Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

For public – contains redacted information

Second committee meeting [ACM2]

Technology appraisal committee A [14 April 2026]

Chair: Radha Todd

External assessment group: Southampton Health Technology Assessments Centre

Technical team: Dilan Savani, Caron Jones, Lizzie Walker

Company: Genmab

Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

- ✓ **Recap and key issues**
- ❑ Draft guidance consultation responses summary
- ❑ Company's additional analysis and EAG critique
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Tisotumab vedotin (Tivdak, Genmab)

Marketing authorisation	• As a monotherapy, 'indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy' • MHRA approval December 2025
Mechanism of action	• Antibody drug conjugate (ADC) that binds to tissue factor (TF) protein that is expressed in cervical cancer and other solid tumours • Upon binding, ADC-TF complex is internalised and local release of monomethyl auristatin E leads to cell death
Administration	Recommended dose: 2 mg/kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity
Price	• [redacted] per vial • Confidential patient access scheme in place

ADC-TF, antibody drug conjugate-tissue factor; MHRA, Medicines and Healthcare products Regulatory Agency

Committee's key conclusions from ACM1

Tisotumab vedotin should not be used; further information needed to decide all preferred assumptions

Issue	Committee's preferred assumption
Comparator(s)	• Single-agent chemotherapy is appropriate comparator
Model structure	• Assuming constant (exponential distribution) post-progression mortality is a limitation with company's semi-Markov model • Minded to prefer a partitioned survival model (PSM) structure • **Further evidence required**
OS assumptions	• Preferred using extrapolated curves over directly using KM data, if further exploration of OS curves provided reliable estimates of OS
Extrapolations of time to progression and pre-progression survival	• Pre-progression survival extrapolations added further uncertainty to the cost-effectiveness analysis using semi-Markov model
Administration costs for paclitaxel	• Preferred using SB13Z cost code for the administration of weekly paclitaxel

ACM1, First Appraisal Committee Meeting; KM, Kaplan-Meier; OS, overall survival; PSM, partitioned survival model

Committee's requests for additional analysis

Issue	Request	Provided?

Model structure	• Exploration of different standard parametric distributions within PSM for PFS and OS
	• Information about validity of distributions, including:
	  • visual fit to observed KM data from InnovaTV 301
	  • underlying hazard functions over time and validation by clinical experts
	  • clinical plausibility of extrapolations
	  • goodness-of-fit statistics
		Yes, but maintains use of semi-Markov model in base case

Administration costs for paclitaxel	• Updated chemotherapy administration costs using the latest NHS reference costs available	Yes, plus analysis using NHS payment scheme prices

see appendix for further information on NHS payment scheme costs and NHS cost collection

OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model

Key issues

Issue	ICER impact	Slide(s)
Appropriateness of semi-Markov model structure	Large	11,12,13,14,15
Direct use of KM data or extrapolations to model overall survival	Large	20, 21
Extrapolations of time to progression and pre-progression survival *(if use semi-Markov structure)*	Large	22
Severity modifier	Large	23

ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier

Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

- ❑ **Recap and key issues**
- ✓ Draft guidance consultation responses summary
- ❑ Company's additional analysis and EAG critique
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Overview of company's response

1 consultation response received from company. No responses received from other stakeholders

Changes in company's updated base case

- SB13Z cost code for administration of weekly paclitaxel
- Chemotherapy administration costs updated using: 1) NHS 2024/2025 reference costs and 2)NHS 2025/2026 payment scheme prices

Company's additional scenario analysis

- Semi-Markov model without direct KM data for first 12 months
- PSM model: gamma for OS for both treatments; log-logistic for PFS for both treatments
- PSM model: gamma for OS for both treatments (and HR=1 from month 18); log-logistic for PFS for both treatments
- PSM model: log-logistic (tisotumab vedotin OS) and gamma (chemotherapy OS); log-logistic (PFS for both treatments)

HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model

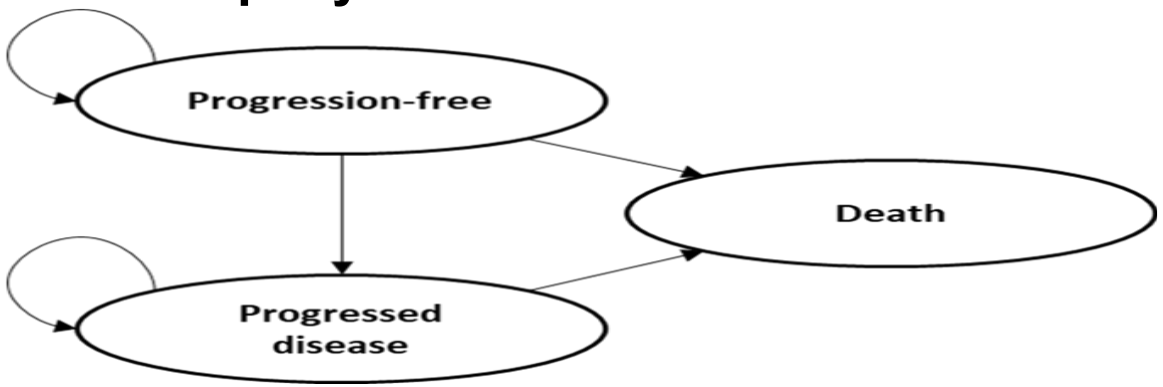
Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

- ❑ **Recap and key issues**
- ❑ Draft guidance consultation responses summary
- ✓ Company's additional analysis and EAG critique
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company's model overview

Company's model structure



Semi-Markov model without tunnel states

- **time horizon: 30 years**
- **cycle length: 1 week**

Tisotumab vedotin affects **costs** by:

- Increasing treatment acquisition costs
- Reducing drug administration cost

Tisotumab vedotin affects **QALYs** by:

- Increasing time to progression
- Increasing overall survival

Estimation of transition probabilities

1) Survival functions generated for each of the 3 health state transitions (PF to PD, PF to death and PD to death) using parametric multistate modelling approach
2) Estimated cause-specific hazards (PF to PD; PF to death and PD to death) converted to weekly transition probabilities
3) Cause-specific transition probabilities combined to reconstruct estimates of PFS and OS*, which are used to calculate health state occupancy

*trial KM data used to directly estimate OS during the first 12 months – see key issue slide for further details

KM, Kaplan-Meier; OS, Overall survival; PD, progressed disease; PF, progression free; PFS, Progression-free survival; QALY, quality-adjusted life year

Key Issue: Appropriateness of semi-Markov model structure (1)

Large impact

Company use semi-Markov model, EAG prefer partitioned survival model

See appendix for hazard plots and goodness of fit statistics

Background

- Company presented a semi-Markov model and assumed that risk of death after progression is constant and same in tisotumab vedotin and chemotherapy arms
- At ACM1, committee said evidence did not support constant post-progression mortality → requested further information about validity of standard parametric distributions, within a PSM structure for PFS and OS
- Committee also noted that survival estimates from extrapolations from chemotherapy arm of InnovaTV301 were higher than expected in clinical practice, which might mean that the tisotumab vedotin extrapolations were also higher than clinical practice

Company

- Maintain preference for use of semi-Markov model as it allows structural link (risk of death dependent on current heath state) between post-progression and death (application of constant post-progression survival using exponential distribution) → more accurate estimation of chemotherapy OS
- Did scenarios fitting standard parametric curves for both treatment arms from InnovaTV 301

ACM1, First Appraisal Committee Meeting; KM, Kaplan-Meier; OS, Overall survival; PFS, progression-free survival; PSM, partitioned survival model

Key Issue: Appropriateness of semi-Markov model structure (2)

In scenario with PSM, company prefer gamma distribution for chemotherapy and log-logistic or gamma distributions for tisotumab vedotin

Company

OS chemotherapy:

- No distribution closely fits the observed chemotherapy KM; log-normal and log-logistic closest visual fit (see OS curves slide) and best statistical fit
- Notable differences in observed vs predicted OS estimates at 1-year and 2-year landmarks from InnovaTV 301 and EMPOWER (cemiplimab vs chemotherapy in a similar population)
- Hazard plot showed early rise followed by modest decline
- Clinicians stated that none of the parametric extrapolations are clinically plausible and all overestimate OS; by 2-year landmark, OS is 10% at best in chemotherapy arm
- If forced to choose extrapolation, 2 clinicians stated gamma distribution, third did not pick
- **Prefers gamma distribution in PSM scenario**

OS tisotumab vedotin:

- Clinicians considered it difficult to advise on OS extrapolation
- Based on visual fit, weibull, log-logistic, gamma, and generalised gamma appear to provide a closest fit to trial data (see OS curves slide); weibull and gamma best statistical fit

OS, Overall survival; PFS, progression-free survival; PSM, partitioned survival model

Key Issue: Appropriateness of semi-Markov model structure (3)

Company

- Hazard plot suggests non-monotonic pattern with increasing hazards through week 70-80 before declining; tails uncertain due to limited number of people at risk
- **Prefers log-logistic and gamma distributions for PSM scenario**
- **Further exploratory analysis for OS:** Hazard ratio trend for gamma extrapolation implausible as chemotherapy more effective than tisotumab vedotin from 18 months onwards
- Scenario conducted with gamma for both treatment arms, with HR=1 from 18 months +
- Explored restricted cubic spline models but did not improve robustness of extrapolations
- **PFS:** log-logistic preferred choice for PSM scenario analysis for both arms based on visual and statistical fit (see appendix)

EAG comments

- Maintain view that PSM structure more appropriate than semi-Markov model structure
- Available evidence does not support assumptions for same and constant OS hazard after disease progression in both treatment arms

EAG, External assessment group; HR, hazard ratio; KM, Kaplan-Meier; OS, Overall survival; PFS, progression-free survival; PSM, partitioned survival model

Key Issue: Appropriateness of semi-Markov model structure (4)

EAG comments

OS chemotherapy: log-logistic, lognormal and generalised gamma distributions have a good visual fit to the InnovaTV301 KM and also best statistical fit

- Agree that shape of hazard function not definitive but initial increase and subsequent gradual decline of smoothed hazard function suggests that distribution with non-monotonic hazard (log-logistic, lognormal or generalised gamma) would be appropriate
- Log-logistic, lognormal and generalised gamma estimates are within [redacted] percentage points of InnovaTV301 KM at 1 year, and within [redacted] percentage points at 2 years
- InnovaTV301 KM OS estimates for chemotherapy are similar to those from EMPOWER at 1 year but considerably higher at 2 years
- Acknowledges uncertainty due overlap of trial KM plots (see appendix) but trial does not provide evidence of persistent survival benefit beyond [redacted]
- Better than expected survival in control arm at 24 months likely due to low patient numbers; also possible that people in trial have better outcomes than in clinical practice
- **Prefers log-logistic with risk of mortality same in both treatment arms from point where OS curves converge (month 45)**

EAG, External assessment group; KM, Kaplan-Meier; OS, Overall survival; PFS, progression-free survival; PSM, partitioned survival model

Key Issue: Appropriateness of semi-Markov model structure (5)

EAG comments

OS tisotumab vedotin: weibull, gamma and generalised gamma curves are all very similar and have a good visual fit to KM; log-logistic also reasonable

  - These 4 curves have best statistical fit to InnovaTV 301 data

- Predictions from best fitting distributions are also close to the KM estimates from phase 2 InnovaTV204 trial at 1 year but weibull, gamma and generalised gamma all lower than InnovaTV204 OS at 2 and 3 years
- Agree that hazard plot suggests initially increasing then decreasing hazards→ weibull, generalised gamma and gamma distributions, which show a continually increasing hazard, are not consistent with observed hazard
- **Prefers log-logistic**
- **PFS:** preference in line with company's PSM scenario (log-logistic for both arms); ICER not sensitive to choice of PFS extrapolation in PSM model

Is it more appropriate to use a semi-Markov model or partitioned survival model?

EAG, External assessment group; ICER, incremental cost-effectiveness ratio, KM, Kaplan-Meier; OS, Overall survival; PFS, progression-free survival; PSM, partitioned survival model

Semi-Markov (company base case curves): overall survival

Landmark survival rates company base

	12 m	24 m	36 m	48 m
Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]

OS curves: Company base case (semi-Markov) including KM for first 12 months, with InnovaTV 301 KM

CHEM; chemotherapy; KM, Kaplan-Meier; OS, Overall survival; TV, tisotumab vedotin

PSM (EAG base case curves): overall survival (2)

Landmark survival rates EAG base case

	12 m	24 m	36 m	48 m
Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]

OS curves: EAG base case (log-logistic OS for chemo and TV), with InnovaTV 301 KM

CHEM; chemotherapy; EAG, External Assessment Group; KM, Kaplan-Meier; OS, Overall survival; PSM, partitioned survival model
TV, tisotumab vedotin

PSM: Standard parametric distribution curves overall survival – chemotherapy (1)

Landmark survival rates chemotherapy: company's PSM scenario

	12 m	24 m	36 m	48 m
TV301 KM	[redacted]	[redacted]	-	-
EMPOWER	34.26%	11.30%	7.23%	-
Gamma (company scenario)	[redacted]	[redacted]	[redacted]	[redacted]

Observed KM and [top four] predicted OS curves for chemotherapy within PSM structure

See appendix for landmark survival rates for other distributions

Note: log-logistic for EAG base case

KM, Kaplan-Meier; OS, Overall survival; PSM, partitioned survival model

PSM: Standard parametric distribution curves overall survival – tisotumab vedotin (2)

Landmark survival rates tisotumab vedotin: company's PSM scenario vs observed

	12 m	24 m	36 m	48 m
TV301 KM	[redacted]	[redacted]	-	-
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

See appendix for landmark survival rates for other distributions

Observed KM and [top four] predicted OS curves for tisotumab vedotin within PSM structure

[redacted]

Note: log-logistic for EAG base case

KM, Kaplan-Meier; OS, Overall survival; PSM, partitioned survival model; TV, tisotumab vedotin

Key Issue: Direct use of KM data or extrapolations to model OS (1)

Large impact

Company use direct KM data to model OS for first 12 months; EAG prefer to not directly use KM

Background

- Rather than using modelled estimates based on transition probabilities to death health state, company used KM data from InnovaTV 301 to override modelled OS for first 12 months
- At ACM1, committee requested further exploration of OS curves, but preferred to use extrapolated curves over directly using KM data

Company

- Standard parametric curves did not provide reliable estimates of OS (see key issue slide)
- Implementing semi-Markov with fitted curves from time zero (included as a scenario) also led to overestimation of chemotherapy OS in first 12 months and underestimation of OS for tisotumab vedotin over same period

Semi-Markov with fitted curves from time 0

ACM1, First Appraisal Committee Meeting; EAG, External assessment group; KM, Kaplan-Meier; OS, Overall survival; PSM, partitioned survival model; TV, tisotumab vedotin

Key Issue: Direct use of KM data or extrapolations to model OS (2)

Company use direct KM data to model OS for first 12 months; EAG prefer to not directly use KM

Company

- Direct use of KM data for first 12 months results in more plausible extrapolations;12-month cutoff used because until this timepoint, number at risk still meaningful
- **Company base case:** InnovaTV 301 OS KM curve for first 12 months then extrapolations based on semi-Markov model

EAG comments

- Risk of bias from post-hoc decision to use KM data to override OS model predictions for first 12 months
- Fitted parametric curves show an acceptable fit to available data from InnovaTV301 trial
- Maintains preference not to use KM data to override model predictions for first 12 months

What is the committee's preferred method for estimating OS?
Company base case: semi-Markov model with KM OS data for first 12 months
EAG base case: partitioned survival model with no direct use of KM data

EAG, External assessment group; KM, Kaplan-Meier; OS, Overall survival; PSM, partitioned survival model

If semi-Markov model used **only**

Large impact

Key issue: Extrapolations of time to progression and pre-progression survival

EAG: in semi-Markov model, cost-effectiveness results sensitive to choice of extrapolation

Background

- At ACM1, committee concludes pre-progression survival extrapolations added further uncertainty to the cost-effectiveness analysis using the semi-Markov model

Company

- Base case: Generalised gamma distribution for time to progression for both treatment arms. For post-progression survival: Gompertz distribution for tisotumab vedotin and lognormal distribution for chemotherapy (see appendix for KM and extrapolations)

EAG comments

- Time to progression extrapolations uncertain due to periodic timing of assessments and diminishing sample size
- Pre-progression survival: high degree of uncertainty due to low number of observed events
  Scenario analyses conducted to assess sensitivity to choice of distribution

If the committee prefers a semi-Markov model structure, what is the preferred distribution for estimating time to progression and pre-progression survival?

ACM1, First Appraisal Committee Meeting; EAG, External assessment group; KM, Kaplan-Meier

QALY weightings for severity

See appendix for summary of company's preferred assumptions for general population QALY shortfall estimates

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 weight driven by EAG's preference for PSM with log-logistic distribution for both arms
- Company: 45 out of 49 PSM scenarios conducted produced incremental QALY consistent with severity weighting of 1.7

	QALYs of people without condition	QALYs with condition on current treatment	Absolute shortfall	Proportional shortfall
Company base case	14.45	[redacted]	[redacted]	[redacted]
EAG base case	14.45	[redacted]	[redacted]	[redacted]

Company base case QALY weight: **1.7**
EAG base case QALY weight: **1.2**

Does the committee agree it is appropriate to apply a QALY weighting for severity?

EAG, External Assessment Group; PSM, partitioned survival model; QALY, quality-adjusted life year

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Model structure	Semi-Markov model with assumption that risk of death is constant and same after progression in both arms	Partitioned survival model with assumption that mortality hazard is the same in both arms from point where OS curves converge
OS curve	Direct use of InnovaTV 301 OS KM curve for first 12 months	No use of direct KM data for OS; use log-logistic distribution in both arms
Cost for administration of paclitaxel	Cost code: SB13Z –NHS payment scheme 2025-26 tariff*	Cost code: SB13Z - NHS 2024-25 'reference costs', or National Cost Collection data*
Severity modifier	x1.7 QALY weighting	x1.2 QALY weighting

*see appendix for further information on NHS payment scheme costs and NHS cost collection

For other issues not included as key issue at ACM1 due to less significant impact on results – see appendix

Cost-effectiveness results

- All ICERs reported in PART 2 slides because they include confidential discounts
- When confidential discounts included, updated company base case above range normally considered cost-effective use of NHS resources
- EAG base case substantially above range normally considered cost-effective use of NHS resources
- Scenarios presented applied to both company and EAG base cases

EAG, External assessment group; ICER, incremental cost-effectiveness ratio;

Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

- ❑ **Recap and key issues**
- ❑ Draft guidance consultation responses summary
- ❑ Company's additional analysis and EAG critique
- ✓ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Equality considerations

No additional equalities issues identified at consultation

Company:

- In England, cervical cancer rates are 65% higher in most deprived socio-economic quintile vs the least deprived
- Screening rates lower among women in deprived populations
- Evidence suggests HPV vaccine uptake is lower among more deprived, and non-white ethnic populations

Clinical expert:

- Use of technology will not be affected by equality issues other than a potential for improved access→ tisotumab vedotin delivered every 3 weeks rather than every week (if using weekly paclitaxel). Weekly administration could be limiting for people with transport difficulties

Patient expert:

- Access to new treatments can be unequal, with geographic, financial, age, and cultural factors affecting who can benefit fully

Are there any additional potential equality issues that need to be considered?

Other considerations

Managed access

Company have not submitted managed access proposal

Potential uncaptured benefits

Benefits not captured in QALY calculation, as per company submission:

- Health-related quality of life of family members not included (as per reference case) but cervical cancer often affects young women often with children → even small improvements in survival would allow people with cervical cancer to spend more time with their families

Are there any benefits that have not been captured in the modelling?

QALY, quality-adjusted life year

Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

- ❑ **Recap and key issues**
- ❑ Draft guidance consultation responses summary
- ❑ Company's additional analysis and EAG critique
- ❑ Other considerations
- ✓ Summary

NICE National Institute for Health and Care Excellence

Key issues

Issue	ICER impact	Slide(s)
Appropriateness of semi-Markov model structure	Large	11,12,13,14,15
Direct use of KM data or extrapolations to model overall survival	Large	20, 21
Extrapolations of time to progression and pre-progression survival *(if use semi-Markov structure)*	Large	22
Severity modifier	Large	23

ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier

Key committee questions

Key issue/ parameter	Key Committee Questions
Model structure	Is it more appropriate to use a semi-Markov model or partitioned survival model?
Direct use of KM data or extrapolations to model OS	What is the committee's preferred method for estimating OS? Company base case: semi-Markov model with KM OS data for first 12 months EAG base case: partitioned survival model without direct use of KM OS data
Extrapolations of TTP and pre-progression survival	If the committee prefers a semi-Markov model structure, what is the preferred distribution for estimating time to progression and pre-progression survival?
Administration cost of paclitaxel	Is it more appropriate to use NHS reference costs or NHS payment scheme prices (company base case) for chemotherapy administration costs?

NICE

EAG, External assessment group; KM, Kaplan-Meier; OS, overall survival; TTP, time to progression

Key committee questions

Key issue/ parameter	Key Committee Questions
QALY weighting	Does the committee agree it is appropriate to apply a QALY weighting for severity?
Other considerations	• Are there any equality issues that need to be considered? • Are there any benefits that have not been captured in the modelling?
Preferred ICER and threshold	• What is the committee's preferred ICER threshold - and why? • What is the committee's preferred ICER?

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

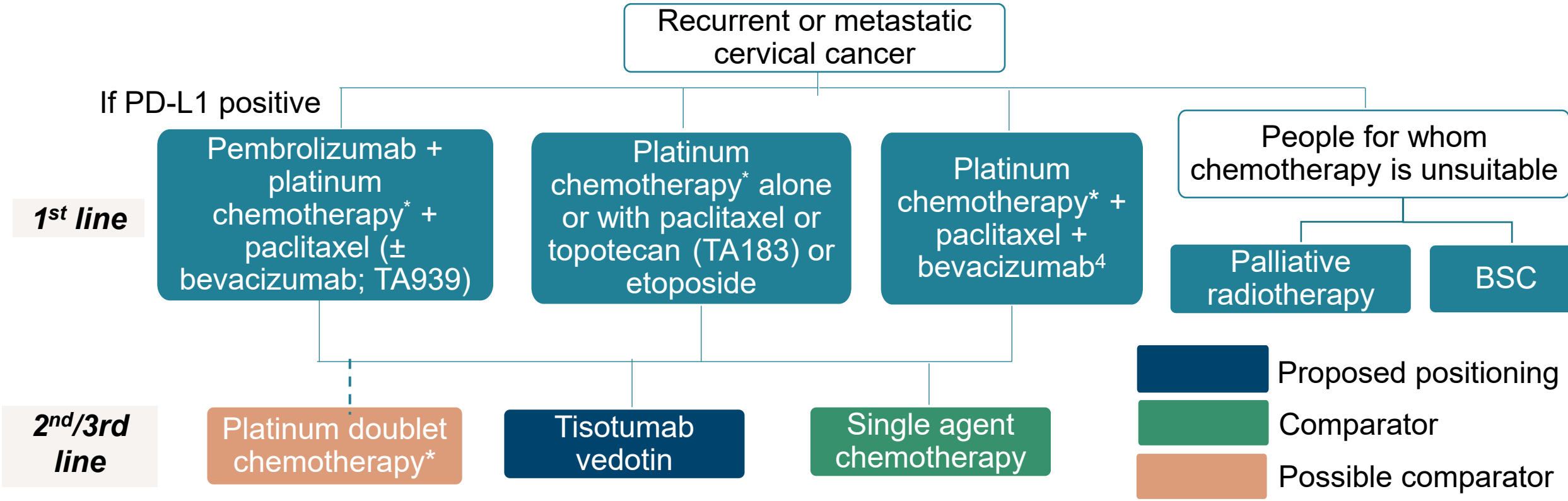
Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

Supplementary appendix

NICE National Institute for Health and Care Excellence

Treatment pathway and positioning

Company positioned tisotumab vedotin in line with single-agent chemotherapy



*Cisplatin or carboplatin

EAG: clinical experts advised platinum doublet therapy commonly used 2nd line

BSC, best supportive care; PD-L1, Programmed Death-Ligand 1

Key clinical trials: InnovaTV 301 (1)

Clinical trial design and outcomes

	InnovaTV 301
Design	Phase 3, randomised, global, open-label study
Population	People with r/m cervical cancer who have received 1 or 2 prior lines of systemic therapy
Intervention	Tisotumab vedotin (n=253)
Comparator(s)	Investigator's choice of chemotherapy (n=249; topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed)
Duration	Overall survival median follow-up times: 10.8 months (95% CI: 10.3, 11.6; primary analysis dated 24 July 2023) [redacted]; ad-hoc follow-up analysis dated 16 January 2024)

CI, confidence interval; r/m, recurrent or metastatic

Key clinical trials: InnovaTV 301 (2)

Clinical trial design and outcomes

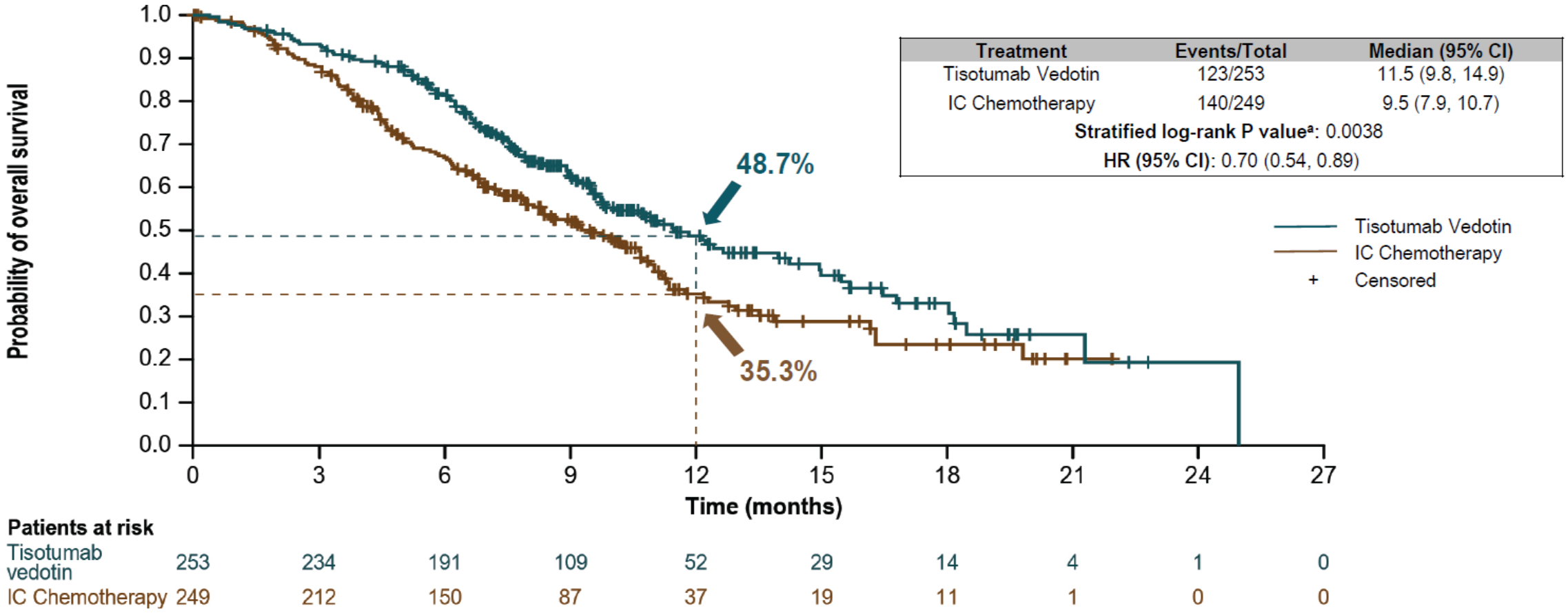
	InnovaTV 301
Primary outcome	Overall survival
Key secondary outcomes	Progression-free survival, response rates, adverse effects of treatment, HRQoL
Locations	168 sites in 27 countries including North America, Asia, Europe, and Latin America. [redacted] participants from the UK were enrolled ([redacted] in each arm)
Used in model?	Yes

HRQoL, health-related quality of life

Key clinical trial results – OS (primary analysis)

Tisotumab vedotin demonstrated a 30% reduction in the risk of death compared to investigator's choice of chemotherapy; results statistically significant

Kaplan-Meier Estimate of Overall Survival with tisotumab vedotin vs. Investigator's Choice Chemotherapy (ITT Population); primary analysis (July 2023)



Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	123/253	11.5 (9.8, 14.9)
IC Chemotherapy	140/249	9.5 (7.9, 10.7)

Stratified log-rank P value[a]: 0.0038

HR (95% CI): 0.70 (0.54, 0.89)

Patients at risk

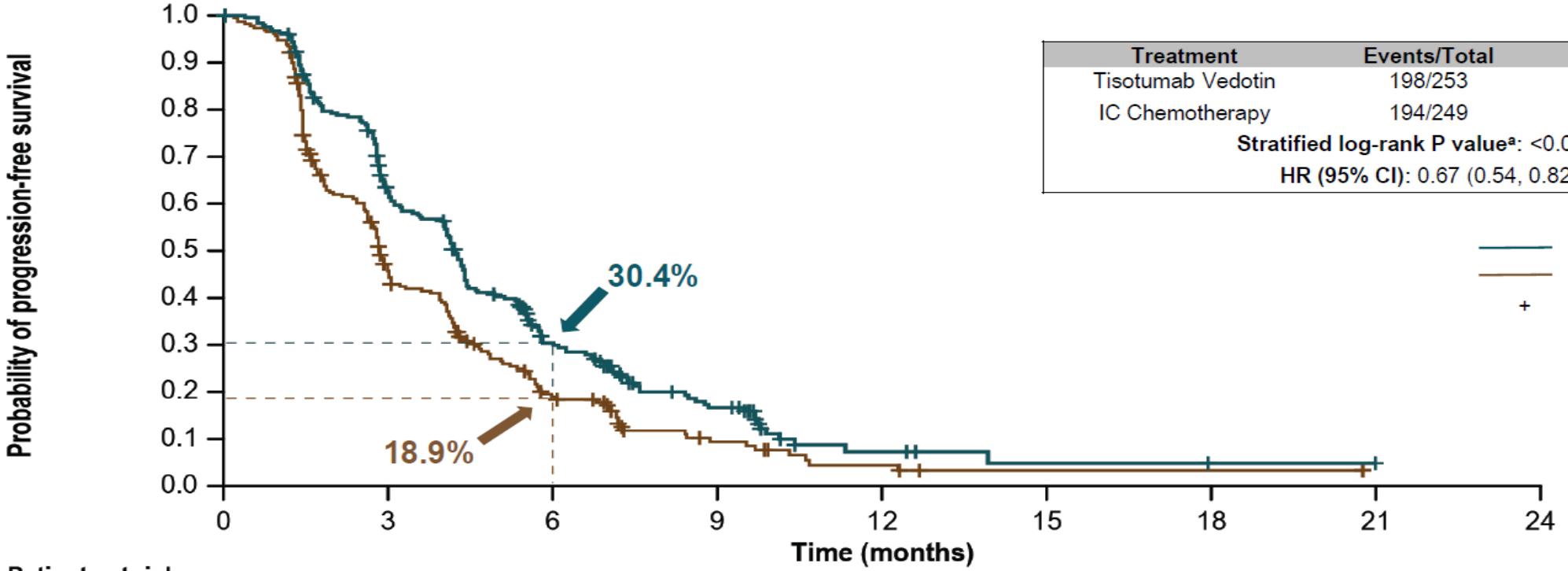
Tisotumab vedotin	253	234	191	109	52	29	14	4	1	0
IC Chemotherapy	249	212	150	87	37	19	11	1	0	0

CI, confidence interval; HR, hazard ratio; IC, investigator's choice; ITT, intention to treat; OS, overall survival

Key clinical trial results – PFS (primary analysis)

Tisotumab vedotin demonstrated a 33% reduction in the risk of disease progression or death compared to investigator's choice of chemotherapy; results statistically significant

Kaplan-Meier Estimate of Progression-Free Survival with tisotumab vedotin vs. Investigator's Choice Chemotherapy (ITT Population); primary analysis (July 2023)



Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	198/253	4.2 (4.0, 4.4)
IC Chemotherapy	194/249	2.9 (2.6, 3.1)

Stratified log-rank P value[a]: <0.0001

HR (95% CI): 0.67 (0.54, 0.82)

Patients at risk

Tisotumab vedotin	253	148	62	25	5	2	1	0	0
IC Chemotherapy	249	96	34	11	4	1	1	0	0

CI, confidence interval; HR, hazard ratio; IC, investigator's choice; ITT, intention to treat; PFS, progression-free survival

Key clinical trial results – OS and PFS (follow up analysis)

KM Estimate of OS with tisotumab vedotin vs. Investigator's Choice Chemotherapy (ITT Population); follow up analysis (January 2024)

KM Estimate of PFS with tisotumab vedotin vs. Investigator's Choice Chemotherapy (ITT Population); follow up analysis (January 2024)

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression-free survival

Key clinical trials: InnovaTV 204

Clinical trial design and outcomes

	InnovaTV 204
Design	Phase 2, single-arm, multicentre study
Population	People with previously treated r/m CC who experienced disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards)
Intervention	Tisotumab vedotin
Duration	Median follow-up time: 10.0 months (IQR 6.1-13.0; primary analysis) Not reported for final analysis
Primary outcome	Confirmed overall response rate (assessed by independent review committee)
Key secondary outcomes	Progression-free survival, confirmed overall response rate (assessed by investigator), time to response, duration of response, incidence of adverse events
Locations	35 sites in the US and Europe
Used in model?	Used validate the predicted efficacy for tisotumab vedotin in model

CC, cervical cancer; IQR, interquartile range; r/m, recurrent or metastatic

InnovaTV 301 chemotherapy OS: survival analysis (1)

Predicted hazard plot from the [top four] fitted models for OS on chemotherapy

AIC and BIC of fitted parametric curves of OS on chemotherapy

Parametric curves	AIC	BIC
Log-logistic	1749.44	1756.48
Log-normal	1753.73	1760.77
Generalised Gamma	1753.96	1764.51
Gamma	1758.16	1765.19
Weibull	1761.88	1768.92
Exponential	1770.30	1773.82
Gompertz	1771.12	1778.16

NICE

AIC, Akaike Information Criterion; BIC, Bayesian information criterion; OS, overall survival

InnovaTV 301 chemotherapy OS: survival analysis (2)

Chemotherapy landmark OS rates

	Observed OS		Predicted OS based on standard parametric functions						
Time point	EMPOWER KM	InnovaTV 301 KM	Exponential	Weibull	Log-Logistic	Log-normal	Gompertz	Gamma	Generalised Gamma
1 years	34.26%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ (predicted – observed in TV301)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	11.30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ (predicted – observed in TV301)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	7.23%	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results are based on parametric survival functions fitted independently, without applying the assumption that TV and chemotherapy OS curves converge and remain identical after the point of convergence

KM, Kaplan-Meier; OS, overall survival; TV, tisotumab vedotin

EMPOWER trial OS

EMPOWER OS in overall trial population

OS, overall survival

InnovaTV 301 tisotumab vedotin OS: survival analysis (1)

Predicted hazard plot from the [top four] fitted models for OS on tisotumab vedotin

AIC and BIC of fitted parametric curves of OS on tisotumab vedotin

Parametric curves	AIC	BIC
Weibull	1816.30	1823.37
Gamma	1816.32	1823.39
Log-logistic	1818.89	1826.96
Generalised Gamma	1817.95	1828.55
Gompertz	1827.49	1834.56
Log-normal	1832.32	1839.39
Exponential	1850.99	1854.52

NICE

AIC, Akaike Information Criterion; BIC, Bayesian information criterion; OS, overall survival

InnovaTV 301 tisotumab vedotin OS: survival analysis (2)

Tisotumab vedotin landmark OS rates

	Observed OS		Predicted OS based on standard parametric functions						
Time point	innovaTV 204 KM	innovaTV 301 KM	Exponential	Weibull	Log-Logistic	Log-normal	Gompertz	Gamma	Generalised Gamma
1 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ (predicted – observed in TV301)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ (predicted – observed in TV301)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results are based on parametric survival functions fitted independently, without applying the assumption that TV and chemotherapy OS curves converge and remain identical after the point of convergence

KM, Kaplan-Meier; OS, overall survival; TV, tisotumab vedotin

InnovaTV 301 chemotherapy PFS: survival analysis (1)

Predicted hazard plot from the [top four] fitted models for PFS on chemotherapy

Observed K-M and [top four] predicted PFS curves for chemotherapy

AIC and BIC of fitted parametric curves of chemotherapy PFS

Parametric curves	AIC	BIC
Log-logistic	1528.51	1535.54
Log-normal	1529.17	1536.21
Generalised Gamma	1530.62	1541.17
Gamma	1556.79	1563.82
Weibull	1568.71	1575.75
Exponential	1580.86	1584.37
Gompertz	1582.86	1589.89

AIC, Akaike Information Criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; PFS, progression-free survival

InnovaTV 301 chemotherapy PFS: survival analysis (2)

Chemotherapy PFS rates

	Observed PFS		Predicted chemotherapy PFS based on standard parametric functions						
Time point	EMPOWER KM	innovaTV 301 KM	Exponential	Weibull	Log-Logistic	Log-normal	Gompertz	Gamma	Generalised Gamma
1 years	6.74%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ (predicted – observed in TV301)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ (predicted – observed in TV301)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results are based on parametric survival functions fitted independently, without applying the cap of PFS by OS curves in the model

KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

InnovaTV 301 tisotumab vedotin PFS: survival analysis (1)

Predicted hazard plot from the [top four] fitted models for PFS on tisotumab vedotin

Observed K-M and predictive PFS curves for tisotumab vedotin

AIC and BIC of fitted parametric curves of tisotumab vedotin PFS

Parametric curves	AIC	BIC
Log-normal	1760.46	1767.53
Log-logistic	1761.29	1768.36
Generalised Gamma	1760.87	1771.47
Gamma	1787.00	1794.07
Weibull	1798.91	1805.98
Exponential	1814.95	1818.48
Gompertz	1816.64	1823.71

AIC, Akaike Information Criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; PFS, progression-free survival; TV, tisotumab vedotin

InnovaTV 301 tisotumab vedotin PFS: survival analysis (2)

Chemotherapy PFS rates

	Observed PFS		Predicted tisotumab vedotin PFS based on standard parametric functions						
Time point	innovaTV 204 K-M	innovaTV 301 K-M	Exponential	Weibull	Log-Logistic	Log-normal	Gompertz	Gamma	Generalised Gamma
1 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ between predicted and observed			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ between predicted and observed			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results are based on parametric survival functions fitted independently, without applying the cap of PFS by OS curves in the model

OS, overall survival; PFS, progression-free survival

Overlay of observed KM and predicted curves for time to progression

Overlay of observed KM and predicted curves of TTP for tisotumab vedotin

Company base case: generalised gamma

Overlay of observed KM and predicted curves of TTP for chemotherapy

Company base case: generalised gamma

EAG, External assessment group; KM, Kaplan-Meier; PF, progression free; TTP, time to progression

Overlay of observed KM and predicted curves for pre-progression survival

Overlay of observed KM and predicted curves of time from PF to death for tisotumab vedotin

Company base case: Gompertz

Overlay of observed KM and predicted curves of time from PF to death for chemotherapy

Company base case: lognormal

EAG, External assessment group; KM, Kaplan-Meier; PF, progression free

Cost sources for chemotherapy administration

The **National Cost Collection** (previously NHS reference costs) comprises aggregated costs (the average unit cost of providing defined services to NHS patients in England) and patient-level costs/PLICS (a cost based on the specific interactions a patient has, and the events related to their healthcare activity).

The **NHS Payment Scheme** is a set of rules, prices and guidance
that determine how providers of NHS-funded healthcare are paid for the services they provide

NICE manual: The national average unit cost of an HRG is reported as part of the annual mandatory collection of reference costs from all NHS organisations in England. Using these costs can reduce the need for local micro-costing (costing of each individual component of care related to a technology).

EAG

- Preference to use 2024-2025 NHS National Cost Collection 2024-2025 (reference costs) for chemotherapy administration costs as reference costs have been used conventionally for costing in NICE guidance

EAG, External assessment group; HRG, Healthcare Resource Groups; PLICS, Patient Level Information and Costing Systems

Other differences between company and EAG base cases (1)

Parameter	Overview
Comparator chemotherapy mix	**Company:** costs for chemotherapy arm analysis calculated based on distribution of single-agent chemotherapies used in UK clinical practice, estimated survey of 8 clinicians **EAG:** EAG's experts advised distribution in company's base case not reflective of UK clinical practice. Rechallenge with platinum-based doublet considered in some cases. Preferred distribution estimates from 1 clinical expert that were renormalised across single-agent chemotherapy options (platinum double excluded because single agent chemotherapy was comparator specified in NICE scope)
Subsequent treatment mix (post progression)	**Company:** for people who receive treatment post-progression, assumed equal split between topotecan, gemcitabine and paclitaxel (33% each) for both arms **EAG:** EAG's clinical experts noted that paclitaxel would be used more frequently than the other single-agent subsequent treatments. Preferred distribution estimated by EAG's clinical experts

EAG, External assessment group

See base case summary slide for company and EAG base case assumptions

Other differences between company and EAG base cases (2)

Parameter	Overview
Resource use for disease management	**Company:** included costs for routine disease management, with assumption that same costs apply before and after progression due to lack of state-specific data. Resource use estimated based on Cancer research UK 'Follow up after cervical cancer treatment' information **EAG:** EAG's clinical experts stated company's follow-up estimates not reflective of UK clinical practice and estimates appeared more consistent with radical chemoradiotherapy rather than metastatic disease management. Preferred resource use estimated by EAG's clinical experts

See base case summary slide for company and EAG base case assumptions

EAG, External assessment group

Additional company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Comparator chemotherapy mix	Topotecan: 4.7%; Vinorelbine: 2.0%; Gemcitabine: 28.4%; Irinotecan: 0.3%; Pemetrexed: 0.3%; Paclitaxel: 64.3%	Topotecan: 11.1%; Vinorelbine: 0%; Gemcitabine: 22.1%; Irinotecan: 0%; Pemetrexed: 0%; Paclitaxel: 66.7%
Subsequent treatment mix (post-progression)	33% each for Topotecan, Gemcitabine and Paclitaxel	Topotecan: 10%; Gemcitabine 30%; Paclitaxel 60%
Resource use for disease management (see next slide for estimates)	Based on Cancer Research UK 'Follow up after cervical cancer treatment' information	Based on estimates by EAG's clinical experts

EAG, External assessment group; KM, Kaplan-Meier; OS, Overall survival

Additional company and EAG base case assumptions (2)

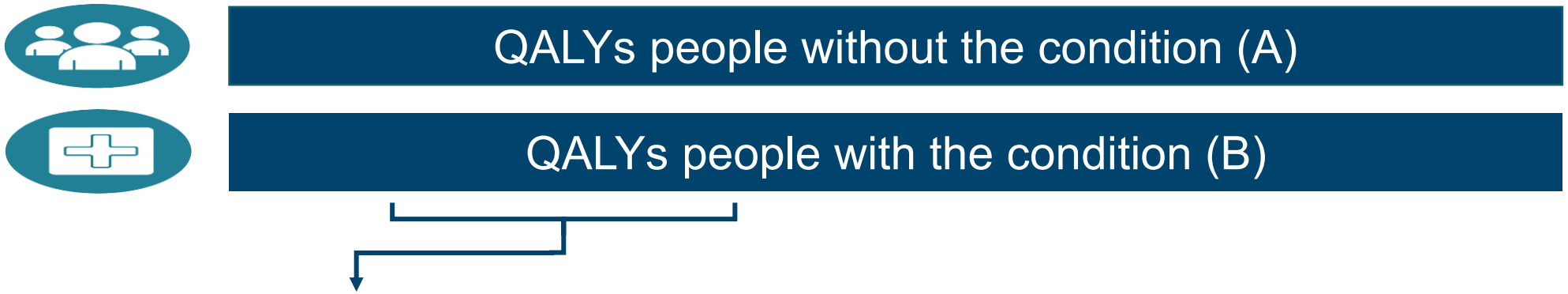
Assumptions in company and EAG base case

Assumption		Company base case			EAG base case		
Annual frequency of resource use for disease management†		**Year 1-2**	**Year 3-5**	**Year 6+**	**Year 1-2**	**Year 3-4**	**Year 5-6**
	Oncologist visit	3	2	1	**4**	**2**	**1**
	Blood tests	3	2	1	4	2	1
	Chemistry panel	3	2	1	4	2	1
	Colposcopy	1	1	1	0	0	0
	PET-CT scan	2	1	1	0	0	0
	Chest X-ray	3	2	1	0	0	0
	MRI scan	2	1	1	0	0	0
	CT scan	0	0	0	4	2	1

CT, computed tomography; EAG, External assessment group; MRI, magnetic resonance imaging; PET, positron emission tomography

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, quality-adjusted life year

QALY weightings summary- general population estimates

Summary of company's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source
Sex distribution	100% female
Starting age	[redacted]
Expected years of life	ONS UK life tables 2021-2023
Quality of life by age	McNamara et al. 2023
Discount rate	Not stated by company, but results are consistent with 3.5% per year

ONS, Office for National Statistics; QALY, quality-adjusted life year