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

For public – contains redacted information

Technology appraisal committee A [10 February 2026]

Chair: Radha Todd

Lead team: Victoria Houghton, Ravi Ramessur, James Fotheringham

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

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

NICE National Institute for Health and Care Excellence

Background on recurrent or metastatic cervical cancer

Causes

- Develops when abnormal cells in lining of cervix grow in an uncontrolled way and form a tumour
- Infection with human papillomavirus (HPV) is associated with development of cervical cancer; HPV detected in 99.7% of cases

Epidemiology

- In UK, average of 3,256 people were diagnosed with cervical cancer each year from 2017 to 2019
- Company estimate that, following disease progression on or after systemic therapy, 117 people with recurrent or metastatic cervical cancer proceed with second-line treatment in England

Diagnosis and classification

- Cervical cancer is defined as recurrent when it has returned following treatment, persistent when it does not respond to treatment, and metastatic when it has spread beyond cervix to other places in body

Symptoms and prognosis

- Advanced cervical cancer symptoms: extreme tiredness, leg swelling or pain, lower back or abdominal pain, cough or problems urinating
- In UK, median overall survival for people with cervical cancer receiving chemotherapy in second-line setting approximately 9.3 months

Patient perspectives

Tisotumab vedotin offers a more targeted option that can ease symptoms but also comes with challenges

Submission from 2 patient experts

- Living with cervical cancer is physically and emotionally exhausting, and treatments take a heavy toll on daily life and independence
- Important progress made in NHS in recurrent or metastatic cervical cancer, especially with introduction of immunotherapy but options after first-line therapy remain limited, leaving many patients frustrated
- Current NHS treatments are demanding→ cumulative side effects such as fatigue, nausea, and nerve pain affect quality of life; more difficult to care for young children
- Survival impact of treatment main focus→ able to 'justify' side effects on basis that treatment gives best chance of survival
- Tisotumab provides sense of hope that cancer is being targeted more precisely and helps keep some normalcy in life
- Tisotumab also comes with challenges→ experienced eye problems, dryness, irritation, nose bleeds and nerve tingling hands and feet

As a patient receiving tisotumab vedotin, I've noticed a real difference compared to my previous treatments. The side effects feel more manageable than standard chemotherapy, and I don't feel as drained after each infusion

Clinical perspectives

Limited treatment options for recurrent or metastatic cervical cancer with disease progression on or after systemic therapy

Submissions from clinical experts

- Main aim of treatment is improving symptoms and quality of life with longer survival
- Limited treatment options; often young patient population (with young families) with high symptom burden
- Current care involves IV chemotherapy every 1 to 3 weeks; tisotumab vedotin given every 3 weeks, reducing burden on chemotherapy suites
- Tisotumab vedotin proven to provide a survival advantage compared with single agent chemotherapy with a slightly lower toxicity profile, except ophthalmic toxicity risk but these were manageable within trial setting
- Administration of tisotumab vedotin would require ophthalmology baseline review and need for cooling eye pads

Patients who progress after first line systemic therapy for metastatic cervical cancer have few good treatment options and often have a high symptom burden. This is a significant area of unmet need, especially in patients who are PDL1 negative and cannot access immunotherapy

IV, intravenous; PDL1, programmed death-ligand 1

Equality considerations

See appendix NICE process and methods guidance on health inequalities

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:

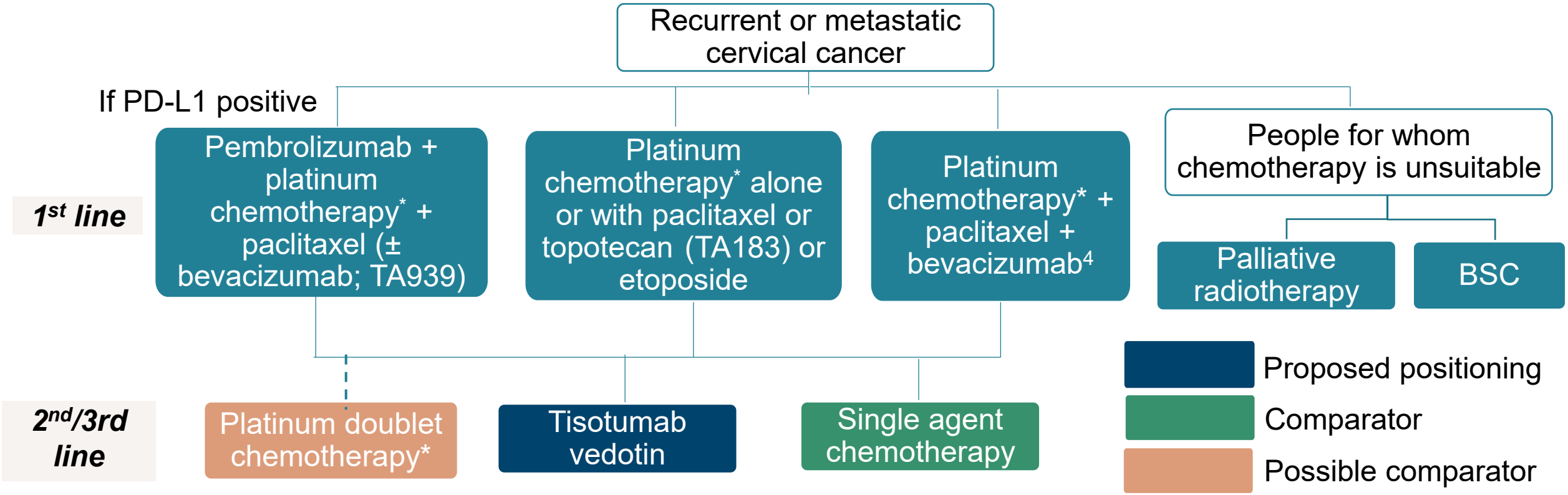
- Access to new treatments can be unequal, with geographic, financial, age, and cultural factors affecting who can benefit fully

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

HPV, human papillomavirus

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

Is the treatment pathway reflective of clinical practice? Is platinum doublet chemotherapy also used 2nd line? What is/are the appropriate comparator(s)? Are 2nd line treatments considered to have similar efficacy?

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

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

Key issues

Issue	Resolved?	ICER impact
Implementation of eye care management plan	No – for discussion	Unknown
Appropriateness of semi-Markov model structure	No – for discussion	Large
Modelling overall survival	No – for discussion	Large
Extrapolations of time to progression and pre-progression survival	No – for discussion	Large
Administration cost for paclitaxel	No – for discussion	Large

ICER, incremental cost-effectiveness ratio

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

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

NICE National Institute for Health and Care Excellence

Key clinical trials: InnovaTV 301

InnovaTV 204 single-arm trial also presented in company submission – see appendix for trial design and outcomes

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)
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

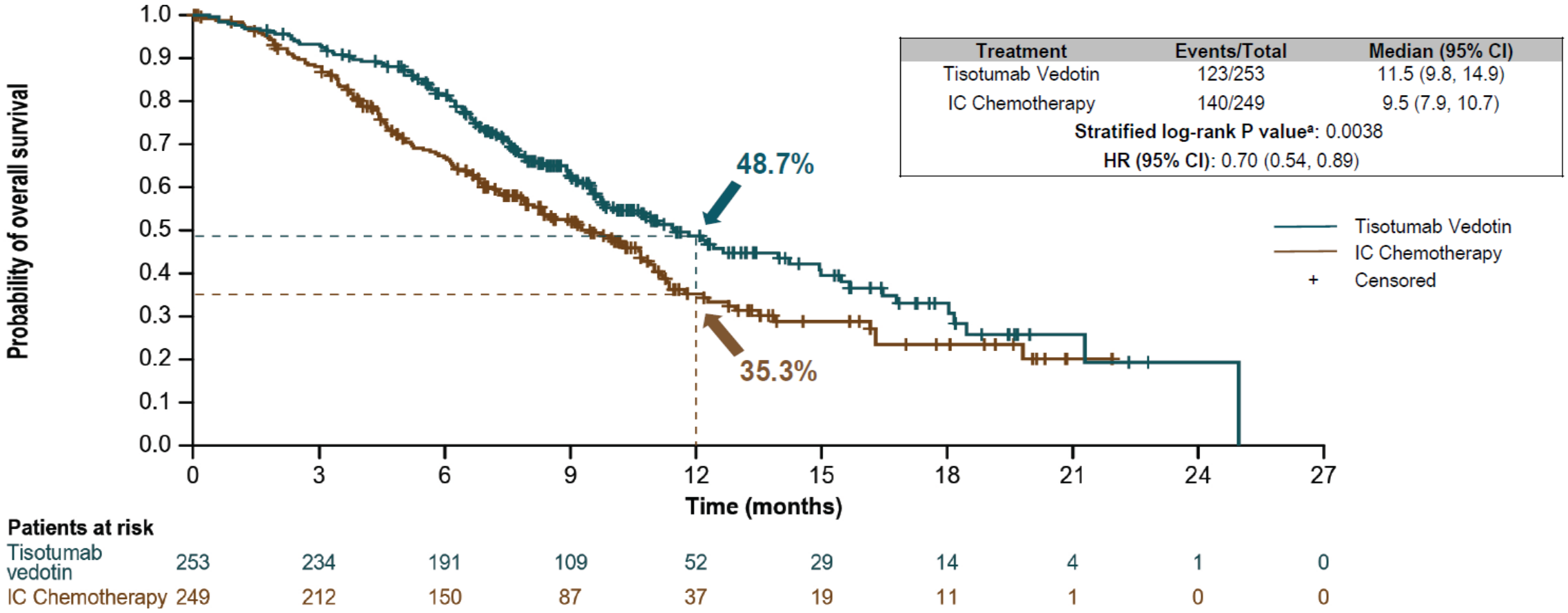
CI, confidence interval; HRQoL, health-related quality of life; r/m, recurrent or metastatic

See appendix for OS follow-up analysis results (January 2024)

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

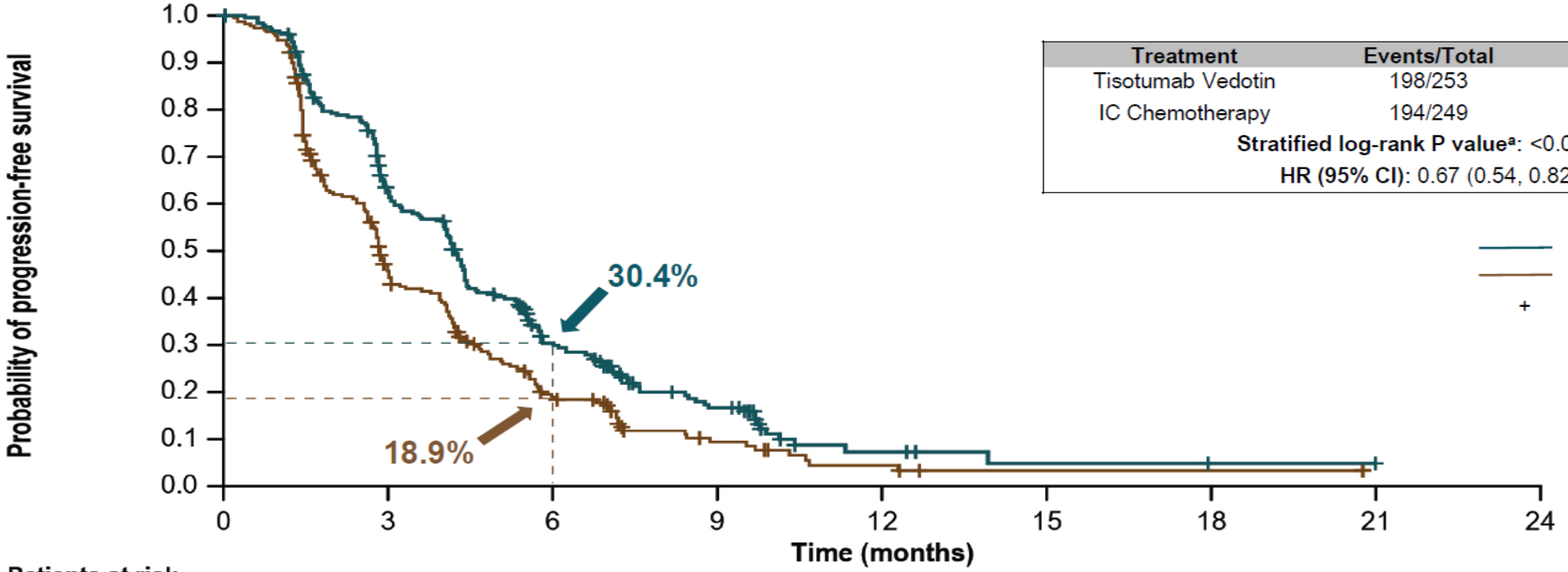
CI, confidence interval; HR, hazard ratio; IC, investigator's choice; ITT, intention to treat; OS, overall survival

Key clinical trial results – PFS (primary analysis)

See appendix for PFS follow-up analysis results (January 2024)

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

Adverse events

Similar proportions of participants in the tisotumab vedotin and chemotherapy arms of the InnovaTV 301 RCT experienced treatment-emergent adverse events

Summary of treatment-emergent adverse events in the InnovaTV 301 and the InnovaTV 204

Adverse Event	InnovaTV 301 RCT		InnovaTV 204 single-arm trial tisotumab vedotin (n=101) n (%)
	Tisotumab vedotin (n=250) n (%)	Chemotherapy (N=239) n (%)	
Any TEAE	246 (98.4)	237 (99.2)	101 (100)
Grade ≥3 TEAE	130 (52.0)	149 (62.3)	61 (60)
Any treatment-emergent SAE	82 (32.8)	94 (39.3)	43 (42.6)
Treatment-emergent SAE considered treatment related	26 (10.4)	35 (14.6)	13 (13)
Treatment-emergent AE leading to death	4 (1.6)	5 (2.1)	4 (4)
Treatment-emergent ocular adverse event	132 (52.8)	15 (6.3)	54 (53)

For patient and clinical experts: What is the impact of ocular adverse events with tisotumab vedotin? How are these managed in clinical practice?

RCT, randomised controlled trial; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Key issues: Implementation of eye care management plan

Unknown impact

Background

Tisotumab vedotin associated with ocular adverse events – see appendix for ocular adverse events in trials

Company

- Eye care management plan developed to be used in UK; aligns with recommendations in SmPC (and management in InnovaTV 301) which includes:
  - recommendations for eye examinations and guidance for referrals to eye specialists
  - schedule for administration for 3 different types of eye drops and
  - recommendations for cooling eye pads - see appendix for eye care management plan
- Eyecare management costs included in model (ocular assessment at initiation, pre-medication eyedrops and subsequent eye examination, if required)

EAG comments

- EAG's clinical experts raised concerns about implementation of management plan in practice, including:
  - whether adequate resource available in treating centres for eye care professional to perform ophthalmic examination before first infusion and when further needed
  - may be challenging for clinicians to judge when referral to eye care professional needed and availability of access to such referrals

Clinical experts: Ophthalmological pretreatment service in process of being set up for antibody drug conjugates such as tisotumab vedotin → need to ensure there is a clear pathway for ophthalmological reviews

- Cooling eye pads not routinely supplied and may not have space → people may need to bring their own

Are there any potential issues with the implementation of the eye care management plan?

EAG, External Assessment Group; SmPC, Summary of Product Characteristics

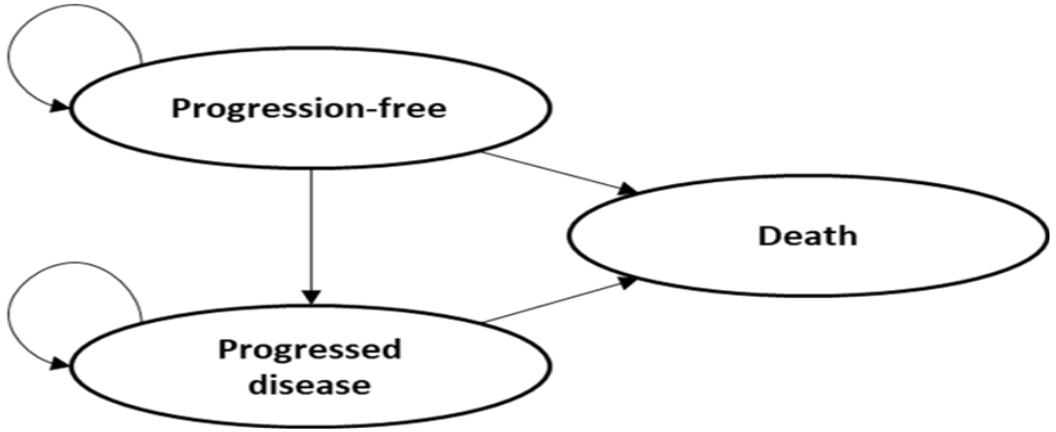
Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

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

NICE National Institute for Health and Care Excellence

Company's model overview

Company's model structure



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

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 **quality-adjusted life years** by:

- Increasing time to progression
- Increasing overall survival

Assumptions with greatest impact on **incremental-cost effectiveness ratio**:

- Overall survival extrapolations
- Time to progression extrapolations
- Pre-progression survival extrapolations
- Direct use Kaplan-Meier data for overall survival
- Administration cost for paclitaxel

Adverse event costs and disutilities for grade 3+ adverse events, reported in ≥5% of patients in either treatment arm included in the model

EAG, External assessment group; KM, Kaplan-Meier; OS, Overall survival; PD, progressed disease; PF, progression free; PFS, Progression-free survival

Key Issue: Appropriateness of semi-Markov model structure

Large impact

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

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

Company

- In InnovaTV 301, OS KM curves of tisotumab vedotin and chemotherapy appear to converge at tails when very few people at risk→ clinical experts considered OS KM estimates for chemotherapy to be clinically implausible and overestimated (~[redacted]% at 2 years; clinicians stated they expect this to be closer to 10% in clinical practice)
- PSM considered but it produced clinically implausible long-term estimates of OS in chemotherapy arm→ semi-Markov model chosen because 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)

EAG comments

- Not possible to change assumption of constant (exponential) hazards because company's semi-Markov model does not have tunnel states (i.e. no memory about time of progression)
- Prefer PSM with PFS and OS extrapolations (log-logistic for both arms – see EAG base case curves) and assumption that risk of mortality same in both treatment arms from point where OS curves converge (month 45)
- Assumption that risk of death after progression is constant and same between treatment arms is not supported by post-progression survival hazard plots or by AIC/BIC statistics – see next slide

Note- use of PSM results in people in tisotumab vedotin arm entering progressed disease health state sooner but longer overall survival than in semi-Markov model

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; EAG, External assessment group; KM, Kaplan-Meier; OS, Overall survival; PFS, progression-free survival; PSM, partitioned survival model

Large impact

Key Issue: Appropriateness of semi-Markov model structure

Hazard plot for post-progression survival using pooled arms

EAG

- Hazard and log cumulative hazard plot across treatment arms show that the hazard [redacted]
- AIC/BIC statistics fitted to post-progression survival data show that [redacted]

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

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Large impact

Key Issue: Modelling overall survival

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

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

Company

- Using modelled estimates based on fitted curves for PF to death and fixed post-progression hazard produced OS curves that overestimated OS for chemotherapy and underestimated OS for tisotumab vedotin (based on clinical input and validation of curves against observed data from InnovaTV301 – see appendix)
- Modelled estimates not accurate due to random variation caused by the diminishing sample size→ 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 (tisotumab vedotin = [redacted]; chemotherapy = [redacted]) and after this number at risk changes substantially

EAG comments

- Overlap of KM plots likely due to diminishing number of patients at risk but uncertainty applies in both arms
- Alternative interpretation of OS KM plots is that survival benefit of tisotumab vedotin does not persist beyond point where KM curves converge (start to converge from around [redacted]; overlap from around [redacted])
- Risk of bias from post-hoc decision to use KM data to override OS model predictions for first 12 months
- Prefer not to use KM data to override model predictions for first 12 months (and PSM – see key issue slide) but provided scenarios with 0, 9 and 15 month cut-off (instead of 12 months)

Company and EAG base case curves presented on following slides

NICE

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

Base case curves: overall survival (1)

Landmark survival rates company base case

	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

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

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), with InnovaTV 301 KM

[redacted]

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

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

- Company use generalised gamma distribution for time to progression for both treatment arms. For pre-progression survival, company use Gompertz distribution for tisotumab vedotin and lognormal distribution for chemotherapy (see following slides for predicted curves)

Company

- Choice of distributions based on visual fit to observed KM data within trial period of InnovaTV 301, clinical plausibility of extrapolations, statistical goodness of fit and assessment of underlying hazard functions over time

EAG comments

- Time to progression extrapolations uncertain due to periodic timing of assessments and diminishing sample size
- Goodness of fit statistics and visual fit of generalised gamma, lognormal and log-logistic distributions similar→ given structural dependency between time to progression and OS in semi-Markov structure, ICERs sensitive to choice of extrapolation
- Pre-progression survival: high degree of uncertainty due to low number of observed events in InnovaTV 301
- For both time to progression and pre-progression survival, 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?

EAG, External assessment group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, Overall 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
EAG scenarios with lognormal and log-logistic

Overlay of observed KM and predicted curves of TTP for chemotherapy

Company base case: generalised gamma
EAG scenarios with lognormal and log-logistic

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
EAG scenarios with exponential and lognormal

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

Company base case: lognormal
EAG scenarios with exponential and lognormal

NICE

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

Key issue: Administration cost of paclitaxel

Large impact

Uncertainty over the most appropriate cost code for administration of paclitaxel

Background

- Different potential cost codes for outpatient administration of chemotherapy using National Cost collection data:
  - SB12Z– 'Deliver Simple Parenteral Chemotherapy at First Attendance' (£152)
  - SB13Z– 'Deliver more Complex Parenteral Chemotherapy at First Attendance' (£202)
  - SB14Z– 'Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance' (£352)

Company

- Initially included higher cost of administration for paclitaxel (SB14Z) compared with administration cost of other single-chemotherapy agents (SB12Z) due to more complex administration
- Following EAG report, provided additional data to support use of different cost code (SB13Z) based on 2 NHS protocols for single-agent paclitaxel, NHS payment scheme for 2025/2026 and National Tariff Chemotherapy Regimens workbook 2017/2018 – see appendix

EAG comments

- EAG's clinical experts advised that single-agent paclitaxel is typically administered as a relatively short infusion around 1 hour and should not differ from other chemotherapies
- EAG prefer to use SB12Z cost code in base case and provide scenarios with cost code SB13Z

NHS England CDF lead: cost code dependent on whether paclitaxel given weekly or three-weekly. If weekly cost code of SB13Z would be used; for three-weekly, cost code of SB14Z would be used

Is SB12Z, SB13Z or SB14Z the most appropriate cost code for administration of paclitaxel?

QALY weightings for severity

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

Severity modifier calculations and components:

QALYs people without the condition (A)

QALYs people with the condition (B)

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 driven by EAG's preference for PSM with log-logistic distribution for both arms

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

	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?

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	£352 (cost code: SB14Z)	£152 (cost code: SB12Z)
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 appendix for estimates)	Based on Cancer Research UK 'Follow up after cervical cancer treatment' information	Based on estimates by EAG's clinical experts

†not included as key issue due to less significant impact on results – see appendix

NICE

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

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

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

NICE National Institute for Health and Care Excellence

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

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

NICE National Institute for Health and Care Excellence

Key issues

Issue	ICER impact	Slide(s)
Implementation of eye care management plan	Unknown 	15
Appropriateness of semi-Markov model structure	Large 	18, 19
Modelling overall survival	Large 	20, 21, 22
Extrapolations of time to progression and pre-progression survival	Large 	23, 24, 25
Administration cost for paclitaxel	Large 	26

ICER, incremental cost-effectiveness ratio

Key committee questions

Key issue/ parameter	Key Committee Questions
Comparators	What is/are the appropriate comparator(s)?
Eye care management plan	Are there any potential issues with the implementation of the eye care management plan?
Model structure	Is it more appropriate to use a semi-Markov model or partitioned survival model?
Modelling overall survival	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
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 SB12Z, SB13Z or SB14Z the most appropriate cost code for administration of paclitaxel?

EAG, External assessment group; 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; OS, overall survival; 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

Equality considerations: NICE process and methods guide

Health inequalities

3.3.28 Evidence on health inequalities in England can be provided to help the committee understand their impacts on eligible populations in NICE's guidance programmes. Analysis of health inequality impacts may be presented as an additional non-reference case analysis.

3.3.29 If a company or stakeholder identifies health inequalities that are relevant to the eligible population, they can provide robust qualitative and quantitative evidence to show that a technology will have a substantial impact. Supporting materials can include:

- descriptive statistics on disease burden
- information on social or structural barriers that are specific to the technology's eligible population and prevent people from accessing care or being included in research.

3.3.30 Important context on health inequalities can be provided by data that shows:

- differences in health outcomes between social groups in the eligible population
- that specific conditions are more common in disadvantaged groups.

Equality considerations: NICE process and methods guide

Structured decision making: health inequalities

6.2.35 If robust evidence shows that the technology substantially affects health inequalities, the committee will consider how this impacts its decision on whether the technology is an effective use of NHS resources (see sections 6.2.37 and 6.2.38).

6.2.36 Consideration of the health inequality impacts of a technology is separate from NICE's legal obligations on equality and human rights, including under the Equality Act 2010.

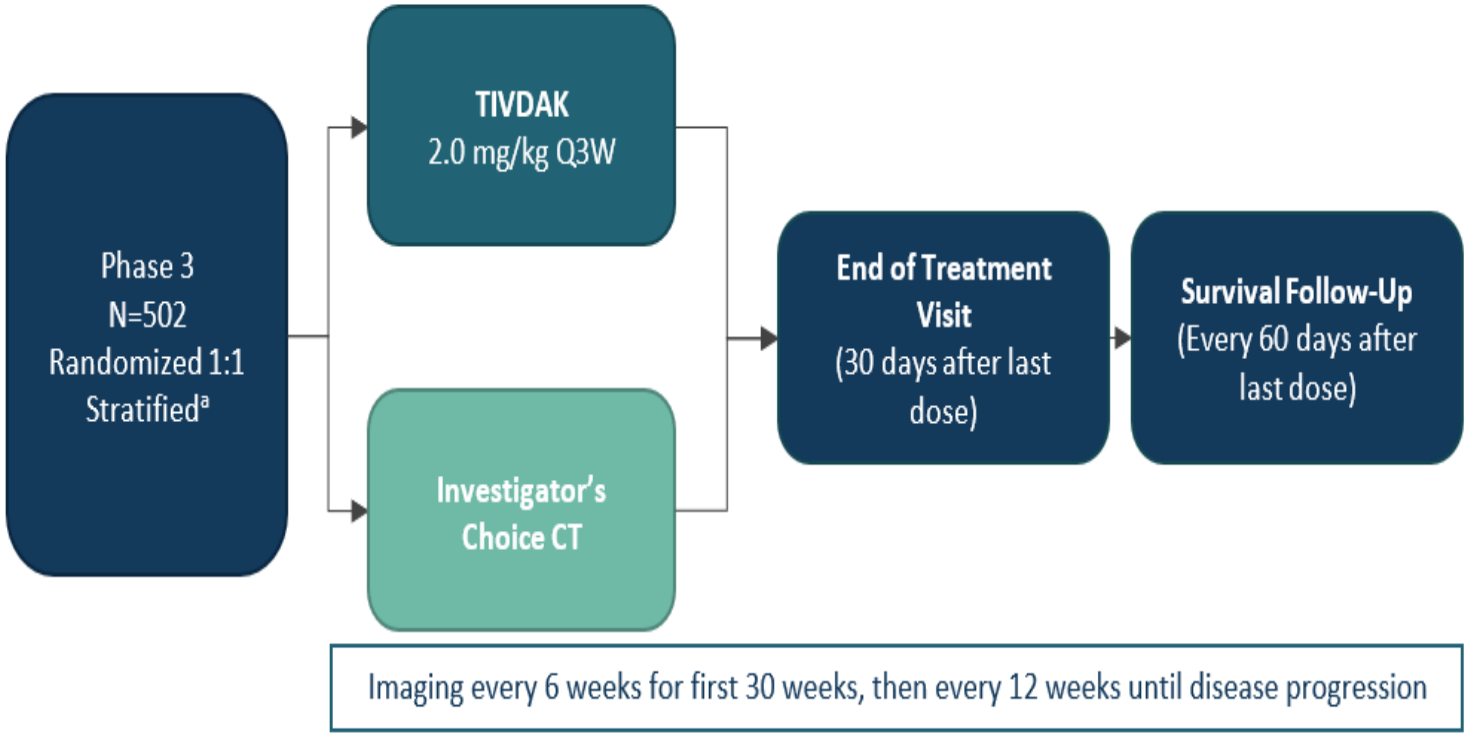
6.2.37 When assessing the relevance of health inequality impacts on the value of the technology, the committee will consider any uncertainty associated with the health inequality evidence and analysis. If robust condition- or disease-specific evidence shows that uncertainty or biases in the health inequality evidence are caused by structural or social barriers to accessing care or participating in research, the committee may accept a higher level of uncertainty in the health inequality evidence and analysis.

Equality considerations: NICE process and methods guide

6.2.38 When considering the relevance of health inequality impacts on the value of the technology, the committee can apply flexibility to the range normally considered a cost-effective use of NHS resources. But, it must consider the effects of healthcare displacement and opportunity cost and provide a rationale for stakeholders. This flexibility should be applied to the most appropriate acceptable ICER decided by the committee for the reference case analysis, as described in sections 6.3.4 to 6.3.8. It should only be applied when the size of the health inequality impacts of a technology are substantial. It should not be used to justify restricting the population of interest to a subgroup based on cost effectiveness (see section 4.9). The committee will not use evidence on health inequality impacts to make optimised recommendations for subgroups based solely on social characteristics.

InnovaTV 301 study design

InnovaTV 301 is an ongoing RCT comparing tisotumab vedotin against investigator's choice of chemotherapy in people with r/m CC who have received 1 or 2 prior lines of systemic therapy



[a]Stratification factors include ECOG PS (0 or 1), prior bevacizumab administration (yes or no), prior anti-PD-1 or anti-PD-L1 therapy administration (yes or no); and region (US, Europe or other).

<u>Key inclusion criteria</u>

- Age ≥18 years
- Recurrent or metastatic CC
- Disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible)
- Received 1 or 2 prior systemic therapy regimens for r/m CC
- ECOG PS of 0 or 1 prior to randomisation

CC, cervical cancer; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; r/m, recurrent or metastatic

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
Comparator(s)	Not applicable (single-arm trial)
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

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

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

Kaplan-Meier 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

Ocular adverse events – InnovaTV 301

InnovaTV 301 frequency and severity of ocular adverse events (Safety Analysis Population)

	Tisotumab vedotin (N=250)	Chemotherapy (N=239)
Any ocular TEAE, n (%)	132 (52.8)	15 (6.3)
Grade 1	49 (19.6)	11 (4.6)
Grade 2	73 (29.2)	4 (1.7)
Grade 3	10 (4.0)	0
Grade 4	0	0
Any serious ocular AE, n (%)	2 (0.8)	0
Any ocular AE leading to permanent discontinuation, n (%)	14 (5.6)	0
Median time to first ocular AE onset, months	1.22 (0.0-4.9)	2.07 (0.0-8.3)
Median time to ocular AE resolution, months	0.59	0.26
Frequency of ocular AE resolution[a] or improvement[b], n (%)		
All events resolved or improved	92/132 (69.7)	11/15 (73.3)
Some events resolved or improved	32/132 (24.2)	1/15 (6.7)

[a]Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'.

[b]For events that are not resolved, improvement is defined as at least one grade decrease from the highest grade as of the last assessment. Time to improvement is time from first occurrence of the highest grade to first improvement (i.e., at least one grade decrease from the highest grade and no grade increase afterwards).

AE, adverse event; TEAE, treatment-emergent adverse event

Ocular adverse events – InnovaTV 204

InnovaTV 204 ocular adverse events

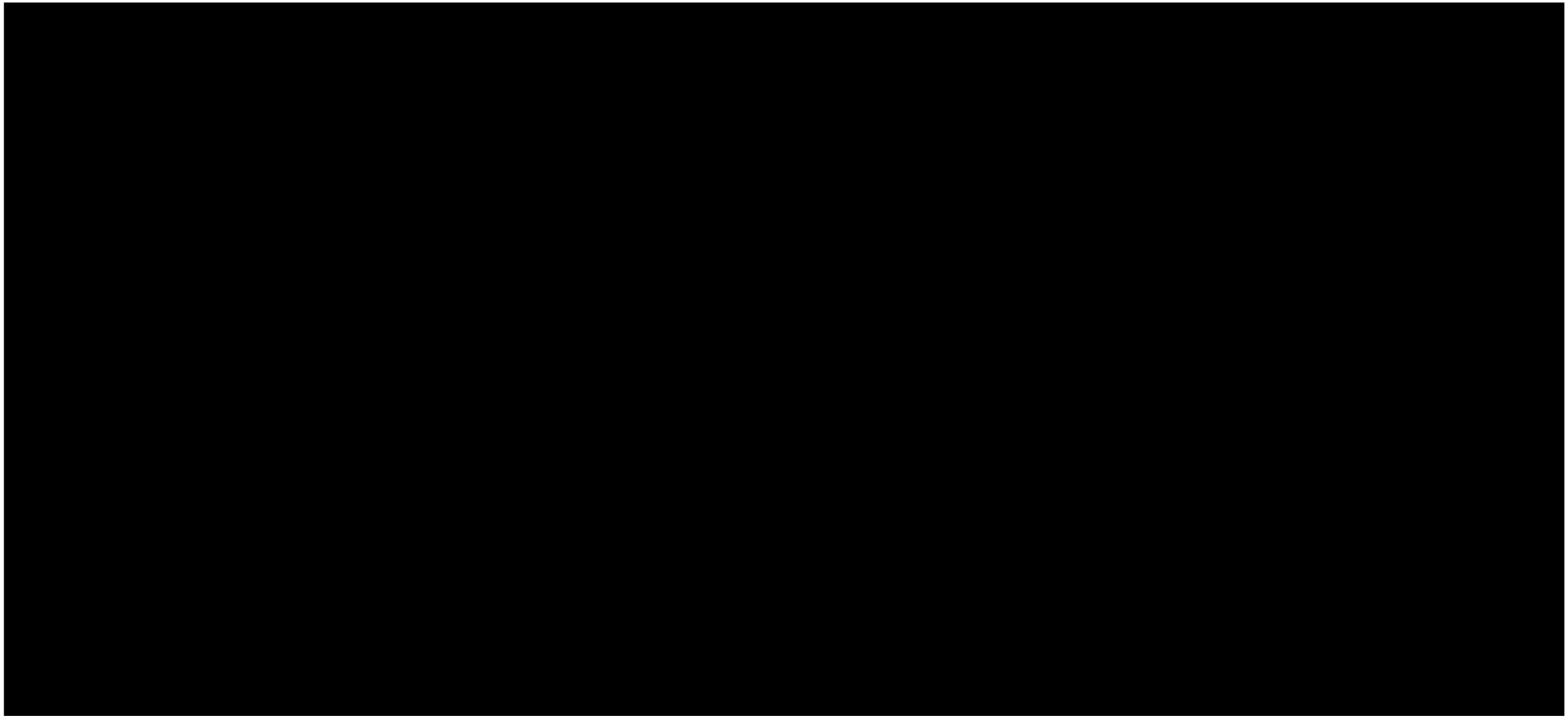
Preferred Term	Tisotumab vedotin (N=101)	
	Any TRAE	Grade ≥3
Any ocular TRAE, n (%)	54 (53)	2 (2)[a]
Most common (≥10%) ocular TRAEs		
Conjunctivitis	26 (26)	0
Dry eye	23 (23)	0
Keratitis[b]	11 (11)	0
Number of events, N	138	
Median time to ocular TRAE onset, months	1.4	
Frequency of ocular TRAE resolution[c], n/N (%)	118/138 (86)	
Median time to ocular TRAE resolution[d], months	0.7	

[a]Two events of ulcerative keratitis.
[b]Two Grade 3 events of ulcerative keratitis were reported separate from people with keratitis.
[c]Resolution defined as events with status outcome of recovered/resolved or recovered/resolved with sequelae within 30 days after the last dose of tisotumab vedotin.
[d]Assessments were limited by the protocol-defined follow-up period for AEs of only 30 days after the last dose.

AE, adverse event; TRAE, treatment-related adverse event

Eye care management plan

Eye care management plan for patients receiving tisotumab vedotin monotherapy in the UK



Log cumulative hazard plot (pooled): company base case

Log cumulative hazard plot for post-progression survival pooled across treatment arms

EAG

- log cumulative hazard plot across treatment arms show that hazard of death post-progression is not constant

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

InnovaTV 301 observed vs predicted OS curves

OS curves: observed vs. predicted OS with fitted data from time 0

Company: Using modelled estimates based on fitted curves for PF to death and fixed post-progression hazard produced OS curves that overestimated OS for chemotherapy and underestimated OS for tisotumab vedotin (based on clinical input and validation of curves against observed data from InnovaTV301)

NICE

OS, overall survival; TV, tisotumab vedotin

InnovaTV 301 hazard plots – progression free to progressed disease

Hazard plot for PF to PD

Log cumulative hazard plot for PF to PD

PD, progressed disease; PF, progression free; TV, tisotumab vedotin

InnovaTV 301 hazard plots – progression free to death

Hazard plot for PF to death

Log cumulative hazard plot for PF to death

PD, progressed disease; PF, progression free; TV, tisotumab vedotin

Key issue: Administration cost of paclitaxel (2)

Company

- Provided additional data to support use of different cost code (SB13Z) based on:
  - Two local NHS protocols for single-agent paclitaxel, both of which require pre-medication 30 minutes prior to infusion, followed by a 60-minute paclitaxel infusion
  - NHS payment scheme for 2025/2026 (Section 5: Chemotherapy and Radiotherapy, Table 1), which indicates that chemotherapy regimens requiring 60 minutes of nurse time and up to 120 minutes of chair time should be assigned to code SB13Z “deliver more complex parenteral chemotherapy”.
  - The National Tariff Chemotherapy Regimens Workbook (2017/18). Although later versions are not publicly accessible, the adult regimens sheet allocates paclitaxel 7-day regimen to administration code SB13Z

Other differences between company and EAG base cases

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
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

Summary of 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 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