Single Technology Appraisal

Tisotumab vedotin for treating recurrent or metastatic cervical cancer after systemic therapy [ID3753]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tisotumab vedotin for treating recurrent or metastatic cervical cancer after systemic therapy [ID3753]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Genmab**
   a. Company addendum to comments on the draft guidance

2. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tisotumab vedotin as monotherapy for treating adults with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy [ID3753]

Company comments on the draft guidance document

March 2026

File name	Version	Contains confidential information	Date
ID3753 Tisotumab vedotin_Evidence Submission Response to NICE Request_25032026 [REDACTED]	1.0	Yes	25 March 2026

Table of Contents

List of Tables

List of Figures

1. Introduction

Following the first appraisal committee meeting (ACM1) of ID3753 tisotumab vedotin for treating adults with recurrent or metastatic cervical cancer (r/mCC) that has progressed on or after systemic therapy, the NICE appraisal committee requested further information relating on preferred modelling assumptions and the impact of uncertainties. The company were asked to explore the different standard parametric distributions within a partition survival model (PSM) framework for progression-free survival (PFS) and overall survival (OS), and provide information related to the validity of the distributions, including assessment of:

- visual fit to observed Kaplan-Meier (K-M) data from innovaTV 301
- the underlying hazard functions over time and validation by clinical experts
- the clinical plausibility of extrapolations
- goodness-of-fit statistics.

The committee also asked the company to update the chemotherapy administration costs with the latest NHS tariff costs available, including the SB13Z HRG code for the administration of weekly paclitaxel.

As requested by the committee, the Company has conducted the additional analyses and clinician validations. The different standard parametric distributions for PFS and OS in the PSM framework, information on their visual fit to the observed data from innovaTV 301, the underlying hazard functions over time, the associated goodness of fit statistics, and the clinician validation of the extrapolations and the underlying hazard functions, are provided in the following sections of this document. In addition, the model scenarios have been updated with the available NHS reference costs including the SB13Z HRG code for the administration of weekly paclitaxel.

Genmab hopes that the totality of the evidence provided will be sufficient to inform the NICE committee's decision-making and to provide timely access to tisotumab vedotin for r/mCC patients who face a high unmet need for safe and effective new treatments.

2. Summary of the Additional Evidence

Summary of key points:

OS: Standard parametric distributions within PSM framework

- Standard parametric functions were independently fitted to OS data for chemotherapy and tisotumab vedotin from innovaTV 301.
- No distribution closely fits the observed chemotherapy Kaplan-Meier (K-M) data; log-logistic and log-normal were the closest visual fit. For tisotumab vedotin, Weibull, log-logistic, gamma and generalised gamma provided the closest visual fit.
- Hazard plots appear inconclusive to inform parametric distribution selection: chemotherapy showed an early rise followed by a modest decline, while tisotumab vedotin showed a non-monotonic pattern, rising to around weeks 70–80 before declining.
- Goodness-of-fit statistics favoured log-logistic and log-normal distributions for chemotherapy OS, and Weibull and gamma distributions for tisotumab vedotin OS.
- External validation against the observed chemotherapy K-M data for the EMPOWER study showed all distributions overestimated chemotherapy OS at 1 and 2 years; Weibull and gamma distributions were closest at 2 years but still overestimated 1-year OS.
- For tisotumab vedotin, external validation against innovaTV 204 showed log-logistic and log-normal provided the closest 1- and 2-year OS predictions.
- Clinical validation found no parametric extrapolation of chemotherapy OS yielded clinically plausible predictions; all were seen as overestimating survival, e.g., while clinicians expected 1-year and 2-year OS of ≤35% and ≤10%, respectively, for patients treated with chemotherapy, all the

parametric extrapolations predicted higher OS at 1 year and 2-years.

- When required to choose one parametric distribution, two clinicians indicated the gamma distribution was the closest for chemotherapy. Although hazard profiles did not clearly support the selection of any single parametric extrapolation.
- Clinicians had limited experience with tisotumab vedotin, in contrast to their experience with chemotherapy, making it more difficult for them to advise on the tisotumab vedotin OS extrapolation. However, one clinician indicated data from innovaTV 204 and innovaTV 301 were broadly consistent with each other, offering confidence in their application. They also viewed the extrapolated tails as uncertain given the limited number of patients at risk.
- With no standard parametric extrapolation providing a good fit to OS data, especially for chemotherapy, restricted cubic spline models were also explored. However, these spline models did not improve the robustness of the extrapolations.

PFS: Standard parametric distributions within PSM framework:

- Standard parametric functions were independently fitted to PFS data for chemotherapy and tisotumab vedotin.
- For both arms, log-logistic and log-normal distributions provided the closest overall fit; generalised gamma distribution also fit tisotumab vedotin well, but none captured the tail plateau adequately.
- Hazard plots showed a non-monotonic pattern in both arms, with early increases followed by decline over time.
- Goodness-of-fit results were broadly aligned with the visual assessment, indicating log-logistic and log-normal distributions as best fit for chemotherapy PFS. For tisotumab vedotin PFS, the log-logistic, log-normal, and generalised gamma distributions provided the best.

- Internal validation showed log-logistic, log-normal, and generalised gamma distributions produced similar 1-year PFS estimates to innovaTV 204 and innovaTV 301, but no distribution matched 2-year PFS well.

Company base case (semi-Markov) vs. PSM scenarios

- Based on the overall PSM evidence, the gamma distribution should be considered for chemotherapy OS extrapolation, albeit also overestimating OS for chemotherapy.
- For tisotumab vedotin OS, log-logistic and gamma distributions were considered the most appropriate distributions.
- For PFS, the log-logistic distribution was selected for both tisotumab vedotin and chemotherapy based on visual fit, goodness-of-fit, and internal validation.
- Further exploratory analyses examined the hazard ratio trend (HRT) for the gamma extrapolation for both tisotumab vedotin and chemotherapy with an 18-month cut-point. This analysis generated an HRT statistic of [redacted], suggesting a clinically implausible reversal of treatment effect.
- Therefore, an additional scenario explored gamma for both tisotumab vedotin and chemotherapy OS curves, with the hazard ratio set to 1 from 18 months onward to explore ICERs under this scenario.
- Compared to the Company base (i.e., the semi-Markov using direct K-M data for the first 12 months followed by health state transition modeling thereafter and conservatively applying the same risk of death post-progression for both treatments), the PSM scenarios all overestimated chemotherapy OS through the 2-year landmark.
- Compared to the company base case, the gamma OS extrapolation overestimated chemotherapy OS by [redacted]% (at 6 months) and [redacted]% (at 1 year), and [redacted]% (at 2 years, i.e., [redacted]% vs. [redacted]%).

- Of note, while the committee indicated an interest in fitted curves from time zero, implementing semi-Markov with fitted curves from time zero also led to substantial overestimation of chemotherapy OS in the first 12 months, while underestimating OS for tisotumab vedotin over the same period. Overall, the additional evidence further demonstrates that the Company base uses the most clinically plausible OS estimates while reflecting the optimal use of the observed data when the numbers of patients at risk remains robust.

Severity modifier:

- A total of 49 parametric extrapolation combinations were explored within the PSM framework and 45 of them produced a severity modifier of 1.7, underscoring the high severity of r/mCC.

Updated NHS costs:

- The modelling scenarios were updated using the latest available NHS reference costs, including tariff-based scenarios requested by NICE.

Updated ICERs:

- Whereas the updated ICERs (all with a 1.7 QALY weight) in the company's base case were £[redacted] (£[redacted]) based on 2024-2025 NHS reference costs and £[redacted] (£[redacted]) based on 2025-2026 NHS tariff, in the PSM scenario using log-logistic for tisotumab vedotin OS, and gamma for chemotherapy OS, and log-logistic for PFS for both arms, the ICERs (with 1.7 QALY weight were £[redacted] (£[redacted]) using 2024–2025 NHS reference costs and £[redacted] (£[redacted]) using 2025–2026 NHS tariff.
- In the PSM scenario using gamma extrapolations for OS in both arms and log-logistic for PFS in both arms, ICERs (with 1.7 QALY weight) were £[redacted] (£[redacted]) using 2024–2025 NHS reference costs, and £[redacted] (£[redacted]) using 2025–2026 NHS tariff.

- In the scenario with gamma extrapolations for OS in both arms and hazard ratio set to 1 from month 18, the ICERs slightly reduce to £[redacted] (£[redacted]) using 2024–2025 NHS reference costs and £[redacted] (£[redacted]) using 2025–2026 NHS tariff.

Conclusion:

- The PSM analyses outlined above have been provided as requested by the appraisal committee and further illustrate the company's original evaluation that OS extrapolations in the PSM framework universally overestimate chemotherapy OS over time.
- These analyses offer further justification for the company's base case combining direct K-M data with health state transition modelling, and a conservative assumption of the same risk of death post-progression generates more clinically plausible chemotherapy OS projections.
- For completeness, the ICERs in the company's initial submission have also been updated in line with committee's feedback on the use of currently available NHS costs and the considerations around the direct use of K-M data for the first 12 months.
- The updated ICERs (all with a 1.7 QALY weight) in the Company base case were £[redacted] (£[redacted]) based on 2024-2025 NHS reference costs and £[redacted] (£[redacted]) based on 2025-2026 NHS tariff.

3. OS Parametric Extrapolations and Hazard Functions in PSM

Overall survival parametric functions were fitted independently for tisotumab vedotin and chemotherapy within the PSM because the log-cumulative hazard plots (**Figure 1**) and hazard function plots (**Figure 2**) indicate deviation from proportional hazards.

Figure 1. Log cumulative hazard plot for OS by treatment arm

Figure 2. Hazard plots for OS by treatment arm

3.1 Chemotherapy OS: Parametric Extrapolations and Hazard Functions in PSM

A comprehensive set of standard parametric functions were independently fitted to the OS data from the chemotherapy arm of innovaTV 301 (Vergote et al. 2024) from time zero. Results are presented for chemotherapy OS parametric extrapolations (**Figure 3** and Appendix **Figure 15**), the underlying hazard functions (**Figure 4** and Appendix **Figure 16**), goodness of fit statistics (**Table 1**), and the predicted OS rates at different time points (**Table 2**).

Based on the **visual inspection** of fitted OS parametric curves against the observed K-M data in **Figure 3**, no parametric function fits the observed chemotherapy data well. Visually, the log-normal and log-logistic provide the closest visual approximation of the chemotherapy data. Overall, there are notable differences in the observed vs predicted OS estimates at 1-year and 2-year landmarks (**Table 2**), albeit with the 2-year observed and predicted estimates being based on data from a limited number of patients at risk.

The **OS hazard plot** for chemotherapy shows an initial increase, followed by a modest decline over time, with a downward trend that is not pronounced. Based on the predicted hazard plots from the fitted models for OS on chemotherapy (**Figure 4**) it is not clear if any parametric distribution can be selected or excluded solely based on the hazard shape.

Based on the **goodness of fit statistics** (AIC and BIC, **Table 1**), log-logistic and log-normal had the lowest AIC and BIC statistics indicating a better fit for the observed chemotherapy OS data than the other parametric functions.

For **external validation,** the chemotherapy OS projections from the different parametric functions were compared to data from EMPOWER trial (Tewari et al. 2022), a trial conducted in a similar trial population, with 1-year and 2-year chemotherapy OS of 34.26% and 11.30%, respectively. All the parametric extrapolations overestimated OS for chemotherapy (**Table 2**), with 1-year and 2-year OS at [redacted]% and [redacted]% for log-logistic, and [redacted]% and [redacted]% for log-normal, respectively. Notably, the parametric functions that predicted 2-year chemotherapy OS closer to that from EMPOWER (i.e., Weibull with [redacted]%, and gamma with [redacted]%) also substantially overestimated the 1-year

chemotherapy OS relative to the other functions. In addition, all parametric functions overestimated the 1-year chemotherapy OS compared to that observed in innovaTV 301.

Given that none of the standard parametric extrapolations fit the OS data well, especially the chemotherapy data, additional explorations of the restricted cubic splines were explored but they did not improve the robustness of the estimates.

Figure 3. Observed K-M and [top four] predicted OS curves for chemotherapy

Figure 4. Predicted hazard plot from the [top four] fitted models for OS on chemotherapy

Table 1. 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

*AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 2. Chemotherapy landmark OS rates*

	Observed OS		Predicted OS based on standard parametric functions						
Time point	**EMPOWER K-M**	**innovaTV 301 K-M**	**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%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*These 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.

3.2 Tisotumab vedotin OS: Parametric Extrapolations and Hazard Functions in PSM

Similarly, a comprehensive set of standard parametric functions were independently fitted to the OS data from the tisotumab vedotin arm of innovaTV 301 from time zero. Results are presented for tisotumab vedotin OS parametric extrapolations (**Figure 5** and Appendix **Figure 17**), the underlying hazard functions (**Figure 6** and Appendix **Figure 18**), goodness of fit statistics (**Table 3**), and the predicted OS rates at different time points (**Table 4**).

Based on visual inspection of fitted OS parametric curves against the observed K-M data, the Weibull, log-logistic, gamma, and generalised gamma distributions **(Figure 5**) appear to provide a closer fit to the observed tisotumab vedotin OS data than the other parametric extrapolations**,** albeit with the 2-year estimates being based on limited observed data from a small number of patients at risk.

The **OS hazard plot** for tisotumab vedotin suggests a non-monotonic pattern with increasing hazards through week 70-80 before declining thereafter. Given the tails of the hazard plots entail uncertainty driven by a limited number of patients at risk, from the hazard plots on their own (**Figure 6**) it is not clear if any parametric distribution can be selected or excluded solely based on the hazard shape.

Based on the **goodness of fit statistics** (AIC and BIC, **Table 3**), the Weibull and gamma, distributions had the lowest AIC and BIC statistics, indicating a better fit to the observed tisotumab vedotin OS data. These were followed by log-logistic and generalised gamma functions.

For **external validation**, the tisotumab vedotin OS projections from the different parametric functions were compared with data from innovaTV 204 (Coleman et al. 2021), a trial conducted in a similar patient population as the innovaTV 301. The 1-year and 2-year OS for innovaTV 204 was [redacted]% and [redacted]%, respectively**.** The closest tisotumab vedotin OS predictions at 1 year and 2 years were from log-logistic ([redacted]% and [redacted]%) and log-normal ([redacted]% and [redacted]%) functions, respectively (**Table 4**). The tisotumab vedotin OS predictions for Weibull were [redacted]% and [redacted]%, and gamma were [redacted]% and [redacted]%, respectively.

Figure 5. Observed K-M and [top four] predicted OS curves for tisotumab vedotin

Figure 6. Predicted hazard plot from the [top four] fitted models for OS on tisotumab vedotin

Table 3. 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

*AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 4. Tisotumab vedotin landmark OS rates*

	Observed OS		Predicted OS 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 (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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*These 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.

3.3 Clinician Validation

The OS extrapolations for chemotherapy and tisotumab vedotin in the PSM framework, their underlying hazard functions, and the corresponding predicted landmark OS estimates were presented separately to three UK clinicians treating r/mCC to advise on their clinical plausibility ([Data on file] ID3753 Tisotumab Vedotin Post ACM1 Clinician Validation of Long-Term Survival Extrapolations). Each clinician that was consulted rejected all parametric extrapolations of chemotherapy OS in the PSM, on the basis that every extrapolation overestimated OS on chemotherapy and none is clinical plausible.

Broadly, these three clinicians reiterated feedback from prior consultations with five other UK clinicians treating r/mCC in that the benefit of chemotherapy is observed in the first year, and that by the 2-year landmark, OS on chemotherapy is at best [redacted]%. If forced to pick one parametric extrapolation, two clinicians indicated they would choose the gamma distribution for chemotherapy OS though they also noted that this distribution also overestimates OS. The third clinician did not pick a specific parametric function. The clinicians' assessment of the underlying OS hazard functions on chemotherapy did not provide a clear candidate for parametric distribution. However, there was recognition that the hazards increase and peak, with some clinicians stating it then falls or plateaus.

Given limited real-world experience with tisotumab vedotin relative to longstanding experience of treating r/mCC with chemotherapy, it was more difficult for clinicians to determine the most appropriate parametric function for extrapolating tisotumab vedotin OS. One clinician indicated that the observed data from innovaTV 204 and innovaTV 301 are consistent with each other, offering confidence in the application of this data.

4. PFS Parametric Extrapolations and Hazard Functions

Consistent with the OS extrapolations, parametric functions were independently fitted on the tisotumab vedotin and chemotherapy data from innovaTV 301 based on the log-cumulative hazard plots (i.e., log[-log(S)] vs. log time) and hazard plot shown in **Figure 7** and **Figure 8**.

Figure 7. Log cumulative hazard plot of PFS by treatment arm

Figure 8. Hazard plot of PFS by treatment arm

4.1 Chemotherapy PFS: Parametric Extrapolations and Hazard Functions in PSM

Results are presented for the chemotherapy PFS extrapolations (**Figure 9** and Appendix **Figure 19**), the underlying hazard functions (**Figure 10** and Appendix **Figure 20**), goodness of fit statistics (**Table 5**), and the predicted PFS rates at different time points (**Table 6**).

Based on the **visual inspection** of fitted PFS curves in **Figure 9** and the difference between observed and predicted PFS landmark estimates in **Table 6** as well as the **goodness of fit statistics**, the log-logistic, log-normal, and generalised gamma distributions fit the chemotherapy PFS data better than the other parametric functions (**Table 5**). The PFS **hazard plots** for chemotherapy demonstrated a non-monotonic pattern, with the hazards increase early in follow-up before declining thereafter (**Figure 10**).

For internal/ external validation, the predicted PFS was compared with the observed 1-year and 2-year chemotherapy PFS estimates from innovaTV 301 (i.e., [redacted]% and [redacted]%) and 1-year PFS from EMPOWER ([redacted]%). The predicted 1-year and 2-year PFS for chemotherapy using the log-logistic function was [redacted]% and [redacted]%, and for generalised gamma was [redacted]% and [redacted]%, respectively (**Table 6**).

4.2 Tisotumab vedotin PFS: Parametric Extrapolations and Hazard Functions in PSM

Results are presented for the tisotumab vedotin PFS extrapolations (**Figure 11** and Appendix **Figure 21**), the underlying hazard functions (**Figure 12** and Appendix **Figure 22**), goodness of fit statistics (**Table 7)**, and the predicted PFS rates at different time points (**Table 8)**. Based on visual inspection of fitted tisotumab vedotin PFS parametric curves (**Figure 11**), the difference between observed and predicted PFS (**Table 8**), and the goodness of fit statistics, the log-normal, log-logistic, and generalised gamma provide the best fit for the tisotumab PFS data (**Table 7**). The hazard pattern appears similar to that of the chemotherapy PFS. Compared with the observed 1-year and 2-year tisotumab vedotin PFS estimates from innovaTV 301 (i.e., [redacted]% and [redacted]%) and innovaTV 204 ([redacted]% and [redacted]%), respectively, the log normal, log-logistic, and generalised gamma appeared to provide the closest PFS fit.

Figure 9. Observed K-M and [top four] predicted PFS curves for chemotherapy within the PSM framework

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

Figure 10. Predicted hazard plot from the [top four] fitted models for chemotherapy PFS within the PSM framework

Table 5. 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

Table 6. Chemotherapy landmark PFS rates*

	Observed PFS		Predicted chemotherapy PFS based on standard parametric functions						
Time point	**EMPOWER K-M**	**innovaTV 301 K-M**	**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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 11. Observed K-M and predictive PFS curves for tisotumab vedotin within the PSM framework

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

Figure 12. Predicted hazard plot from the fitted models for tisotumab vedotin PFS within the PSM framework

Table 7. AIC and BIC of fitted parametric curves of PFS for tisotumab vedotin

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

Table 8. Tisotumab vedotin landmark 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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

5. Company Base Case vs. PSM Scenarios

Based on a multi-criteria assessment of the parametric extrapolations within the PSM framework, the gamma distribution should be considered for the chemotherapy OS extrapolations albeit also overestimating OS for chemotherapy (Appendix **Figure 24**). The log-logistic and gamma distributions would be considered for the tisotumab vedotin OS extrapolations (Appendix **Figure 23** and Appendix **Figure 24**). Log-logistic extrapolations would be selected for both tisotumab vedotin PFS and chemotherapy PFS data based on visual fit, goodness of fit statistics, and internal validations.

Further exploratory analyses examined the hazard ratio (HR) trend (HRT) for an OS extrapolation scenario that uses the gamma distribution for both chemotherapy OS and tisotumab vedotin OS in PSM, with 18 months as the cut-point. The hazard ratio trend (HRT) summarises the direction of the treatment effect in the model: HRT < 1 indicates an amplifying effect, HRT = 1 indicates a stable effect, and HRT > 1 indicates an attenuating effect. The analysis showed an HRT statistic of [redacted] indicating a clinically implausible reversal of the treatment effect. Therefore, an additional scenario was explored using a gamma distribution for tisotumab vedotin OS and chemotherapy OS but capping the HR at 1 from 18 months onwards, to explore ICERs under scenario.

Based on the assessment above, the Company has presented the following results under a PSM structure: Gamma or log-logistic for TV OS, gamma for chemo OS, Log-logistic for TV PFS and log-logistic for chemo PFS.

Compared to the company base (i.e., the semi-Markov using direct K-M data for the first 12 months followed by health state transition modelling thereafter and conservatively applying the same risk of death post-progression for both treatments), the PSM scenarios all overestimated chemotherapy OS.

Compared to the Company base case, the gamma OS extrapolation (Appendix **Figure 24**) overestimated chemotherapy OS by [redacted]% (at 6 months) and [redacted]% (at 1 year), and [redacted]% (at 2 years, i.e., [redacted]% vs. [redacted]%) (**Figure 13**).

Of note, while the committee indicated an interest in fitted curves from time zero,

implementing semi-Markov with fitted curves from time zero also led to substantial overestimation of chemotherapy OS in the first 12 months and underestimation of OS for tisotumab vedotin over the same period (**Figure 14**). Overall, the additional evidence further demonstrates that the Company base uses the most clinically plausible OS estimates while reflecting the optimal use of the observed data when the numbers of patients at risk remains robust.

Figure 13. OS: Company base case vs. Partition survival modelling (PSM)

Structure	A. Company Base Case	B . PSM (Gamma for OS, both treatments)
		

Time point	innovaTV 301		Company Base Case		PSM (Gamma for OS, both treatments)	
Chemotherapy	**Patients at risk**	**Observed OS%**	**Predicted OS%**	**Δ OS%** (predicted – observed)	**Predicted OS%**	**Δ OS%** (predicted – observed)
3 months						
6 months						
12 months						
18 months						
24 months						
Tisotumab vedotin						
3 months						
6 months						
12 months						
18 months						
24 months						

Figure 14. OS: Company base case vs. Semi-Markov with fitted curves from time zero

Structure	A. Company Base Case	C. Semi-Markov with fitted curves from time zero
	[redacted]	[redacted]

Time point	innovaTV 301		Company Base Case		Semi-Markov with fitted curves from time zero	
Chemotherapy	**Patients at risk**	**Observed OS%**	**Predicted OS%**	**Δ OS%** (predicted – observed)	**Predicted OS%**	**Δ OS%** (predicted – observed)
3 months	[redacted]					
6 months						
12 months						
18 months						
24 months						
Tisotumab vedotin						
3 months	[redacted]					
6 months						
12 months						
18 months						
24 months						

6. Severity Modifier

A total of 49 parametric extrapolation combinations were explored within the PSM framework. Across these extrapolations, largely considered by clinicians as overestimating survival on chemotherapy, 45 produced a severity modifier of 1.7, underscoring the high severity of r/mCC.

7. Updated NHS Costs

The modelling scenarios, both the company base case and the PSM scenarios were updated with currently available NHS reference costs, including scenarios with tariffs as requested by NICE.

8. Updated ICERs

The updated ICERs (all with a 1.7 QALY weight) in the company's base case were £[redacted] (£[redacted]) based on 2024-2025 NHS reference costs and £[redacted] (£[redacted]) based on 2025-2026 NHS tariff **(Table 9, Table 10).**

The ICERs (all with a 1.7 QALY weight) in the PSM with log-logistics OS extrapolations for tisotumab vedotin and gamma OS extrapolations for chemotherapy, with log-logistic PFS extrapolations for both, were £[redacted] (£[redacted]) based on 2024-2025 NHS reference costs, and £[redacted] (£[redacted]) based on 2025-2026 NHS tariff.

When gamma extrapolations are used for both tisotumab vedotin OS and chemotherapy OS, with log-logistics for both tisotumab vedotin PFS and chemotherapy PFS, the ICERs (with 1.7 QALY weight) were £[redacted] (£[redacted]) based on 2024-2025 NHS reference costs, and £[redacted] (£[redacted]) based on 2025-2026 NHS tariff. When the hazard ratio is capped at 1 from month 18, these ICERs change to £[redacted] (£[redacted]) based on 2024-2025 NHS reference costs, and £[redacted] (£[redacted]) based on 2025-2026 NHS tariff.

Table 9. Overview of the new evidence within the PSM framework

		Justification
Model structure	**PSM**	**Updated in response to NICE request**
Use of observed KM OS data for first 12 months	Parametric predictions applied from time zero (no KM used)	Updated in response to NICE request
OS extrapolation for tisotumab vedotin and chemotherapy	Log-logistic or gamma for tisotumab vedotin Gamma for chemotherapy	See Section 3
PFS extrapolation for tisotumab vedotin and chemotherapy	Log-logistic for tisotumab vedotin Log-logistic for chemotherapy	See Section 4
PFS capped by OS	Yes	In line with EAG*
Resource use per week estimates for colposcopy	365.25 days per year in conversion	In line with EAG*
Rate for ocular adverse event for ocular assessments prior to tisotumab vedotin infusions	52.8%	In line with EAG*
NHS reference costs	2024/2025	Updated in line with NICE recommendation**
NHS tariff costs	2025/2026	Added as per communication from Cancer Drugs Fund lead after ACM1
Paclitaxel	SB13Z per 2024/2025 NHS reference cost or 2025-2026 tariff	Updated in line with NICE recommendation**
Tisotumab price per vial	£[redacted]	Updated to reflect the company's latest PAS proposal*

*For the company base case, these implementations were already included in previous company evidence submission
**For the company base case, these implementations are in the current update to company base case

Table 10. Updated ICERs for the Company base case vs. Other scenarios including PSM

#	Admin cost source	OS in the first 12 months	QALY weight	ICER value (with QALY weight)
Company base case (semi-Markov with direct use of 12 months K-M data, health state transition thereafter & common risk of mortality post-progression)				
1	NHS 2024-2025 reference costs	Observed	1.7	£[redacted] (£[redacted])
2	NHS 2025-2026 tariff	Observed	1.7	£[redacted] (£[redacted])
Semi-Markov without direct K-M data for first 12 months, but with a common risk of mortality post-progression				
3	NHS 2024-2025 reference costs	Predicted	1.7	£80,459 (£47,329)
4	NHS 2025-2026 tariff	Predicted	1.7	£72,876 (£42,869)
PSM model: Gamma for OS for both treatments**; Loglogistic for PFS for both** treatments				
5	NHS 2024-2025 reference costs	Predicted	1.7	£[redacted] (£[redacted])
6	NHS 2025-2026 tariff	Predicted	1.7	£[redacted] (£[redacted])
PSM model: Gamma for OS for both treatments (and **HR=1 from month 18**); **Loglogistic for PFS for both** treatments a				
7	NHS 2024-2025 reference costs	Predicted	1.7	£[redacted] (£[redacted])
8	NHS 2025-2026 tariff	Predicted	1.7	£[redacted] (£[redacted])
PSM model: Loglogistic (tisotumab vedotin OS) and **gamma** (chemotherapy OS); **loglogistic** (PFS for both treatments)				
9	NHS 2024-2025 reference costs	Predicted	1.7	£[redacted] (£[redacted])
10	NHS 2025-2026 tariff	Predicted	1.7	£[redacted] (£[redacted])

9. Conclusion

The PSM analyses outlined above have been provided as requested by the appraisal committee. However, they are further evidence that the PSM extrapolations overestimate chemotherapy OS over time, and justify the company's initial consideration to use direct K-M data for the first 12 months when the benefit of these treatments is robustly represented by data from a substantial number of patients still at risk, combined with a health state transition modelling approach (i.e., semi-Markov). Compared to the PSM scenarios, the company base case uses more clinically plausible chemotherapy OS. As such, the ICERs in the company's initial submission have been updated in line with the committee's feedback on use of currently available NHS costs.

The updated ICERs (all with a 1.7 QALY weight) in the company's base case were £[redacted] (£[redacted]) based on 2024-2025 NHS reference costs and £[redacted] (£[redacted]) based on 2025-2026 NHS tariff.

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[Data on file] ID3753 Tisotumab Vedotin Post ACM1 Clinician Validation of Long-Term Survival Extrapolations. Data on file provided alongside this document.

Appendix

Figure 15. Observed K-M and all predicted OS curves for chemotherapy within the PSM framework

Figure 16. Predicted hazard plots from all the fitted OS curves for chemotherapy within the PSM framework

Figure 17. Observed K-M and all predicted OS curves for tisotumab vedotin within the PSM framework

Figure 18. Predicted hazard plots from all the fitted models for OS on tisotumab vedotin within the PSM framework

Figure 19. Observed K-M and all predicted PFS curves for chemotherapy within the PSM framework

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

Figure 20. Predicted hazard plots from all the fitted models for chemotherapy PFS within the PSM framework

Figure 21. Observed K-M and all predictive PFS curves for tisotumab vedotin within the PSM framework

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

Figure 22. Predicted hazard plots from all the fitted models for tisotumab vedotin PFS within the PSM framework

Figure 23. Tisotumab Vedotin (Log-logistic) and Chemotherapy (Gamma) within the PSM framework

Treatment	Time point	Observed	Predicted	Difference (Predicted - Observed)
Tisotumab vedotin	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	18 months	[redacted]	[redacted]	[redacted]
	24 months	[redacted]	[redacted]	[redacted]
Chemotherapy	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	18 months	[redacted]	[redacted]	[redacted]
	24 months	[redacted]	[redacted]	[redacted]

Figure 24. Tisotumab Vedotin (Gamma) and Chemotherapy (Gamma) within the PSM framework

Treatment	Time point	Observed	Predicted	Difference (Predicted - Observed)
Tisotumab vedotin	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	18 months	[redacted]	[redacted]	[redacted]
	24 months	[redacted]	[redacted]	[redacted]
Chemotherapy	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	18 months	[redacted]	[redacted]	[redacted]
	24 months	[redacted]	[redacted]	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tisotumab vedotin as monotherapy for treating adults with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy [ID3753]

Company evidence submission addendum 2

March 2026

File name	Version	Contains confidential information	Date
ID3753 Tisotumab vedotin Evidence Submission_Addendum_17032026 [CON]	**2.0**	**Yes**	**20 March 2026**

3. Cost effectiveness

The results in this addendum are generated using the updated Patient Access Scheme (PAS) price of [redacted] per vial. This represents a [redacted] discount off the list price of [redacted] per vial, which has also been updated since submission.

The reported results are underpinned by the "EAG's corrected Company base case" (see row 2 of Table 2 of the EAG report).

The chemotherapy delivery costs have been updated in the model as follows:

- SB13Z (Deliver more Complex Parenteral Chemotherapy at First Attendance) replaces SB14Z as the delivery code for weekly paclitaxel
- Delivery costs are informed by the 2025-2026 tariff costs provided by the CDF lead following ACM1 (Table 1)
- A scenario is also provided which uses the most recent NHS reference costs (Table 1)

Otherwise, the results are generated using the EAG's model and most recent PAS.

Table 1: updated chemotherapy delivery costs

	NHS 2025-2026 tariff[1]	**NHS 2024-2025 reference costs[2]**
SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance	£184.00	£256.03
SB13Z Deliver more Complex Parenteral Chemotherapy at First Attendance	£367.00	£300.81

1 Provided by CDF lead to the company via personal communication after the first committee meeting

2 https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

3.10. Base-case results

3.10.1. Base-case incremental cost-effectiveness analysis results

Table 2: Base-case results of costs, effectiveness, and incremental outcomes

	Total			Incremental			ICER
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Tisotumab vedotin	[redacted]	1.18	[redacted]	[redacted]	0.21	[redacted]	60,643
Chemotherapy	[redacted]	0.96	[redacted]				
Severity-weighted results					**QALY weight**	**Incremental QALYs**	**Weighted ICER**
					1.7	[redacted]	£35,673

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; TV, tisotumab vedotin.

Table 3: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]				
Severity-weighted results			**Severity weight**	**Incremental QALYs**	**NHB at £20,000**	**NHB at £30,000**
			1.7	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

3.11. Exploring uncertainty

3.11.1. Probabilistic sensitivity analysis

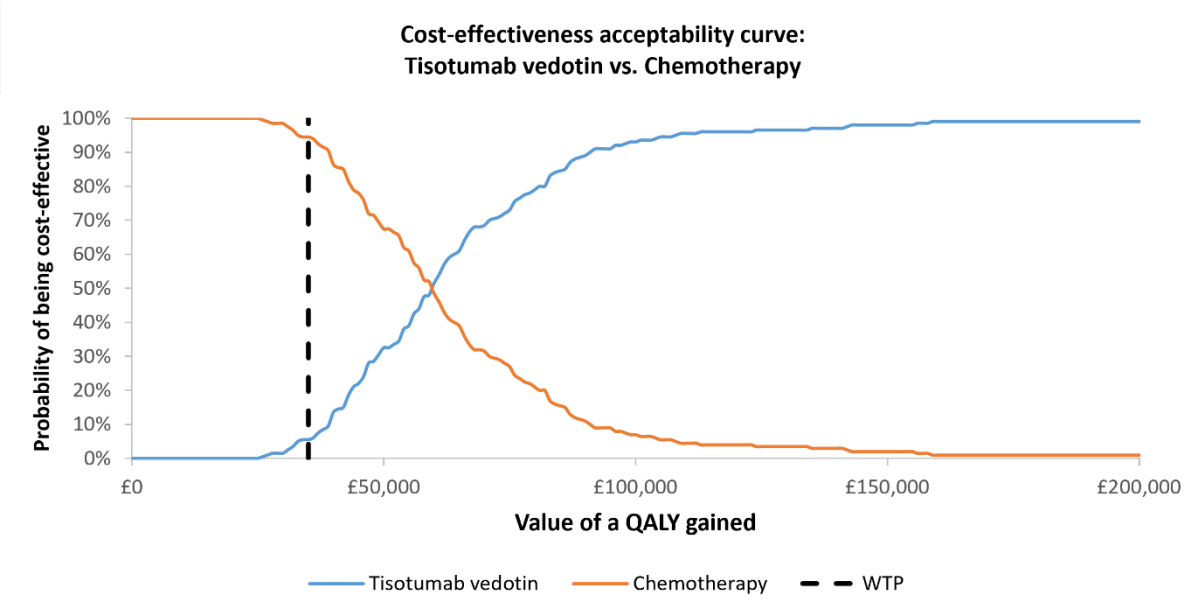
Table 4 shows the PSA results. The probabilistic ICER per QALY gained for tisotumab vedotin versus chemotherapy is slightly higher than the base-case deterministic results (Table 2). Cost-effectiveness acceptability curves and cost-effectiveness scatterplots, including the application of the severity modifier, are shown in Figure 1 and Figure 2, respectively. The cost-effectiveness acceptability curve suggested a 0% and 5.5% probability of tisotumab vedotin being cost-effective relative to chemotherapy at WTP thresholds of £25,000 and £35,000/QALY, respectively, with the severity modifier.

Table 4: PSA results

	Total			Incremental					ICER (£) per QALYs	Weighted ICER (£) per QALYs
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	Median severity weight	Weighted incremental QALYs		
Tisotumab vedotin	[redacted]	1.20	[redacted]	[redacted]	0.23	[redacted]	[redacted]	[redacted]	57,463	33,802
Chemotherapy	[redacted]	0.97	[redacted]							

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; TV, tisotumab vedotin.

Figure 1: Cost-effectiveness acceptability curves (tisotumab vedotin vs. chemotherapy)



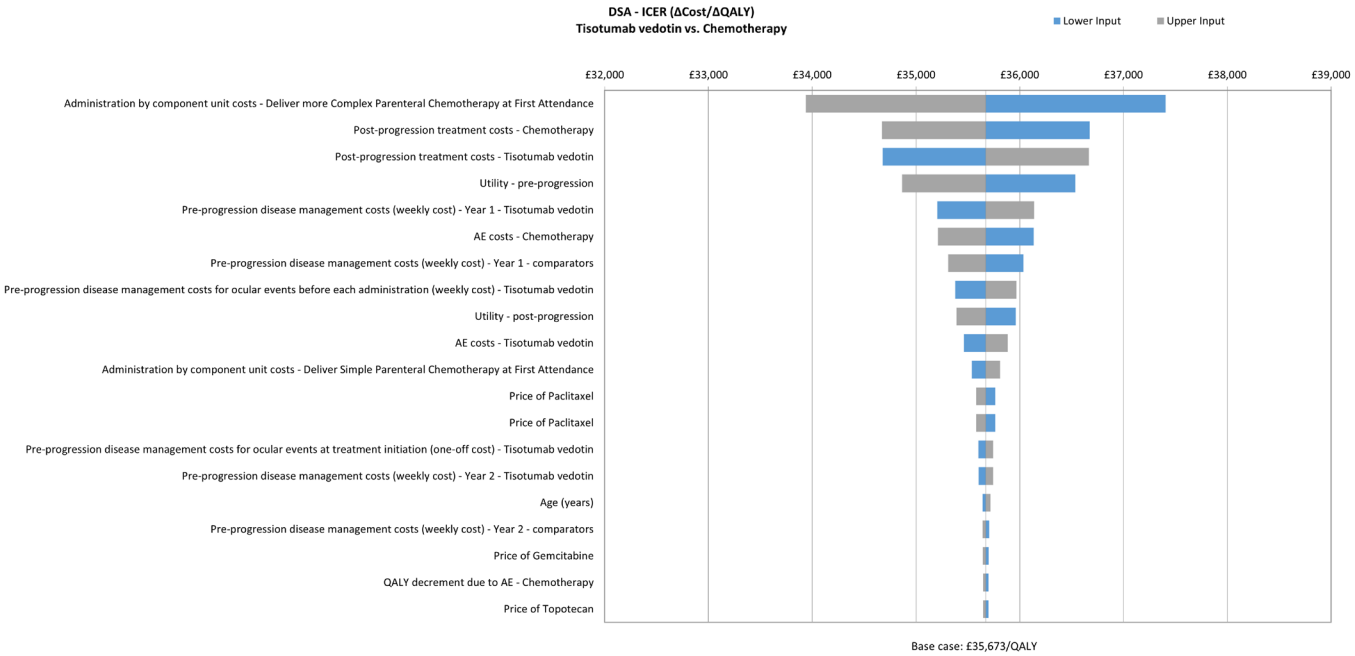
Abbreviations: QALY, quality-adjusted life year; WTP: willingness-to-pay.

Figure 2: Cost-effectiveness scatterplot (tisotumab vedotin vs. chemotherapy)

Abbreviations: QALY, quality-adjusted life year; WTP: willingness-to-pay.

3.11.2. Deterministic sensitivity analysis

Figure 3: Tornado diagrams for DSA (tisotumab vedotin vs. chemotherapy)



Abbreviations: AE, adverse event; DSA, deterministic sensitivity analysis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS: progression-free survival; RDI, relative dose intensity.

3.11.3. Scenario analysis

.

Table 5: Scenario analysis results

Scenarios	Scenario analysis setting	Base case setting	Incremental QALYs (weighted*)	Incremental Costs (£)	ICER/QALY (£)
Base case	-	-	[redacted]	[redacted]	**35,673**
Chemotherapy treatment distribution from the InnovaTV 301 trial	topotecan: 7.90%, vinorelbine: 7.10%, gemcitabine: 45.60%, irinotecan: 5.90%, pemetrexed: 33.50%, paclitaxel: 0.00%	Survey of 8 UK clinicians	[redacted]	[redacted]	48,144
InnovaTV 301 trial – mixed effects model utilities	pre-progression: 0.711, post-progression: 0.566	InnovaTV 301 trial (GEE) utilities	[redacted]	[redacted]	35,734
Literature - Zheng 2023 utilities	pre-progression: 0.850, post-progression: 0.520	InnovaTV 301 trial (GEE) utilities	[redacted]	[redacted]	31,026
Literature – Liu 2023 utilities	pre-progression: 0.817, post-progression: 0.779	InnovaTV 301 trial (GEE) utilities	[redacted]	[redacted]	42,714
Exclude AE disutility	Exclude AE disutilities	Include AE distuility	[redacted]	[redacted]	35,683
Exclude AE costs	Exclude AE costs	Include AE costs	[redacted]	[redacted]	38,179
Tisotumab vedotin/chemotherapy PF to PD parametric curve	Tisotumab vedotin/chemotherapy PF to PD parametric curve	Tisotumab vedotin/chemotherapy PF to PD parametric curve	[redacted]	[redacted]	44,607

Scenarios	Scenario analysis setting	Base case setting	Incremental QALYs (weighted*)	Incremental Costs (£)	ICER/QALY (£)
distribution – Lognormal (based on second lowest AIC and BIC)	distribution - Lognormal	distribution - Generalised Gamma			
Distribution for the Parametric Curve - PF to death - tisotumab vedotin: lognormal, chemotherapy: Gompertz (based on second lowest AIC and BIC)	Tisotumab vedotin/chemotherapy PF to death parametric curve distribution - tisotumab vedotin: lognormal, chemotherapy: Gompertz	Distribution for the Parametric Curve - PF to death - tisotumab vedotin: Gompertz, chemotherapy: Lognormal	[redacted]	[redacted]	39,925
Use NHS reference costs for chemotherapy administration	Use NHS reference costs for chemotherapy administration	NHS drug tariff	[redacted]	[redacted]	39,335

Abbreviations: DoT, duration of treatment; GEE, generalised estimating equation; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS: progression-free survival; TV, tisotumab vedotin.
Notes: Chemotherapy OS and PFS parametric function scenarios referred to the parametric function scenarios in the dependent model, in which both TV and chemotherapy parametric functions changed.
*Incremental QALYs are presented based on inclusion of the severity modifier

External Assessment Group (EAG) Report

Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment [ID3753]

EAG's critique of the company's response to the draft guidance document

Produced by **Southampton Health Technology Assessments Centre (SHTAC)**

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[redacted]

Table of contents

List of tables

List of Figures

List of Abbreviations

AIC	Akaike information criterion
BIC	Bayesian information criterion
CI	Confidence interval
CIC	Commercial in confidence
CS	Company submission
DG	Draft guidance
EAG	External Assessment Group
HRG	Healthcare Resource Group
ICER	Incremental cost-effectiveness ratio
KM	Kaplan-Meier
NHB	Net Health Benefits
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression free survival
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
TSD	Technical Support Document
UK	United Kingdom

1 Introduction

This document is the External Assessment Group's (EAG's) critique of the response by the company, Genmab A/S, to the National Institute for Health and Care Excellence's (NICE's) draft guidance (DG) document (issue date February 2026) for the technology appraisal of tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment (ID3753). The EAG received the company's comments on the DG document, associated documents and updated model on 26th March 2026.

The company's DG response contains the following documents:

- Company's evidence submission response.
- Company evidence submission addendum (version 2.0), reporting updated model results.
- A confidential data on file document reporting clinician feedback and validation of long-term survival extrapolations for the cost-effectiveness analysis.
- An updated version of the company's economic model.

In this report, we present the following:

- Our critique of the company's DG response (section 2).
- Validation of the company's revised cost-effectiveness results (section 3).
- Results of the EAG base case and scenario analyses (section 4).
- A summary of EAG conclusions (section 5).

All cost-effectiveness results reported in this document are calculated using the updated proposed confidential Patient Access Scheme (PAS) discounted price for tisotumab vedotin of [redacted], as reported to the EAG in the NICE Pricing tracker form dated January 2026. All other drugs are costed at list price. We report cost-effectiveness results including all available drug price discounts in a confidential addendum to this document.

2 Critique of the company's DG response

The company discuss the validity of parametric survival distributions for overall survival (OS) and progression free survival (PFS) fitted directly to InnovaTV301 trial data in sections 3 and 4 respectively of their evidence submission response document (see sections 2.1 and 2.2 below).

2.1 Section 3 of the company's DG response: OS parametric extrapolations and hazard functions in PSM

2.1.1 Assessment of the proportional hazards assumption

Figures 1 and 2 in the company's DG response show the InnovaTV301 OS log cumulative hazard and hazard plots respectively, by treatment arm. The EAG agrees with the company's conclusion that the assumption of proportional hazards is not supported for OS, as the log cumulative hazard curves cross and the observed hazard trends differ between arms. It is therefore appropriate that the company fit OS curves independently for chemotherapy and tisotumab vedotin: see sections 2.1.2 and 2.1.2.4 respectively for EAG critique of this process.

We note that both smoothed hazard plots in company response Figure 2 are initially increasing, but the rate of increase is sharper for chemotherapy, with a peak at around 7-8 months, followed by a gradual decline. By comparison, tisotumab vedotin shows a slower increase in the hazard, with a weak decline only after about [redacted], when the number of patients at risk is low. There is high uncertainty at the tail of both hazard functions, due to the low effective sample size.

2.1.2 Fitted OS parametric extrapolations for chemotherapy

2.1.2.1 OS chemotherapy: visual fit to KM data from InnovaTV 301

Company response Figure 3 shows the KM estimates and four standard parametric curves fitted to chemotherapy OS InnovaTV301 trial data (Figure 15 in the response appendix includes all seven standard parametric distributions). The company conclude that 'no parametric function fits the observed chemotherapy data well', but that the log-normal and log-logistic provide the 'closest visual approximation'.

The inclusion of KM estimates from the chemotherapy arm of the EMPOWER trial in company response Figures 3 and 15 makes it difficult to visualise the fit of the parametric curves to the InnovaTV301 trial data, which provides the comparative evidence base for tisotumab vedotin. Figure 1 below provides a clearer focus on the fit of the OS parametric curves for chemotherapy to InnovaTV301 KM estimates (mean and 95% confidence limits). We discuss evidence relating to the external validity of the OS curves for chemotherapy in section 2.1.2.4 below.

Based on Figure 1, the EAG considers that the log-logistic, lognormal and generalised gamma distributions have a good visual fit to the InnovaTV301 KM for chemotherapy. We note that the gamma has a worse visual fit, but retain it for consideration as it provides a less favourable long-term projection which may be considered more clinically realistic. The exponential and Gompertz curves clearly have a very poor visual fit to the KM estimates in the initial months, falling below the 95% confidence limit, and have been excluded from Figure 1 for clarity. We also exclude the Weibull, as this has a very similar shape and long-term projection to the gamma, but with a slightly worse fit.

2.1.2.2 OS chemotherapy: Underlying hazard functions over time

The company show hazard plots for InnovaTV301 chemotherapy data and the fitted parametric distributions in Figures 4 and 16 of their response document. They conclude that it is not clear if any parametric distribution can be selected or excluded solely based on the hazard shape. We agree that the shape of the hazard function is not definitive, however the initial increase and subsequent gradual decline of the smoothed hazard function based on InnovaTV301 trial data does suggest that a distribution with a non-monotonic hazard (log-logistic, lognormal or generalised gamma) would be appropriate.

2.1.2.3 OS chemotherapy: Goodness-of-fit statistics

Goodness-of-fit statistics for the chemotherapy OS parametric distributions (company response Table 1) are consistent with the above conclusions based on visual fit. The ranking of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics indicate that the log-logistic distribution has the best fit, followed by log-normal, generalised gamma and then gamma.

Figure 1 Chemotherapy OS: InnovaTV301 KM estimates and four best-fitting parametric curves

Source: Produced by the EAG from the company's economic model

2.1.2.4 OS chemotherapy: Landmark OS estimates

Table 2 in the company's response compares chemotherapy OS predictions from the parametric distributions at landmark timepoints with InnovaTV301 KM estimates (internal validation) and with KM estimates from the EMPOWER trial (external validation).[1,2] As noted in the footnote to Table 2, the predictions do not account for adjustments in the EAG preferred PSM version of the economic model which prevent overlap of the OS curves. The company comment that there are 'notable differences' between the predictions from the parametric distributions and the InnovaTV301 KM estimates at both 1 and 2 years. We do not agree that these differences are 'notable' for the best fitting parametric functions. Predictions from the log-logistic, lognormal and generalised gamma are within [redacted] percentage points of InnovaTV301 KM estimates at 1 year, and within [redacted] percentage points at 2 years. These differences are not large, and not surprising given the small remaining number of people at risk at these timepoints.

With regard to the external validation, the InnovaTV301 KM OS estimates for chemotherapy are similar to those from EMPOWER at 1 year ([redacted] versus 34.26%). However, the InnovaTV301 KM estimates are considerably higher at 2 years ([redacted] versus 11.30%) so the OS predictions from the fitted distributions at year 2 exceed the EMPOWER KM estimates. We note that the 3-year predictions from the parametric models are closer to the EMPOWER KM estimate (7.23%): very similar with the generalised gamma extrapolation ([redacted]), higher with the log-logistic and lognormal ([redacted] and [redacted] respectively), and lower with the gamma ([redacted]). Oaknin et al. (2025)[2] report updated final results for the EMPOWER trial. The OS KM curves in Figure 1 of the Oaknin paper show that a small proportion of patients in the chemotherapy arm of EMPOWER had an extended survival (approximately 6% at month 48). As with InnovaTV301, EMPOWER is subject to uncertainty due to the diminishing sample remaining at risk over time.[2]

2.1.3 Fitted OS parametric extrapolations for tisotumab vedotin

2.1.3.1 OS tisotumab vedotin: visual fit to KM data from InnovaTV 301

Figure 5 in the company's response includes four fitted parametric curves which the company consider have a closer fit to the InnovaTV301 KM estimates (Weibull, log-

logistic, gamma and generalised gamma). Figure 17 in the response appendix shows all 7 standard parametric distributions. Again, we provide another version of this graph (Figure 2 below) to help visual assessment of the fit to the pivotal InnovaTV301 trial KM (mean and 95% confidence limits). We exclude the exponential curve, which has a very poor visual fit, and the Gompertz and lognormal which underestimate OS in in the first 6-7 months. The Weibull, gamma and generalised gamma curves are all very similar and have a good visual fit to the KM. The log-logistic also has a reasonable visual fit, but with higher OS in the initial period and after about 18 months.

2.1.3.2 OS tisotumab vedotin: Underlying hazard functions over time

Company response Figures 6 and 18 show the OS hazard plots for tisotumab vedotin. We agree with the company's assessment that the hazard plot suggests a non-monotonic trend, with initially increasing and then decreasing hazards and that this is subject to uncertainty due to the declining number of patients at risk. This suggests that the Weibull, generalised gamma and gamma distributions, which show a continually increasing hazard, are not consistent with the observed hazard from the InnovaTV301 trial.

2.1.3.3 OS tisotumab vedotin: Goodness-of-fit statistics

The goodness-of-fit statistics in company response Table 3 indicate that the Weibull, gamma, log-logistic and generalised gamma have the best fit to InnovaTV301 data. The AIC and BIC values are similar for these four distributions, indicating a similar fit.

2.1.3.4 OS tisotumab vedotin: Landmark OS estimates

Table 4 in the company response summarises OS estimates for tisotumab vedotin from the InnovaTV301 KM and fitted distributions. The four best-fitting distributions all have close fit to the KM at years 1 and 2. Predictions from the best fitting distributions are also close to the KM estimates from the phase 2 InnovaTV204 trial at 1 year, but the Weibull, gamma and generalised gamma all underestimate InnovaTV204 OS at 2 and 3 years. The log-logistic provided long-term (2 and 3 year) predictions close to those observed in the InnovaTV204 trial.

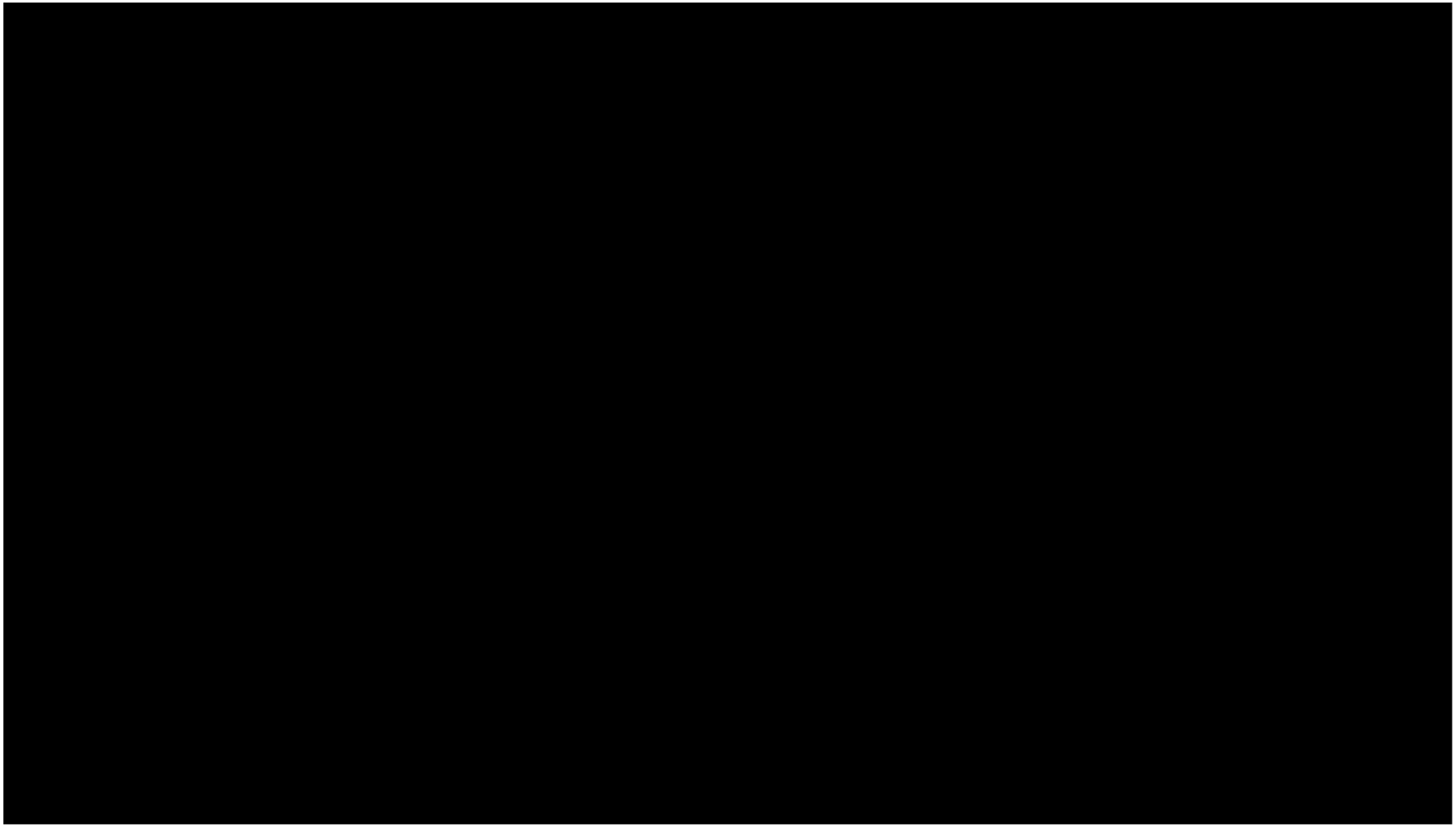

Figure 2 Tisotumab vedotin OS: InnovaTV301 KM estimates and fitted parametric curves

Source: Produced by the EAG from the company's economic model

2.1.4 Clinical validation of OS extrapolations

The company report feedback from three additional UK clinicians with experience of treating relapsed or metastatic cervical cancer (CG response section 3.3). The clinicians considered that none of the chemotherapy extrapolations were clinically plausible, and estimated 2-year survival at no more than [redacted]. Two clinicians indicated that the gamma was most plausible for chemotherapy, the other did not express a preference. The clinicians did not indicate which OS extrapolation was more plausible for tisotumab vedotin, due to limited experience of this treatment.

2.2 Section 4 of the company's DG response: PFS parametric extrapolations and hazard functions in PSM structure)

The company fitted independent parametric distributions for PFS in the chemotherapy and tisotumab vedotin arms. They conclude that for both chemotherapy and tisotumab vedotin, the log-logistic, log-normal and generalised gamma distributions have the best statistical and visual fit to InnovaTV trial data, and reflect the non-monotonic hazard trends (initially increasing and then decreasing). For their PSM scenarios, the company use a log-logistic PFS distribution for both arms, which is consistent with the EAG's preference. The ICER is not sensitive to the choice of PFS extrapolation in the PSM model (see Table 3 below).

The company have not provided additional information regarding the choice of extrapolation for pre-progression survival or time to progression with their semi-Markov model structure.

2.3 Section 5 of the company's DG response: Company base case vs. PSM scenarios

The company retain the semi-Markov model for their base case, but report alternative scenarios in a PSM structure in response Tables 10 and 11. They argue that for PSM OS should be modelled using a gamma for chemotherapy and either log-logistic or gamma for tisotumab vedotin, with log-logistic for PFS in both arms. They also argue that using a gamma distribution for OS in both arms results in an implausible hazard ratio trend, and report an additional scenario with a hazard ratio of 1 applied from 18 months onwards.

2.4 Section 6 of the company's DG response: Severity modifier

The company report that 45 out of 49 PSM scenarios that they have run produced an incremental QALY that would be consistent with a severity weighting of 1.7. All of the results in the company's DG response and Addendum are reported with a 1.7 QALY weight. For EAG analyses (section 4 below), we report ICERs with the appropriate severity weight for the incremental QALY produced by the respective analysis.

2.5 Section 7 of the company's DG response: Updated NHS costs

As requested in the DG, the company updated their analyses using the HRG code SB13Z for the cost of administering paclitaxel (SB12Z is used for tisotumab vedotin and the other chemotherapies). The company cite two sources for these costs: see company response Addendum Table 1.

- NHS 2024-25 'reference costs', or National Cost Collection (NCC) data which reports the cost per episode of patient care as reported by NHS providers (National schedule of NHS costs).
- NHS 2025-26 tariff – which reflects NHS payments for provision of services (NHS England » 2025/26 NHS Payment Scheme).

The results in the main company response document are reported at both reference costs and tariff prices. Results in the Addendum to the company's response are reported at tariff prices, with a scenario is included with reference costs.

The EAG analyses reported below use reference costs (NCC costs), as we understand that this is the convention for costing in NICE appraisals. We report results using the tariff prices in a scenario.

3 EAG validation of the company's revised cost effectiveness results

3.1 Validation of the company's economic model

The EAG conducted face-validity and verification checks on the company's model provided with the company's DG response dated 25/03/2026. The company's post-DG economic model is not based on the latest economic model version used after the factual accuracy check on 13/11/2025, which included EAG modifications. In order to verify the model, we compared the post-FAC and post-DG versions of the model. The main differences are listed in the company's DG response document in Table 9, and the EAG has verified that these changes have been appropriately applied in the post-DG model:

1. The company implemented the EAG corrections to the model observed in the EAG report, section 5.2.3.
2. They include a control to allow the user to cap the overall survival hazard ratio at 1 for PSMs. It is possible to specify the month in which the cap applies.
3. The administration procedure code SB14Z was replaced with SB13Z.
4. All costs based on the NHS Reference cost 2023-2024 were replaced with 2024-2025 National Cost Collection costs.
5. The company included the "NHS Payment Scheme 2025-2026, Unbundled chemotherapy delivery" as an alternative to the NHS Reference cost 2024-2025 for chemotherapy administration.

Reverting modifications 3 to 5, we replicated the company's base-case result with EAG corrections in the EAG report (EAR Table 25). The company made some additional modifications to the model that did not seem to affect the results. The most relevant are listed below (the other changes appear to be intended to improve the appearance of the model):

- The willingness to pay threshold, used to calculate Net Health Benefits (NHB), changed from £20,000 to £30,000 to the new threshold (£25,000 to £35,000) in line with NICE resolution on 02/04/2026.

- In the "Effectiveness_calc" sheet, the company extended the formulas in columns CR, CZ, and DE, from row 33 to row 2559. Previously, these formulas were replicated up to row 1598. This does not affect the results.
- In the "Effectiveness_calc" sheet, the company changed the range of the formula in cell DK29 to only test for OS curves crossover after 50 initial cycles instead of 10 initial cycles (one cycle = one week). This information is only used for the PSM option ("Partitioned survival model - independent model, with a common mortality rate once the OS curves of TV and chemotherapy converge"). This does not affect the results, as the OS crossover in this model occurs close to 18 months.

The EAG did not identify any errors in the company's revised economic model. We re-implemented the modifications necessary to run the EAG preferred assumptions (see EAR section 5.2.5) and the scenario analysis.

3.2 Validation of the data sources

The company included two new data sources for costs: the "NHS Cost Collection 2024-2025" and the "NHS Payment Scheme 2025-2026". Both can be used for the administration costs, and the first one is considered for the outpatient costs. The EAG checked the values of all relevant input parameters, and they are consistent between the cited sources, the company's DG response and the model.

3.3 Validation of the company's cost-effectiveness results

The company's base case and additional scenarios results are shown in the company's DG response Table 10, with both the NHS Cost Collection 2024-2025 and the NHS Payment Scheme 2025-2026 for the administration cost. The EAG has verified that these results match the company's post-DG economic model.

The Company's DG response Addendum 2 shows their base case results (section 3.10.1 Table 2), probabilistic sensitivity analysis (section 3.11.1 Table 4, Figures 1 and 2), deterministic sensitivity analysis (section 3.11.2 Figure 3) and the scenario analysis from CS Table 70 (section 3.11.3 Table 5) considering only the NHS Payment Scheme 2025-2026 for the administration cost. The EAG was able to replicate all reported results.

4 EAG analyses

4.1 EAG's preferred assumptions

The EAG preferred assumptions are presented in EAR section 5.2.5. After the critique of the company's DG response, we updated our preferred assumptions as shown in Table 1 below.

Table 1 EAG revised preferred assumptions

ID	EAG preferred assumptions in the EAR report	EAG revised preferred assumptions after critique of the company's DG response
1	Do not use OS Kaplan Meier data directly in the OS selected curve	No change
2	PSM, with an assumption that the mortality hazard is the same for tisotumab vedotin and chemotherapy from the point where the OS curves converge. For our base case, we use log-logistic extrapolations for PFS and OS in both arms	No change
3	Cost for administration of paclitaxel: use a reduced cost for simple parenteral administration of paclitaxel (code SB12Z)	In line with the DG recommendation, we use of the SB13Z code. The EAG agree with this assumption. We also update costs for chemotherapy as recommended.
4	Chemotherapy mix: Use the EAG expert estimates for the single-agent chemotherapy mix	No change
5	Subsequent treatment mix: Use the EAG expert estimates for the subsequent therapy mix	No change
6	Healthcare management costs: Use the EAG expert estimates for single-agent chemotherapy mix	No change

Source: EAG created the table
DG, draft guidance; PSM, partitioned survival model; PFS, progression free survival; OS, overall survival; EAG external assessment group

The EAG used the 2024-2025 NHS National Cost Collection 2024-2025 (reference costs) for chemotherapy administration costs, as we understand that reference costs have been used conventionally for costing in NICE guidance. We report results for a scenario with the NHS Payment Scheme (tariff) costs 2025-2026 in Table 3 below.

The cumulative cost-effectiveness results from applying the EAG preferred model assumptions, one at a time, to the company's post-DG base case ICER are shown in Table 2 below. This table and other results in this report include a confidential PAS discount for tisotumab vedotin, and list price for the other treatments. We provide a separate EAG confidential PAS addendum with confidential price discounts for all drugs in the economic model.

Incorporating all of the EAG preferred assumptions, the deterministic ICER for tisotumab vedotin compared with chemotherapy increases to [redacted]). The 1.2 severity multiplier is appropriate given the incremental QALY gain in this analysis. If a 1.7 severity modifier is applied with the EAG's preferred assumptions, the estimated ICER is [redacted] per QALY.

4.2 Scenario analyses conducted in the EAG's base case

The scenario analyses applied to the EAG base case are summarised in EAR Table 33. The scenario results are presented in Table 3 below. We have not included the scenario related to the administration cost for paclitaxel, as the NICE DG recommends use of the procedure cost code SB13Z. We include an additional scenario with the alternative source for the administration costs (NHS Payment Scheme 2025/2026) provided in the company's DG response document.

Table 2 Cumulative cost-effectiveness results using EAG's preferred assumptions with and without severity weighting

Preferred assumption	Treatment	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs (with weight)	Cumulative ICER £/QALY (with weight)	QALY weight applied
Company's revised base case post-draft guidance	Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.7
	Tisotumab vedotin	[redacted]	[redacted]		[redacted]	[redacted]	
Semi-Markov without OS KM data for first 12 months	Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.7
	Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PSM: PFS and OS log-logistic in both arms (EAG preferred)	Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.2
	Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Single agent chemotherapy mix EAG experts' estimates	Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.2
	Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent treatment mix EAG experts' estimates	Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.2
	Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Healthcare management cost EAG experts' estimates	Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.2
	Tisotumab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EAG's revised base case	Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.2
	Tisotumab vedotin	[redacted]	[redacted]		[redacted]	[redacted]	

Source: EAG created table. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PSM, partitioned survival model; PFS, progression free survival; OS, overall survival; NA, not applicable; EAG external assessment group, TV: tisotumab vedotin, CHEM: chemotherapy
Note: The administration cost is based on the NHS Reference Cost 2024-2025

Table 3 EAG scenario analysis applied to the EAG's preferred analysis

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (with weight)	ICER £/QALY (1.2 weight)	QALY weight applied
	EAG's revised base case	[redacted]	[redacted]	[redacted]	1.2
1	Chemotherapy treatment mix based on company expert estimates (company's assumption)	[redacted]	[redacted]	[redacted]	1.2
2	Subsequent treatment mix based on the company expert estimates (company's assumption)	[redacted]	[redacted]	[redacted]	1.2
3	Healthcare management costs based on company expert estimates for single agent chemotherapy	[redacted]	[redacted]	[redacted]	1.2
4	Company's semi-Markov model with KM data for OS during the first 12 months	[redacted]	[redacted]	[redacted]	1.7
5	Company's semi-Markov model with no KM data (OS fitted from time 0)	[redacted]	[redacted]	[redacted]	1.7
6	EAG PSM scenario: generalised gamma for OS in both arms (EAR Figure 13)	[redacted]	[redacted]	[redacted]	1.7
7	EAG PSM scenario: Weibull for TV OS and log-logistic for chemo OS (EAR Figure 14)	[redacted]	[redacted]	[redacted]	1.7

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (with weight)	ICER £/QALY (1.2 weight)	QALY weight applied
8	Company PSM scenario: Gamma for OS for both treatments; Log-logistic for PFS for both treatments	[redacted]	[redacted]	[redacted]	1.7
9	PSM: PFS scenario with log-normal in both arms	[redacted]	[redacted]	[redacted]	1.2
10	PSM: PFS scenario with generalised gamma in both arms	[redacted]	[redacted]	[redacted]	1.2
11	Consider OS KM curve for the first 12 months. (company's assumption)	[redacted]	[redacted]	[redacted]	1.2
12	Pre and post progression utility from the lower values of the 95% CI (0.69, 0.54) (EAG exploratory scenario)	[redacted]	[redacted]	[redacted]	1.2
13	Pre and post progression utility from the upper 95% CI values (0.73, 0.59) (EAG exploratory scenario)	[redacted]	[redacted]	[redacted]	1.2
14	Use the NHS Payment Scheme 2025/2026 (tariff prices) as source for the administration cost.	[redacted]	[redacted]	[redacted]	1.2

Source: EAG created the table based EAR Table 34
CI, confidence interval; EAG external assessment group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PD, progressed-disease; PF, progression-free; PFS, progression-free survival; PSM, partitioned survival model; QALY, quality-adjusted life year; TV, tisotumab vedotin

5 EAG conclusions

The EAG analyses in Table 2 and Table 3 demonstrate the sensitivity of the ICER to changes that decrease the gap between the projected OS curves for tisotumab vedotin and chemotherapy, including omitting the direct use of KM data in the company's semi-Markov model, and the choice of parametric curves for extrapolation of OS in the EAG's preferred PSM structure. These effects are amplified by changes in the severity weight applied to QALYs.

Following EAG review of the company's response to the draft guidance, we maintain our view that the PSM framework for cost-effectiveness analysis is more appropriate than the company's semi-Markov approach. The available evidence does not support the assumptions required for the company's model structure: the same, constant OS hazard after disease progression in both treatment arms.

The company have reported some additional information on the modelled OS extrapolations, including additional clinical opinion and hazard plots for fitted distributions. We consider that the fitted parametric curves in Figure 1 and Figure 2 above all show an acceptable fit to the available data from the pivotal InnovaTV301 trial. There is uncertainty due to the overlap of the trial KM plots and the better than expected survival in the control arm at 24 months. This is likely due to the low number of patients remaining at risk towards the end of trial follow-up. It is also possible that the patients recruited to the InnovaTV301 trial have better outcomes than the broader population of patients in clinical practice. Nevertheless, it is clear that the trial does not provide evidence of a persistent survival benefit with tisotumab vedotin beyond [redacted] of follow-up.

We have not changed the OS extrapolations in the EAG preferred analysis, as we still consider that log-logistic curves for both arms provide the best fit to the available trial data, with a declining survival benefit from the point where the KM curves cross (see EAR Figure 12). From a clinical perspective, the projected survival with chemotherapy in this analysis may be considered overly optimistic. We have therefore previously reported alternative scenarios with less favourable longer-term survival projections that are still consistent with the comparative KM data from the trial (scenarios 6 and 7 in Table 3 above). The company have also reported a similar

scenario with gamma OS curves for both arms (Table 3 scenario 8). However, we consider that the company's alternative scenario with a log-logistic extrapolation for tisotumab vedotin and gamma for chemotherapy (company response Figure 23) assumes a persistent survival benefit that is not supported by the trial data.

References

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