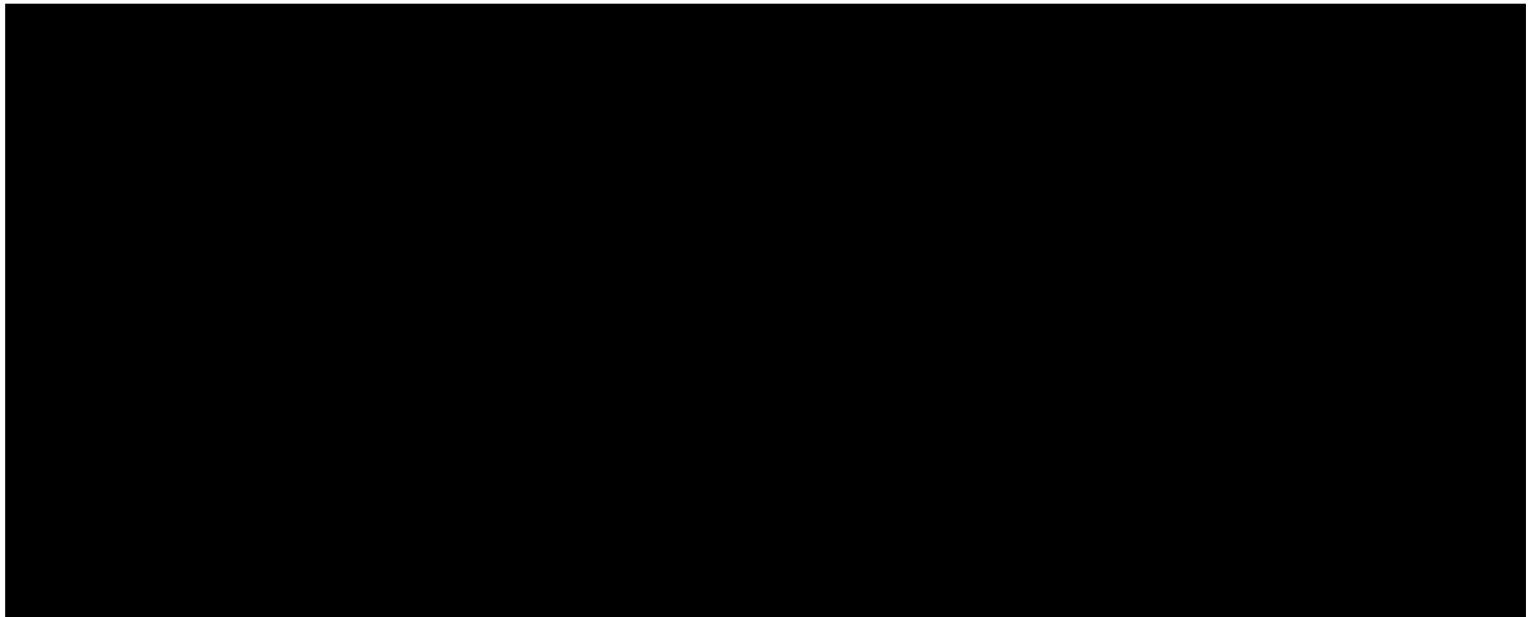
PFS hazards with parametric models for PBC+Gem (ITT)



PFS, progression-free survival; ITT, intention-to-treat

PFS hazards with spline models for EV+P (ITT)

PFS hazards with spline models for PBC+Gem (ITT)



PFS, progression-free survival

EAG: overall survival hazards over 30 years

EV, enfortumab vedotin; P, pembrolizumab; PBC, platinum-based chemotherapy; Gem, gemcitabine