

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:

[Access the **final scope** and **final stakeholder list** on the NICE website.](#)

- 1. Company submission from Genmab:**
 - a. Full submission
 - b. Submission addendum
 - c. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Expert perspectives from:**
 - a. Gemma Eminowicz – Consultant Clinical Oncologist, nominated by Genmab
 - b. b. Lisa Barraclough – Consultant Clinical Oncologist, nominated by Genmab
 - c. Joan Campbell - Patient expert
- 4. External Assessment Report** prepared by Southampton Health Technology Assessments Centre
 - a. EAG addendum
- 5. External Assessment Report – factual accuracy check**

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

Company evidence submission

October 2025

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Abbreviations

Acronym	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
AIC	Akaike information criterion
BGCS	British Gynaecological Cancer Society
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CASP	Critical Appraisal Skills Programme
CC	Cervical cancer
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CMH	Conchran-Mantel-Haenszel
CR	Complete response
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Chemotherapy
CT scan	Computed tomography scan
C1D1	Cycle 1 Day 1
DCR	Disease control rate
DOR	Duration of response
DOT	Duration of treatment
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DX	Diagnosis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC-	European Organization for Research and Treatment Quality of Life

QLQ-CX24	Questionnaire Cervical Cancer Specific module
EORTC-QLQ-C30	European Organization for Research and Treatment Quality of Life Questionnaire Core 30
EQ-5D-3L	EuroQol 5 Dimension 3 Level
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ESGO	European Society of Gynaecological Oncology
ESMO	European Society for Medical Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
FAS	Full analysis set
FFPE	Formalin-fixed paraffin-embedded
FIGO	Federation of Gynaecology and Obstetrics
GEE	Generalized estimating equation
GHS	General health score
HCP	Healthcare professional
HPV	Human papillomavirus
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HRU	Healthcare resource utilisation
HTA	Health technology assessment
IC	Investigator's choice
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IPD	Individual participant data
IQR	Interquartile range
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan Meier
LACC	Locally advanced cervical cancer

LOT	Line of treatment
LS	Least squares
LY	Life year
LYG	Life years gained
mCC	Metastatic cervical cancer
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
ml	Millilitres
MMAE	Monomethyl auristatin E
MRI	Magnetic resonance imaging
N	Number
NHB	Net-health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OR	Overall response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PD(L)1	Programmed cell death-ligand 1
PET	Positron emission tomography
PF	Progression-free
PFS	Progression free survival
PK	Pharmacokinetics
PN	Peripheral neuropathy
PR	Partial response
PRO	Patient reported outcome
PPS	Post-progression survival
PSA	Probabilistic Sensitivity Analysis
PS	Performance status
PSM	Partitioned survival model
PSS	Personal social services

PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	Quality of life
Q1W	Once weekly
Q3W	Once every three weeks
RCT	Randomised controlled trial
RDU	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
r/m	Recurrent or metastatic
RNA	Ribonucleic acid
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Stable disease
sd	Standard deviation
SE	Standard error
SG	Standard gamble
SJS	Stevens-Johnson syndrome
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SoC	Standard of care
STA	Single technology appraisal
TAb	Tisotumab vedotin antibodies
TEAE	Treatment-emergent adverse event
TF	Tissue factor
TLF	Tables, listings and figures
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TTR	Time to response
TTP	Time to progression
TV	Tisotumab vedotin (Tivdak)
UK	United Kingdom

US	United States
VAS	Visual analogue scale
WTP	Willingness to pay
YLD	Years of life lived with disability
YLL	Years of life lost

1. Decision problem, description of the technology and clinical care pathway

1.1. *Decision problem*

The submission covers the technology's full marketing authorisation for this indication. Tisotumab vedotin (Tivdak®) is indicated as a monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer (r/m CC) with disease progression on or after systemic therapy.

The decision problem that this submission addresses is outlined in **Table 1**.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with recurrent or metastatic cervical cancer that has progressed on or after systemic treatment	Adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy	Population wording updated to align with expected MHRA marketing authorisation
Intervention	Tisotumab vedotin (Tivdak) as a monotherapy	Tisotumab vedotin (Tivdak) as a monotherapy	Not applicable
Comparator(s)	- Single-agent chemotherapy (including but not limited to paclitaxel, doxorubicin, gemcitabine and topotecan) - Best supportive care	Single-agent chemotherapy (including topotecan, gemcitabine, irinotecan, vinorelbine, pemetrexed)	There is currently no standard of care in second line r/m CC. The chemotherapies included in the comparator list (i.e., topotecan, gemcitabine, irinotecan, vinorelbine, pemetrexed) reflect chemotherapies from InnovaTV 301 and represent single-agent chemotherapy as a comparator in the economic model. Since tisotumab vedotin is an antibody-targeted chemotherapy the majority of patients unsuitable for chemotherapy would likely also be unsuitable for treatment with tisotumab vedotin. BSC would

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			therefore not comprise a suitable comparator to tisotumab vedotin since BSC is generally reserved for patients who are unsuitable for chemotherapy. During clinician engagement at the UK Cervical Cancer advisory board and an additional survey of 8 UK based oncologists with expertise in gynaecological cancers, Q1W paclitaxel was identified as a frequently used chemotherapy monotherapy in this population. Clinicians also agreed at the UK Cervical Cancer advisory board that the absence of paclitaxel from the clinical trial is not a concern as there are no data supporting a difference in efficacy between the trial comparators and Q1W paclitaxel. Q1W paclitaxel is included in the base-case modelling scenario as a cost comparator to reflect this element of UK clinical practice.
Outcomes	The outcome measures to be considered include: • Progression free survival (PFS) • Overall survival (OS)	The outcome measures to be considered include: • PFS • OS	Not applicable

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	• Response rates • Adverse effects of treatment • Health-related quality of life (HRQoL)	• Response rates • Adverse effects of treatment • HRQoL	
Economic analysis	Cost-effectiveness expressed as incremental cost per quality-adjusted life year as per the reference case.	Cost-effectiveness expressed as incremental cost per quality-adjusted life year as per the reference case.	Not applicable
Special considerations including equity or equality issues	NR	Cervical cancer affects females, often in their younger child-bearing years and while they are actively raising families. The disease burden of cervical cancer is greater among those with lower socioeconomic status and non-white ethnic populations in the UK.	Not applicable

Abbreviations: HRQoL, health-related quality of life; MHRA, Medicines and Healthcare products Regulatory Agency; NR, not reported; OS, overall survival; PFS, progression-free survival; Q1W, weekly; r/m CC, recurrent or metastatic cervical cancer; UK, United Kingdom.

1.2. Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Tisotumab vedotin (Tivdak®)
Mechanism of action	Tisotumab vedotin is a novel antibody-drug conjugate (ADC) that binds to tissue factor (TF), a cell surface protein expressed in cervical cancer and other solid tumours. Upon binding, the ADC-TF complex is internalised and local release of monomethyl auristatin E (MMAE) occurs via proteolytic cleavage which leads to cell death.
Marketing authorisation status	Tisotumab vedotin does not currently have a marketing authorisation in the UK for treating recurrent or metastatic cervical cancer. MHRA approval is expected in [REDACTED]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated marketing authorisation for tisotumab vedotin in the UK is as a monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.
Method of administration and dosage	The recommended dose of tisotumab vedotin is 2 mg/kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 minutes every 3 weeks. Detailed information on dose modification and discontinuation can be found in the SmPC linked in Appendix A: Summary of product characteristics (SmPC) and UK public assessment report.
Additional tests or investigations	Not applicable.
List price and average cost of a course of treatment	[REDACTED] The average cost per treatment cycle of tisotumab vedotin is [REDACTED]
Patient access scheme (if applicable)	A discount of [REDACTED]% is proposed via a simple patient access scheme (PAS), which equates to a net price of [REDACTED] per vial of tisotumab vedotin.

Abbreviations: ADC-TF, antibody-drug conjugate-tissue factor; MHRA, Medicines and Healthcare products Regulatory Agency; MMAE, monomethyl auristatin E; PAS, patient access scheme; SmPC, Summary of Product Characteristics; UK, United Kingdom.

Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

1.3. Health condition and position of the technology in the treatment pathway

Summary of key points

- Cervical cancer (CC) is the 14th most common cancer in women in the UK, accounting for 2% of all new cancer cases (2017-2019) (1).
- According to GLOBOCAN 2022, there are an estimated 3,235 new cases of CC in the UK per year (2).
- CC mainly affects young women aged between 30-45 years; therefore, these patients and their families experience significant societal and economic burden (3).
- Women with CC report significantly worse HRQoL compared with individuals without CC (4, 5), with functioning and HRQoL further decreasing as patients progress to recurrent or metastatic disease (6).
- Recurrent or metastatic CC (r/m CC) is incurable; thus, treatment options are palliative, with the goal of prolonging survival, controlling disease, and improving or maintaining quality of life (QoL). No standard of care exists currently for 2L+, however, single agent chemotherapies are often used (7).
- Single-agent chemotherapies offer poor survival benefits for patients and were mostly evaluated in single-arm clinical trials in relatively small sample sizes of r/m CC patients (8-19). The overall survival of UK r/m CC patients treated with chemotherapy in the 2L setting was found to be 9.3 months (20)
- There remains a significant unmet need in r/m CC for 2L+ treatments that:
 - Are more effective than current therapies
 - Offer an alternative option to repeated chemotherapy exposure
 - Are suitable for patients who have progressed on or after standard first-line immunochemotherapy.
- Tisotumab vedotin (Tivdak) is the first antibody drug conjugate (ADC) to demonstrate statistically significant and clinically meaningful improvements

in survival (OS and PFS) and tumour response (ORR and DCR) compared with investigator's choice chemotherapy in a broad, heavily pre-treated population of patients with r/m CC with very limited treatment options.

- The proposed positioning of tisotumab vedotin is as a monotherapy for the treatment of adult patients with r/m CC with disease progression on or after systemic therapy (Figure 10).

1.3.1. *Overview of cervical cancer*

Cervical cancer (CC) is a rare type of cancer resulting from a persistent infection of the lower genital tract from one of about 15 high-risk human papillomavirus (HPV) types (21). Although most women will acquire at least one high-risk HPV type throughout their lifetime, only one-tenth of the infections will become persistent, leading to the development of precancerous lesions. In addition to HPV infection, additional cofactors include some sexually transmittable infections (human immunodeficiency virus and chlamydia trachomatis), weakened immune system, smoking, a higher number of childbirths, long-term use of oral contraceptives, and lack of regular cervical screening (22, 23).

There are three main subtypes of cervical cancer:

- **Squamous cell carcinoma (SCC)** accounts for 70% to 90% of CC cases (2, 24-28). It originates in the squamous cells of the cervix.
- **Adenocarcinoma** accounts for most of the remaining 10% to 30% of CC. It develops from the glandular cells of the cervix. Adenocarcinoma is more difficult to diagnose by cervical screening test because it starts higher in the cervix and is more difficult to reach with the brush or spatula used in routine cervical screening.
- In a small number of patients (~10%), CC involves both squamous and glandular cells, which are known as **adenosquamous carcinomas or mixed carcinomas** (29, 30).

Clinical and pathological assessments are used to stage CC based on tumour size and extent of disease. These stages inform prognosis and dictate treatment

approaches. The International Federation of Gynecology and Obstetrics (FIGO) staging system, last updated in 2018, is a standardised classification system used to stage gynaecological cancers (Figure 1) (21).

Figure 1. International Federation of Gynecology and Obstetrics Staging for Cervical Cancer

Stage I	Strictly confined to the cervix IA: Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm IB: Invasive carcinoma with measured deepest invasion >5 mm (> Stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter
Stage II	Invades beyond the uterus, but not into the lower third of the vagina or to the pelvic wall IIA: Involvement limited to the upper two-thirds of the vagina without parametrial involvement IIB: With parametrial involvement but not up to the pelvic wall
Stage III	Involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes IIIA: The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall IIIB: Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause) IIIC: Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases), irrespective of tumour size and extent (with r and p notations) ^a
Stage IV	Extends beyond the pelvis or involves mucosa of bladder or rectum IVA: Spread of the growth to adjacent pelvic organs IVB: Spread to distant organs

Note: ^aAdding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC.

Source: Bhatla et al. (2021) (21).

For early-stage CC patients, clinical follow-up in the first 2 to 3 years after index treatment is important, as the median time to disease recurrence may range from 7-36 months following primary treatment (31). Risk factors for disease recurrence include lymph node or parametria involvement, as well as tumour volume (Table 3) (32).

Table 3. Risk Factors for Cervical Cancer Recurrence

Risk Factor	• Minimally invasive vs. open hysterectomy • Positive lymph nodes • Positive parametria (fibrous and fatty connective tissue surrounding the uterus) • Positive surgical margins • Tumour diameter > 4 cm • Lymphovascular space invasion • Invasion of outer 1/3 of cervical stroma

Source: Bhatla et al. (2021) (21).

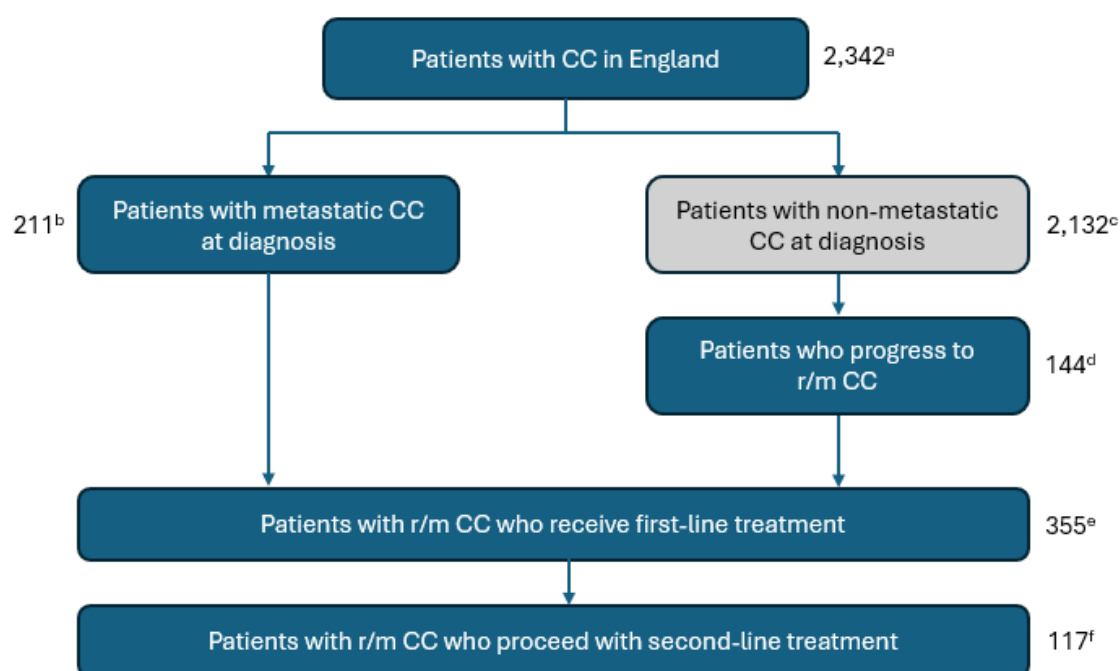
Recurrent or metastatic (r/m) CC generally refers to a subgroup of CC patients who are either diagnosed at stage IVB or have recurred with distant metastasis and who are no longer responsive to definitive treatment. Frequent sites of metastasis with CC include local/regional lymph nodes; most common sites of distant metastasis include lung, liver, and bone (22). Clinical outcomes of patients newly diagnosed with mCC depend on tumour biology, extent, and localisation of metastasis. For recurrent patients, the location of recurrence affects clinical outcomes.

1.3.2. Epidemiology

Worldwide, CC is the eighth most common cancer by incidence, with an estimated 662,301 new cases in 2022 (2). In the UK, an average of 3,256 female patients were diagnosed with CC each year from 2017 to 2019 (1).

There are an estimated 2,342 patients with CC in England, of which approximately 355 patients with r/m CC have received first-line treatment. Following disease progression on or after systemic therapy, it is estimated that 117 patients with r/m CC will be eligible for tisotumab vedotin (Figure 2).

Figure 2: Patient population eligible for tisotumab vedotin in England



Source: ^aUK Cancer Research Cervical Cancer Incidence Statistics 2017-2019 .

^bNHS Cervical Screening Programme (33).

^cNHS Cervical Screening Programme (33).

^dLi et al. (2022) (33, 34).

^eAssumption that 100% of r/m CC patients receive first-line treatment.

^fMusa et al. (2022) (35).

1.3.3. Burden of Disease

1.3.3.1. Clinical Burden

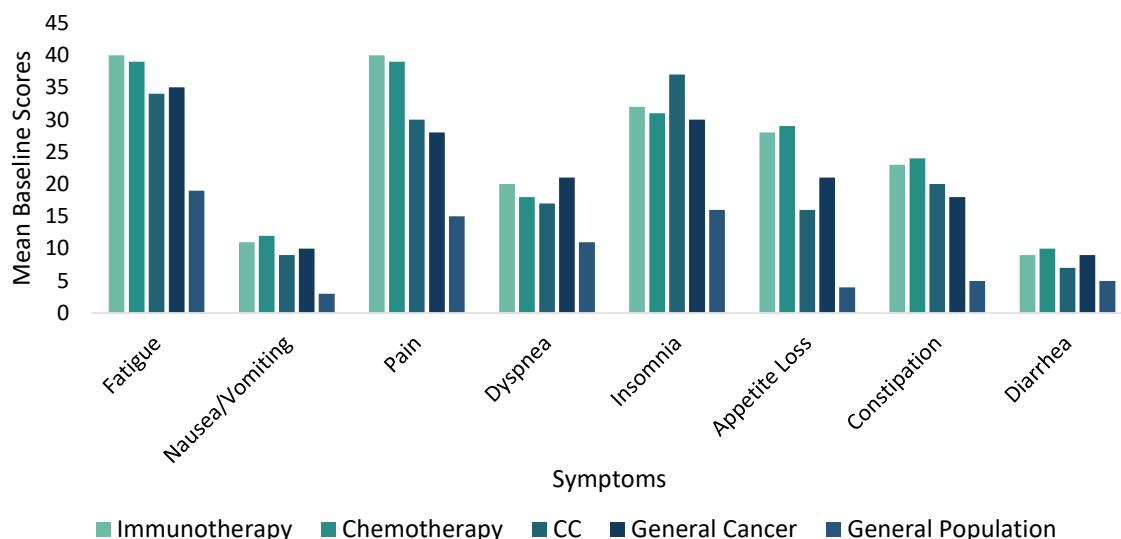
Symptoms associated with r/m CC

CC is often asymptomatic, however, early CC symptoms may include: vaginal bleeding between periods, after menopause or after sex; pain during sex; pain in the pelvis; menstrual bleeding that is heavier or lasts longer than usual or unusual vaginal discharge (21, 22). Advanced CC symptoms may include extreme tiredness, leg swelling or pain, lower back or abdominal pain, cough or problems urinating (21, 22).

Figure 3 shows that patients with r/m CC (assessed at baseline in a study comparing immunotherapy with chemotherapy) demonstrated greater symptom burden (except for insomnia) compared with CC in general, other types of cancer, and the general Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

European population.

Figure 3: Symptom Scores for Women with r/m CC vs. All CC, Other Types of Cancer and the General Population



Abbreviations: CC, cervical cancer; r/m CC, recurrent or metastatic cervical cancer.

Notes: ^aData are baseline values from EMPower CERVICAL-1 (27), a multinational, phase 3 trial of cemiplimab vs. physicians' choice chemotherapy. Baseline EORTC-QLQ-C30 values are shown for r/m CC (cemiplimab and chemotherapy arms) and for CC in general (where available) (36), any cancer (36), and the general population (37). Data have been estimated from published figures.

Source: Oaknin et al. (2022) (6).

1.3.3.2. Mortality

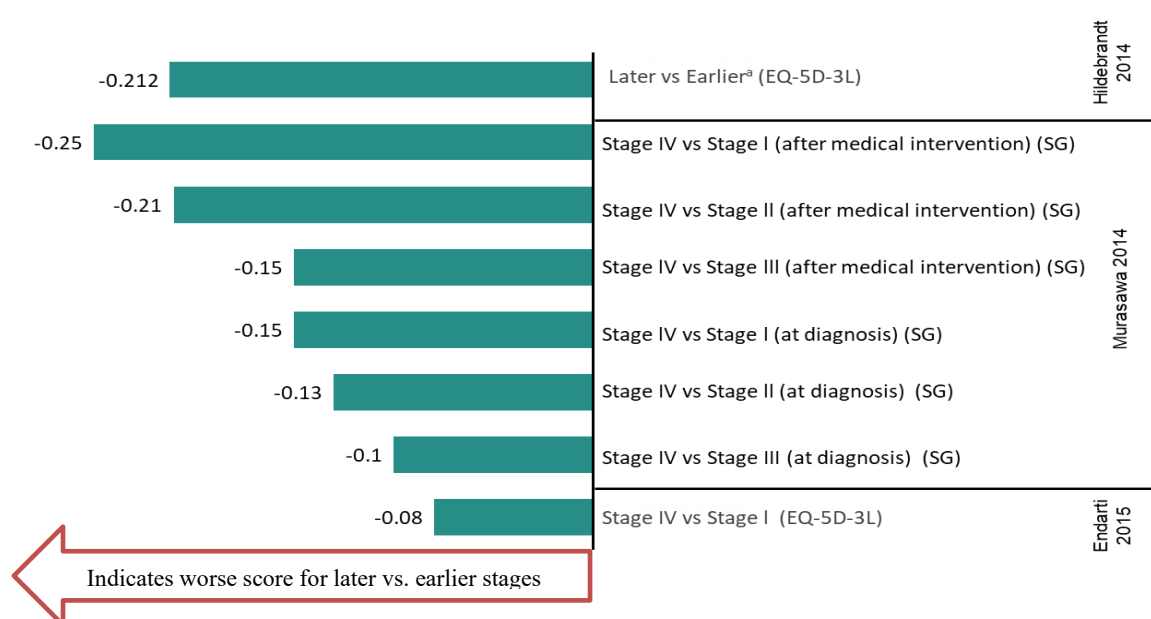
Compared with early-stage CC, survival is substantially lower among women with metastatic disease (38-40). A retrospective analysis of 75 UK women initiating 1L systemic treatment for r/m CC between 2004-2014 in one hospital found the 5-year OS rate was 30% (41-43).

In another retrospective analysis (from 2012-2019) of women with advanced CC (N=1,112) in England, with approximately 2-year follow-up, 42% of 1L and the majority (62.1%) of 2L patients died. Of note, CC was based on a documented diagnosis of CC and use of ≥ 1 systemic chemotherapy (44). The overall survival of UK r/m CC patients treated with chemotherapy in the 2L setting was found to be 9.3 months (20). Therefore, as r/m CC patients progress through line of treatments (LOTs), survival generally decreases.

1.3.3.3. Humanistic burden

Women with CC report significantly worse HRQoL compared with individuals without CC (4, 5). Data from a systematic literature review (SLR) of published health state utility values in CC show greater disutility with later-stage disease (Stage IV) compared with earlier stages of the disease (Figure 4). Disutility values presented were calculated for each stage as a change in utility from previous stages.

Figure 4. Disutility by Cervical Cancer Stage



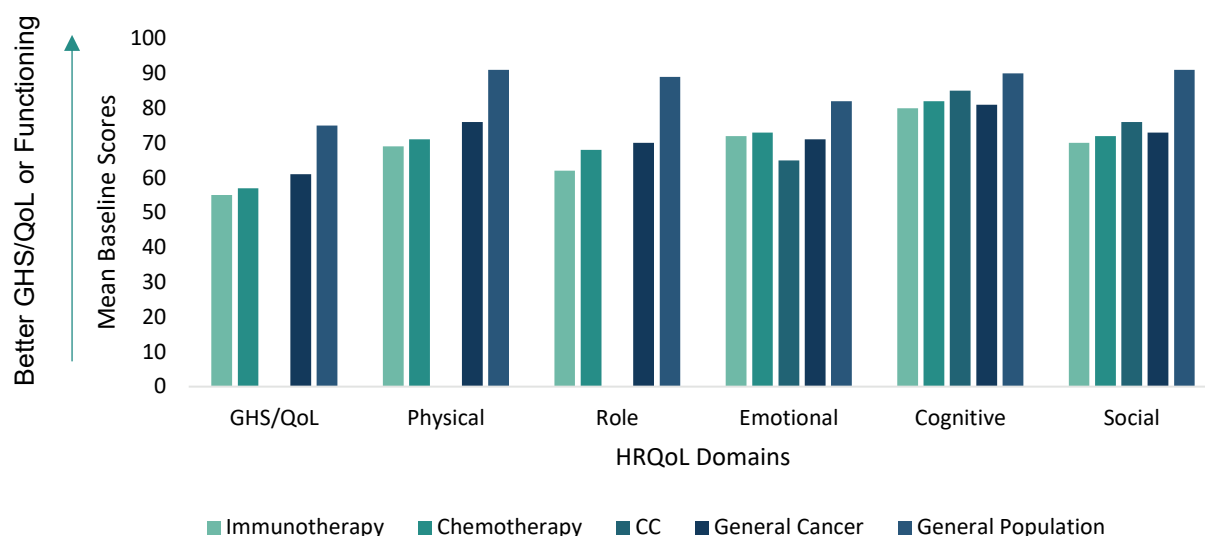
Abbreviations: EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; SG, standard gamble.

Notes: ^aHealth states that signified localized cancers were labelled as “earlier” stage and distant or metastasized as “later” stage.

Source: Pourrahmat et al. (2021), Hildebrandt et al. (2014), Murasawa et al. (2014), Endarti et al. (2015) (45-48).

Moreover, functioning and HRQoL decrease as patients progress to recurrent or metastatic disease. Figure 5 shows patients with r/m CC (assessed at baseline in a study comparing immunotherapy with chemotherapy) generally had worse HRQoL and functioning as assessed via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) compared with CC in general, other types of cancer, and the general European population.

Figure 5 EORTC QLQ-C30 Scores for Women with r/m CC vs. All Cervical Cancer, Other Types of Cancer and the General Population^a



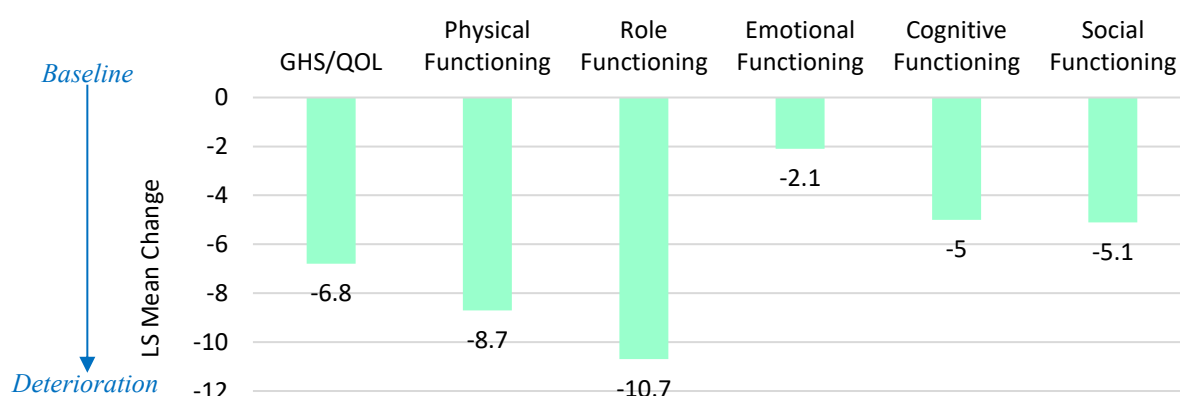
Abbreviations: CC, cervical cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, General Health Score; HRQoL, health related quality of life; QoL, quality of life; r/m CC, recurrent or metastatic cervical cancer.

Notes: ^aData are baseline values from EMPOWER CERVICAL-1 (6), a multinational, phase 3 trial of cemiplimab vs physicians' choice chemotherapy. Baseline EORTC-QLQ-C30 values are shown for r/m CC (cemiplimab and chemotherapy arms) and for CC in general (where available) (49), any cancer (49), and the general population (50). Data have been estimated from published figures.

Source: Oaknin et al. (2022) (6).

Since no SoC currently exists for the 2L+ treatment of women with r/m CC, monotherapy with various chemotherapy medications are often utilised despite poor benefit/risk profiles, inadequate supportive clinical data, and poor outcomes. Patients with r/m CC often experience a substantial decrease in HRQoL following treatment with chemotherapy due to toxicity (3). Among patients receiving investigator's choice single-agent chemotherapy for 2L+ treatment of r/m CC, HRQoL declined overall and in all domains following 7 cycles of treatment (Figure 6) (6).

Figure 6. Change^a in EORTC-QLQ-30 GHS/QOL with Chemotherapy in Recurrent or Metastatic Cervical Cancer^b



Abbreviations: 2L, second-Line; EORTC-QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, Global Health Status; LS, least squares; QOL, quality of life; r/m CC, recurrent or metastatic cervical cancer.

Notes: ^aChange from baseline to Cycle 16 or disease progression. Data were available for a sufficient number of patients through Cycle 7. Each treatment cycle was 6 weeks. ^bData are from a global clinical trial of cemiplimab vs. investigator's choice single-agent chemotherapy (pemetrexed, topotecan, irinotecan, gemcitabine, vinorelbine) as 2L+ treatment of r/m CC.

Source: Oaknin et al (2022) (6).

1.3.3.4. Societal and economic burden

CC mainly affects young women aged between 30-45 years; therefore, these patients and their families experience significant societal and economic burden (3). Clinical advisors consulted as part of the UK Cervical Cancer advisory board supported this, emphasising that patients with CC are relatively young, productive and of family-raising age (51)

Direct costs

Total costs per patient have been reported in CC patients compared to matched controls without CC (4, 5, 52). In the UK, the average annual total cost of treating all CCs in 2011 was estimated at £9,233 per person (53). This calculation was based on 2,288 reported CC cases in England from patients aged between 25-79 years, however, it does not consider cost variation according to stage of diagnosis whereby more advanced stages (stage 2 or above) generally incur higher costs (53). In patients with newly diagnosed CC, significant predictors of greater costs include (52):

- Advanced age,
- Advanced cancer stage at diagnosis, and

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- Comorbidities (Charlson comorbidity score)

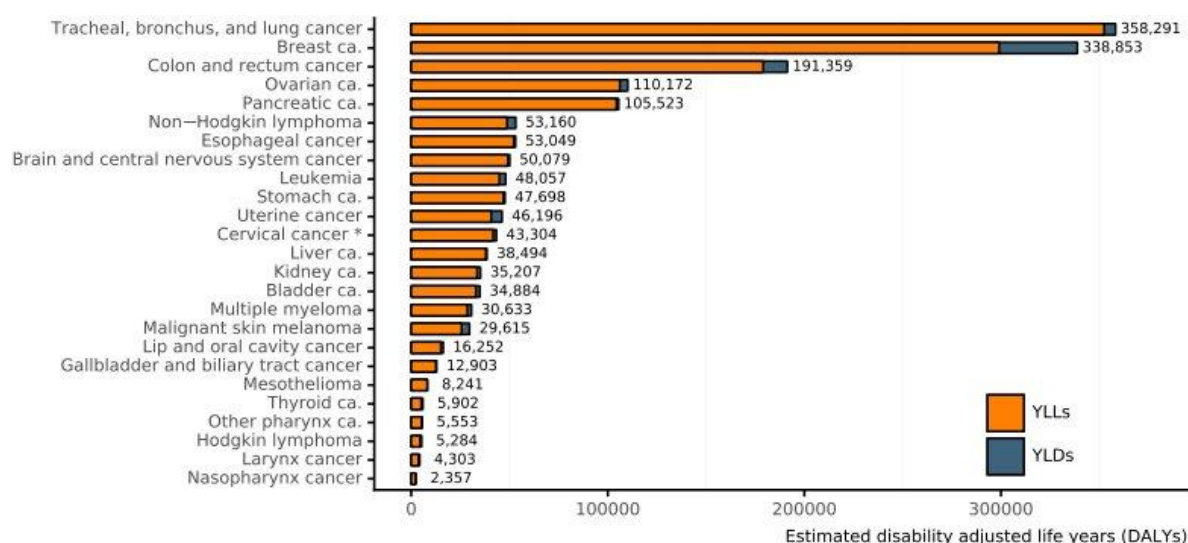
HRU and cost is also associated with disease progression/recurrence (38, 54). In an Italian retrospective cohort study, mean ($\pm$ sd) costs associated with disease progression/recurrence amounted to €17,218 $\pm$ 17,830 per patient with locally advanced cervical cancer (LACC) and €10,172 $\pm$ 13,969 per patient with early CC (54).

Indirect costs

In 2019, CC was the 12th leading cause of premature death and disutility due to cancer in UK women, with years of life lost (YLL) and years of life lived with disability (YLD) reported as 41,651 and 1,653, respectively (Figure 7) (55).

In the UK, modelled estimates suggest that 18,504 women would be alive in 2017 if they had not died of CC and 7,322 of these would have been in the workforce (56). As a result, total productivity loss due to CC was estimated at £303.2 million in 2017 (56).

Figure 7 Annual Premature Deaths and Disability from CC and other Cancers in Women in the UK and Northern Ireland (2019)¹



Abbreviations: CC, cervical cancer; YLD, years of life lived with disability; YLL, years of life lost.

Notes: ^aBased on an economic model of 7,322 individuals who would have been part of the work force if they had not died due to CC.

Source: Bruni et al. (2023) (55).

1.3.4. Clinical pathway of care

Recurrent or metastatic CC is incurable; thus, treatment options are palliative, with the goal of prolonging survival, controlling disease, and improving or maintaining quality of life (QoL) (7). There is no SoC in 2L+, and treatment is often heterogeneous with r/m CC patients receiving one of several single-agent chemotherapies that offer suboptimal clinical benefit, despite having already used chemotherapy combinations in 1L (20, 42, 57). These include, but are not limited to, topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed or paclitaxel (42, 57, 58).

Other guidelines are available (outlined in Section 1.3.4.2 below) and are often used to help inform and shape UK clinical practice, where appropriate. As with guidelines in any disease area, there are differences across jurisdictions, and can be out of date. Few guidelines reflect the real-world perspectives and preferences of patients, their carers, and their families; therefore, treatment and care may need to be tailored wherever possible.

1.3.4.1. Current treatment pathway in the UK

During the UK Cervical Cancer advisory board, advisors emphasised that clinical decisions for r/m CC are primarily directed by NICE treatment approvals and drug availability (Section 1.3.4.2) (51).

Clinical advisors also acknowledged that weekly (Q1W) paclitaxel is considered in the UK for r/m CC, and this was supported by findings from the subsequent Genmab survey of HCPs from England. However, they also confirmed that there is no standard of care for 2L r/mCC in UK.

Of note, clinicians consulted during the UK Cervical Cancer advisory board agreed there is no data to show that the efficacy of Q1W paclitaxel differs from other chemotherapies, therefore exclusion of Q1W paclitaxel from the InnovaTV 301 trial and as an efficacy comparator in this submission is not viewed as a concern (51). In addition, published real-world evidence demonstrates that paclitaxel has comparable efficacy to the chemotherapies in the control arm of InnovaTV 301, referencing retrospective UK data (20). For completeness, the economic model for this submission considers comparable efficacy of single agent chemotherapies for the comparator and includes the costs of weekly paclitaxel among other scenarios (see Section 3.2.3.2 for

more detail).

1.3.4.2. Clinical guidelines

Formal clinical guidelines published for r/m CC are outlined below.

British Gynaecological Cancer Society (BGCS) (2021)

The BGCS guidelines predate the European Medicines Agency (EMA) marketing authorisation of pembrolizumab (29 April 2022) for the treatment of CC (Table 4) (59).

Table 4: Recommended treatments for CC from the BGCS

1L Combination	2L Treatments
Preferred • Cisplatin + paclitaxel bevacizumab • Carboplatin + paclitaxel bevacizumab	• No specific recommendation. However, retreating with platinum/paclitaxel could be considered. • Mitomycin/5FU, vinorelbine, docetaxel, gemcitabine, weekly paclitaxel and topotecan have some activity but there is no standard of care

Note: Pembrolizumab is not mentioned since guidelines were written before European approval of pembrolizumab in any line of therapy.

Source: Reed et al. (2020) (3).

Whereas the 2020 BGCS guidelines mention rechallenge with platinum chemotherapy doublet as a consideration where there has been a long enough platinum free interval, platinum chemotherapy rechallenge has not been specifically studied in cervical cancer and rechallenge with platinum chemotherapy doublet was not mentioned by clinicians at the UK Cervical Cancer advisory board. That said, in a subsequent survey of HCPs in England, 5 of 8 responders said they would consider platinum rechallenge for some cases in 2nd line r/mCC.

Of note, survey responders comprised of clinicians from large academic centres and teaching hospitals, with only one academic centre-based responder indicating use of platinum chemotherapy rechallenge vs all four of the responders from teaching hospitals. The UK Cervical Cancer advisory board was mainly attended by oncologists

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from large academic centres, therefore it is likely that clinical practice patterns may vary across treatment centres in the UK (51, 60). In contrast to other settings, patients at large academic centres may have greater access to treatment in clinical trials. Further detail on methods used for engagement with clinicians at the UK Cervical Cancer advisory board and for the clinician survey are included in Section 2.3.3.

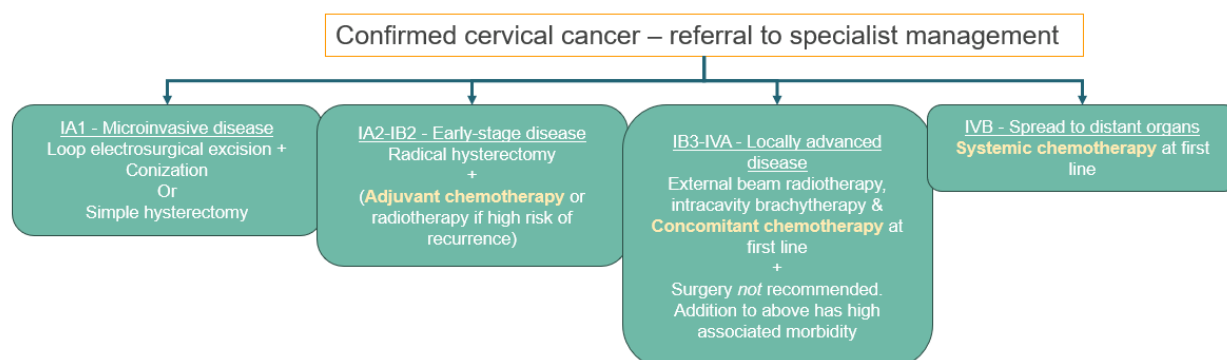
European Society of Gynaecological Oncology (ESGO) / European Society for Radiotherapy & Oncology / European Society of Pathology (2023)

Guidelines from ESTRO and ESP are reflective of the use of newer immunotherapies as 1L or 2L treatments for r/m CC as they were published in 2023. Both ESTRO and ESP guidelines recommend the use of pembrolizumab added to platinum-based chemotherapy ± bevacizumab or bevacizumab-based triplet therapy in eligible 1L patients (61, 62). In immunotherapy-naïve patients, cemiplimab is recommended for use, regardless of PD-(L)1 tumour status (21). Of note, cemiplimab is not currently reimbursed for the treatment of cervical cancer in England (63).

National Institute for Health and Care Excellence (2022)

Current NICE guidance is based mainly on the British Gynaecological Cancer Society (BGCS) and European Society of Gynaecological Oncology (ESGO) joint clinical guidelines. However, the guidance is not up to date (published in 2022) and focuses on first-line interventions (Figure 8).

Figure 8: First-line treatment recommendations for CC from NICE following initial confirmed diagnosis

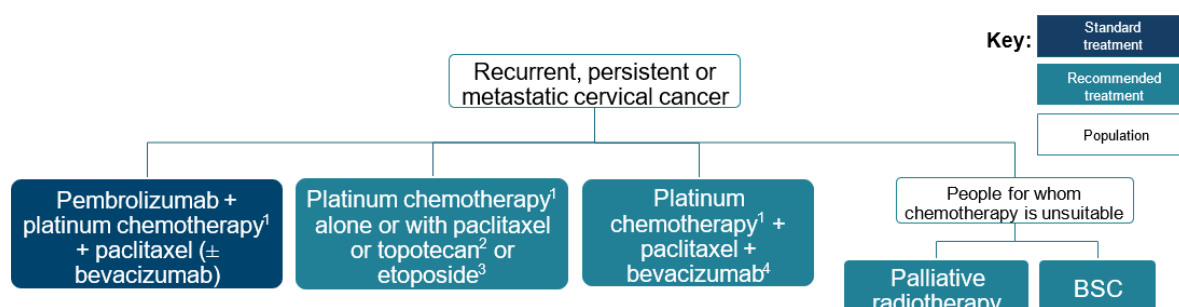


Notes: Situations where patients may receive chemotherapy in a first-line setting are highlighted yellow.
Source: NICE (2022) (64).

The guidance becomes less detailed as patients progress to later lines of r/m CC treatment. NICE management advice suggests a patient centred approach focusing on individual wishes, previous treatments, location of disease, disease free interval, symptoms, comorbidities, and performance status. Salvage surgery (pelvic exenteration) is recommended where recurrence is confined to the cervix or upper vagina and where chemotherapy has failed. Chemotherapy and/or radiotherapy are recommended if initial surgery is not successful in controlling the disease (64).

Further detail on the UK treatment landscape is provided in public materials for TA885 (Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer), where a more detailed 1L landscape for r/m CC is presented (Figure 9) (65).

Figure 9: First-line treatment recommendations for r/m CC from NICE



Abbreviations: BSC: best supportive care.

Notes: ¹Cisplatin or carboplatin. ²NICE recommends topotecan with cisplatin as an option for treating recurrent or stage 4B cervical cancer in people who have not previously received cisplatin (TA183), ³Source: Cancer Research UK and NHS chemotherapy protocol (indicated for small cell gynaecological cancers including those affecting the cervix, endometrium and ovaries). ⁴Bevacizumab with paclitaxel and platinum chemotherapy available in routine commissioning for untreated recurrent or metastatic cervical cancer

Source: Adapted from NICE Public Committee Slides ACM1 - TA885 (Committee Slide 4) (65).

European Society for Medical Oncology (2017)

The ESMO treatment guidelines for 2L r/m CC are outdated (published before 2020) and are not reflective of results from recent clinical trials of immunotherapy agents.

These guidelines, written prior to the availability of immunotherapies, also state there is no SoC in 2L and generally recommend the use of single-agent chemotherapies, but acknowledge there is little evidence demonstrating a clinical benefit in 2L (3, 28, 66).

1.3.5. Proposed positioning of tisotumab vedotin in the current treatment pathway

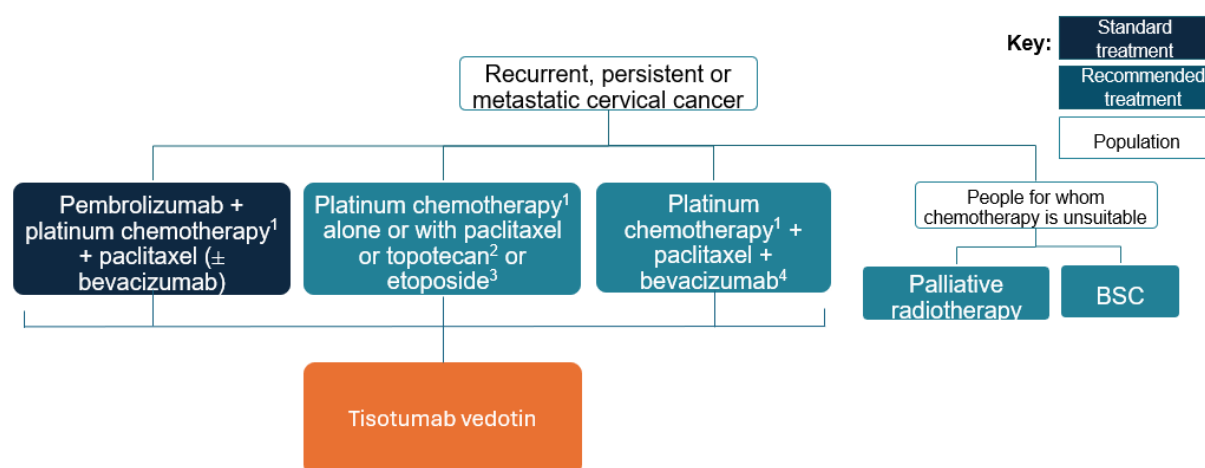
Clinical advisors consulted as part of the UK CC advisory board stated that immuno-oncology therapies are expected to remain the SoC in 1L r/m CC, as supported by widespread PD-L1 testing and high positivity rates (50-70%) observed in clinical practice (51).

However, there remains a significant unmet need in r/m CC for 2L+ treatments which are more effective than current therapies, that offer an alternative option to repeated chemotherapy exposure and are suitable for patients who have progressed on or after standard first-line immunochemotherapy. Unmet need is described in more detail in Section 1.3.6.

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The proposed positioning of tisotumab vedotin is as a monotherapy for the treatment of adult patients with r/m CC with disease progression on or after systemic therapy, presenting an alternative to chemotherapy for these patients (Figure 10). Since tisotumab vedotin is an antibody-targeted chemotherapy the majority of patients unsuitable for chemotherapy would likely also be unsuitable for treatment with tisotumab vedotin. BSC would therefore not comprise a suitable comparator to tisotumab vedotin since BSC is generally reserved for patients who are unsuitable for chemotherapy (Figure 10). Of note, clinicians in England who were consulted during an additional survey conducted by Genmab supported the proposed position for tisotumab vedotin (60).

Figure 10: Proposed positioning of tisotumab vedotin for treating r/m CC in patients with disease progression on or after systemic therapy



Abbreviations: BSC: best supportive care.

Notes: ¹Cisplatin or carboplatin. ²NICE recommends topotecan with cisplatin as an option for treating recurrent or stage 4B cervical cancer in people who have not previously received cisplatin (TA183), ³Source: Cancer Research UK and NHS chemotherapy protocol (indicated for small cell gynaecological cancers including those affecting the cervix, endometrium and ovaries). ⁴Bevacizumab with paclitaxel and platinum chemotherapy available in routine commissioning for untreated recurrent or metastatic cervical cancer

Source: Adapted from NICE Public Committee Slides ACM1 - TA885 (Committee Slide 4) (65).

1.3.6. Unmet need

Cervical cancer is most often diagnosed in relatively young women in their most productive years. The impact of the disease is devastating, not only for the patient, but for the family they are often raising at this time in their lives (3). The prognosis for patients with CC is notoriously poor, with 5-year overall survival less than 19% among

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patients with distant disease (67, 68). Health-related quality of life (HRQoL) is also poor in CC patients. One systematic review of psychiatric disorders in gynaecologic cancer patients found that CC patients in particular have a high prevalence of psychiatric symptoms including depression (33%-52%) (69).

Recurrent or metastatic CC is incurable; thus, treatment options are palliative and lacking for those who have experienced disease progression on or after systemic therapy. Moreover, HRQoL is further reduced in women who progress to r/m CC compared to that of the general CC population (45). Consequently, there remains a significant unmet need for treatments which prolong survival, control disease, and improve or maintain quality of life (QoL) for these patients (7).

Historically, patients receiving treatment for r/m CC have had limited 2L+ treatment options which are largely single agent chemotherapies (see Section 1.3.4). Evidence supporting the efficacy of single-agent chemotherapies in 2nd line r/m CC is weak, relying primarily on single arm studies with small sample sizes. What evidence there is suggests poor survival benefit (8-19). Table 5 highlights the poor survival benefits and suboptimal benefit-risk profiles of single-agent chemotherapies in a 2L treatment setting (median OS ≤9 months) (8-19).

Table 5: Efficacy of single-agent chemotherapies in 2L treatment

Study and Treatment Regimen (All Corner Populations)			Survival Outcomes Median (months)	
Treatment	Study	N	PFS	OS
Investigator's choice ^a	Tewari 2022 (18)	304	2.9	8.5
Docetaxel	Garcia 2007 (9)	23	3.8	7.0
Erlotinib	Schilder 2009 (16)	25	1.87	4.96
Gemcitabine	Schilder 2005 (15)	22	2.1	6.5
Irinotecan	Verschraegen 1997 (19)	42	6.4	NR
Liposomal doxorubicin	Rose 2006 (11)	27	3.2	8.9
Nab-paclitaxel	Alberts 2012 (8)	35	5.0	9.4
Pemetrexed	Miller 2008 (14)	27	3.1	7.4
Topotecan	Coronel 2009 (12)	18	3.5	7.0

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Vinorelbine	Muggia 2004 (17)	44	NR ^a	NR ^a

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response.

Notes: ^aIncludes investigator's choice of single-agent chemotherapy (pemetrexed [37%], topotecan [7%], irinotecan [6%], gemcitabine [40%] or vinorelbine [11%]). ^aPFS and OS were not reported for vinorelbine in Muggia (2004); the study follow-up time is also not reported.

Sources: Detailed in table above.

Moreover, immunotherapies such as pembrolizumab are well-established for 1L treatment of r/m CC, however there is limited evidence supporting immunotherapy rechallenge. Clinical advisors consulted during the UK Cervical Cancer advisory board emphasised the absence of clinical data to support immunotherapy rechallenge in r/m CC. In the UK, rechallenge in later lines is not recommended or reimbursed once patients progress on immunotherapy in 1L (51).

A significant unmet need therefore remains in the 2L+ treatment of r/m CC for therapies that:

- Are more effective than current options
- Offer an alternative option to repeated chemotherapy exposure, for patients who have progressed on or after standard first-line immunochemotherapy

Tisotumab vedotin is the first ADC to demonstrate statistically significant and clinically meaningful OS benefit compared with investigator's choice chemotherapy in a broad population of patients with previously treated r/m CC.

The benefit of tisotumab vedotin has been confirmed in InnovaTV 301, a robust, randomised, global, open-label, phase 3 trial of tisotumab vedotin compared to investigator's choice of chemotherapy in 2L or 3L r/m CC. The patient population included in InnovaTV 301 had a global footprint and included individuals enrolled from 25 countries, including ■■■ UK patients in the tisotumab vedotin arm and ■■■ UK patients in the chemotherapy arm (70, 71).

Additionally, the InnovaTV 301 trial is the first study of its kind conducted in a contemporary patient population. Patients were required to have 1 or 2 lines of prior systemic therapy for r/m CC and to have experienced disease progression during or after treatment with a SoC chemotherapy doublet, or platinum-based therapy with bevacizumab and an anti-PD-(L)1 agent, which reflects the most current SoC for 1L treatment, if these regimens were available and if the patients were not contraindicated (70, 71).

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Thus, the results of InnovaTV 301 provide evidence confirming the survival benefit and tolerability of tisotumab vedotin in a broad patient population, making it closely reflective of current and anticipated UK clinical practice in patients requiring treatment for 2L+ r/m CC. With proven efficacy (refer to Section 2.6.1) and a unique mechanism of action, tisotumab vedotin therefore offers a treatment for patients with r/m CC whose disease has progressed on or after systemic therapy, eliminating the need for re-use of single agent chemotherapies or anti-PD-(L)1 therapies (70-72).

1.4. *Equality considerations*

Cervical cancer is a disease that affects young women in their productive and family-raising years. In England, CC rates are 65% higher in the most deprived socioeconomic quintile vs the least deprived (73). Cervical cancer screening rates are known to be lower among women in deprived populations (74), and while studies examining HPV vaccine uptake by ethnicity and/or socioeconomic status are scarce, evidence suggests uptake is lower among the more deprived, and non-white ethnic populations (75, 76).

These factors demonstrate the current inequalities in the burden and impact of cervical cancer and access to interventions in England, which bear consideration in the evaluation of tisotumab vedotin.

2. Clinical effectiveness

Summary of key points:

Study identification:

- A clinical systematic literature review (SLR) identified two trials (InnovaTV 301 and InnovaTV 204) which provide direct clinical evidence for the efficacy and safety of tisotumab vedotin for the treatment of r/m CC.
- InnovaTV 301 is an ongoing, global, randomised (1:1), open-label, phase 3 study comparing tisotumab vedotin against investigator's choice of chemotherapy in patients with r/m CC who have received 1 or 2 prior lines of systemic therapy (i.e., 2L or 3L) (70-72).
- The primary analysis data cut for the InnovaTV 301 trial was on 24 July 2023.
- Due to regulatory queries, an ad-hoc follow-up analysis for OS and PFS was conducted on 16 January 2024. OS and PFS data from this follow-up analysis informs the economic model (refer to Section 3).
- InnovaTV 204 was a multicentre, phase 2, single-arm, open-label study of tisotumab vedotin in patients with previously treated r/m CC who experienced disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards) (77, 78).
- Two data cuts are available for the InnovaTV 204 trial: primary analysis data cut (06 February 2020) and the final analysis data cut (04 October 2022).

Efficacy:

- In InnovaTV 301, tisotumab vedotin significantly improved OS with a 30% reduction in the risk of death compared to investigator's choice of chemotherapy (median OS 11.5 months vs 9.5 months; HR 0.70, p=0.004) and a 38% improvement in OS at 12 months vs chemotherapy in 2nd and 3rd line r/m CC (Figure 12).
- PFS was superior for tisotumab vedotin compared to investigator's choice of chemotherapy, with a 33% reduction in the risk of disease progression or

death (median PFS 4.2 months vs 2.9 months; HR 0.67, $p < 0.001$) (70, 71). In InnovaTV 204, median OS and PFS were 12.1 months and 4.2 months, respectively. There was a 61% improvement in PFS vs chemotherapy at 6 months in 2nd and 3rd line r/m CC (Figure 13) (78).

- Confirmed ORRs were higher for tisotumab vedotin compared to investigator's choice of chemotherapy in InnovaTV 301 (17.8% vs 5.2%, respectively). The confirmed ORR for tisotumab vedotin in InnovaTV 204 was 24% (70, 71, 78).
- Treatment with tisotumab vedotin in InnovaTV 301 led to a numerically higher disease control rate (DCR, i.e. CR + PR + stable disease [SD]) compared with chemotherapy (75.9% vs. 58.2%) (70-72). In InnovaTV 204, a DCR of 72% was observed and most responses were rapid (median TTR = 1.4 months), indicating potential antitumour activity within the first 2 cycles of treatment (78).
- The median duration of response for tisotumab vedotin was 5.3 months (79) and 8.3 months (InnovaTV 204), which indicates sustained antitumour activity (70, 71, 78).
- The percentage of patients who reported an improvement in the QLQ-C30 global health status–QoL scores of 10 points or more from baseline to cycle 5 was higher in the tisotumab vedotin group than in the chemotherapy group (13.9% vs. 3.4%) (70, 71).
- EQ-5D Visual Analogue Scale (VAS) scores in the tisotumab vedotin and chemotherapy arms were stable from baseline to Cycle 5 (70, 71).

Safety:

- The median duration of exposure to tisotumab vedotin in InnovaTV 301 (data cutoff: July 2023) was 3.65 months compared to 2.76 months in the chemotherapy arm (70, 71). In InnovaTV 204, the median duration of exposure to tisotumab vedotin was 4.2 months (78).
- Tisotumab vedotin had a manageable safety profile, and no unanticipated AEs were observed. In InnovaTV 301, treatment discontinuations (14.8% of

patients) in the tisotumab vedotin arm were primarily driven by protocol-mandated dose modifications in response to ocular and peripheral neuropathy (70, 71). Only 12% of patients discontinued tisotumab vedotin treatment due to AEs (78).

- Rates of any TEAE were balanced between treatment arms. Grade ≥ 3 TEAEs occurred in 52% of patients treated with tisotumab vedotin versus 62% in the chemotherapy arm in InnovaTV 301, and in 28% of patients treated with tisotumab vedotin in InnovaTV 204.
- In InnovaTV 301, 132 patients (53%) treated with tisotumab vedotin reported ocular treatment-related AEs (TRAEs), and nearly all of these patients (94%) experienced complete resolution or partial improvement of symptoms. Only 4% of patients experienced a Grade 3 ocular event and all patients with Grade ≥ 3 ocular AEs had relevant medical history or preceding low grade ocular AEs (70, 71).
- In InnovaTV 204, ocular TRAEs occurred in 55 patients, with the majority (96%) of those affected experiencing either Grade 1 or 2 events. None of the ocular TRAEs in InnovaTV 204 were serious (78).
- Another TRAE is peripheral neuropathy, which was reported by 96 patients (38%) following treatment with tisotumab vedotin in InnovaTV 301. Many of these patients (44%) experienced either complete resolution or partial improvement of symptoms (70, 71). In InnovaTV 204, peripheral neuropathy TRAEs occurred in 33 patients, with the majority (79%) of those affected experiencing either Grade 1 or 2 events (78).

2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence associated with the decision problem outlined in Section B.1.1. Full details of the SLR are provided in Appendix B: Identification, selection and synthesis of clinical evidence.

2.2. *List of relevant clinical effectiveness evidence*

The clinical SLR identified two trials which provide direct clinical evidence for the efficacy and safety of tisotumab vedotin for the treatment of r/m CC (Table 6).

InnovaTV 301 (also known as SGNTV-003; NCT04697628) is the pivotal Phase 3, randomised controlled trial (RCT) providing evidence for the efficacy and safety of tisotumab vedotin vs investigator's choice chemotherapy in patients with r/m CC who had previously received 1 or 2 prior lines of systemic therapy (Table 6) (70-72).

InnovaTV 204 (also known as GCT1015-04; NCT03438396) is a Phase 2, single-arm trial providing evidence for the efficacy and safety of tisotumab vedotin in patients with previously treated r/m CC who experienced disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards) (77, 78).

Table 6: Clinical effectiveness evidence

Study	InnovaTV 301 (NCT04697628)	InnovaTV 204 (NCT03438396)
Study design	Phase 3, randomised, global, open-label study.	Phase 2, single-arm, multicentre study.
Population	Patients with r/m CC who have received 1 or 2 prior lines of systemic therapy.	Patients with previously treated r/m CC who experienced disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards).
Intervention(s)	Tisotumab vedotin (TIVDAK)	Tisotumab vedotin (TIVDAK)
Comparator(s)	Investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed)	Not applicable
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	Not applicable	Not applicable
Reported outcomes specified in the decision problem	Overall survival (OS) Progression-free survival (PFS) Response rates Adverse effects of treatment Health-related quality of life (HRQoL)	Overall survival (OS) Progression-free survival (PFS) Response rates Adverse effects of treatment Health-related quality of life (HRQoL)
All other reported outcomes	Not applicable	Not applicable

Abbreviations: AE: adverse events; HRQoL: health-related quality of life; OS: overall survival; r/m CC: recurrent or metastatic cervical cancer; PFS: progression free survival.

Notes: Outcomes in bold reflect those directly used in the economic modelling.

Sources: Vergote et al. (2024), InnovaTV 301 CSR (2023), Coleman et al. (2021) (70, 71, 78).

2.3. Summary of methodology of the relevant clinical effectiveness evidence

2.3.1. Study designs

2.3.1.1. InnovaTV 301

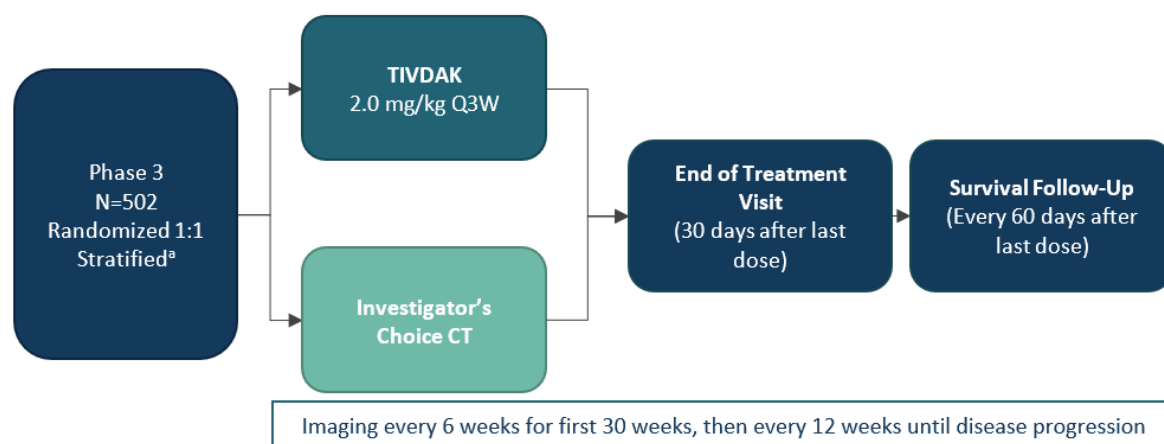
InnovaTV 301 is an ongoing, global, randomised (1:1), open-label, phase 3 study comparing tisotumab vedotin against investigator's choice of chemotherapy in patients with r/m CC who have received 1 or 2 prior lines of systemic therapy (i.e., 2L or 3L). It is the first randomised study to show benefit in a contemporary population of previously treated patients with r/m CC, including those with any prior anti-PD-(L)1 treatment, any prior bevacizumab treatment, or any prior taxane or platinum use (70-72, 80).

Eligible patients were randomised 1:1 to tisotumab vedotin 2.0 mg/kg Q3W or investigator's choice of chemotherapy. Randomisation was stratified by Eastern Cooperative Oncology Group performance status (ECOG PS; 0 vs. 1), prior bevacizumab administration (yes vs. no), region (US, European Union [EU] or other), and prior anti-programmed cell death protein 1 or anti-programmed cell death-ligand 1 (PD-(L)1) therapy administration (yes vs. no) (70-72).

A total of 502 participants underwent randomisation in the InnovaTV 301 trial (Figure 11). Of these, 253 participants were assigned to receive tisotumab vedotin, and 250 participants received at least one dose of tisotumab vedotin (70-72).

Participants received tisotumab vedotin on Day 1 of each 21-day treatment cycle until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, study termination by the sponsor, pregnancy, or death, whichever occurred first.

Figure 11: InnovaTV 301 study design



Abbreviations: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; US, United States.

Notes: ^aStratification 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).

Source: Adapted from Vergote et al. (2024) (70).

Imaging was obtained every 6 weeks (42 days $\pm$ 7 days) for the first 30 weeks and then every 12 weeks (84 days $\pm$ 7 days) thereafter, calculated from Cycle 1 Day 1 (C1D1) of treatment administration. Imaging continued until evidence of radiographic disease progression per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 as assessed by the investigator or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurred first (70-72).

The primary efficacy endpoint was OS, defined as the time from randomisation to the date of death from any cause. The key secondary efficacy endpoint was PFS, defined as the time from randomisation to the first documentation by the investigator of disease progression according to RECIST v1.1, or to the date of death from any cause, whichever occurred first. Other secondary efficacy endpoints included time to response, duration of response, safety, side-effect profile, and patient-reported outcomes.

A summary of the InnovaTV 301 trial methodology is provided in Table 7.

Table 7: Summary of InnovaTV 301 trial methodology

Trial	InnovaTV 301 (NCT04697628)
Location	Conducted across 168 sites in 27 countries including North America, Asia, Europe, and Latin America.
Trial design	A Phase 3, open-label, randomised (1:1), global, multicentre, active-comparator trial to evaluate the efficacy and safety of tisotumab vedotin vs investigator's choice chemotherapy in patients with r/m CC who had previously received 1 or 2 prior lines of systemic therapy (i.e., 2L or 3L).
Eligibility criteria for participants	<u>Key inclusion criteria:</u> • Age ≥18 years, or considered an adult by local regulations, at time of consent. • Recurrent or metastatic CC with squamous cell, adenocarcinoma, or adenosquamous histology, and: • Experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible), defined as either^a: – paclitaxel+cisplatin+bevacizumab+ anti-PD-(L)1 agent, or – paclitaxel+carboplatin+bevacizumab+ anti-PD-(L)1 agent, or – paclitaxel+topotecan/nogitecan+bevacizumab+ anti-PD-(L)1 agent • Received 1 or 2 prior systemic therapy regimens for r/m CC. This could include single agent therapy with an anti-PD(L)1 agent, but not chemotherapy, administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy. • Measurable disease according to RECIST v1.1 as assessed by the investigator. • ECOG PS of 0 or 1 prior to randomisation. • Life expectancy ≥3 months. <u>Key exclusion criteria:</u> • Primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned as part of the inclusion criteria above. • Clinically significant bleeding issues or risks including known past or current coagulation defects leading to an increased risk of bleeding; diffuse alveolar hemorrhage from vasculitis; known bleeding

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	diathesis; ongoing major bleeding; trauma with increased risk of life-threatening bleeding or history of severe head trauma or intracranial surgery within 8 weeks of trial entry. - Any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening is allowed). - Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis (e.g., Wagner syndrome, atopic keratoconjunctivitis, autoimmune disease affecting the eyes), ocular Stevens-Johnson syndrome or toxic epidermal necrolysis, mucus pemphigoid, and participants with penetrating ocular transplants. Note, cataracts alone were not an exclusion criterion. - Major surgery within 4 weeks or minor surgery within 7 days prior to the first study treatment administration. - Peripheral neuropathy Grade ≥ 2. - Prior treatment with MMAE-containing drugs.
Settings and locations where the data were collected	Tisotumab vedotin (IV infusion) was administered within a hospital chemotherapy unit over a 30-minute time period. Patients were supervised by a physician experienced in anti-cancer treatment. Imaging for tumour response assessment was conducted at the study sites every 6 weeks (42 days ± 7 days) for the first 30 weeks and then every 12 weeks (84 days ± 7 days) thereafter, until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurred first. Survival follow-up was performed by telephone contact (from the participant or a family member) or during a routine visit, if such a visit was scheduled for other reasons not related to the study.
Trial drugs	Intervention: - Tisotumab vedotin 2.0 mg/kg IV Q3W Comparators: - Investigator's choice of chemotherapy:

	○ Topotecan 1 or 1.25 mg/m² intravenous on Days 1 to 5, every 21 days ○ Vinorelbine 30 mg/m² IV on Days 1 and 8, every 21 days ○ Gemcitabine 1000 mg/m² IV on Days 1 and 8, every 21 days ○ Irinotecan 100 or 125 mg/m² IV weekly for 28 days, every 42 days ○ Pemetrexed 500mg/m² IV on Day 1 every 21 days
Permitted and disallowed concomitant medication	Permitted concomitant medication: • Determined by investigator discretion as per local labelling or institutional guidelines. Disallowed concomitant medication: Prohibited for those receiving tisotumab vedotin: • Chronic prophylactic treatment with acetylsalicylic acid (eg, aspirin) or chronic anti-platelet therapy in combination with any other anti-coagulation therapy. Prohibited for participants receiving tisotumab vedotin or chemotherapy: • Investigational agents • Any other anti-cancer therapy, (eg, immunotherapy, monoclonal antibodies, hormonal therapy) • MMAE-derived drugs • Radiotherapy ((note: radiation therapy of a symptomatic solitary non-target lesion or to the brain may be allowed at the investigator's discretion) Prohibited for participants receiving chemotherapy: • Any drugs that are contraindicated for use with the assigned chemotherapy • Any other anti-cancer therapy that has not been identified as investigator's choice
Primary outcomes	• Overall survival (OS)

Other outcomes used in the economic model/specified in the scope	• PFS • Response rates • Adverse effects of treatment • HRQoL
Pre-planned subgroups	Conducted for the primary endpoint (OS) and key secondary endpoint (PFS). Pre-specified subgroups included but were not limited to: • Region (US, Europe, Asia, Other) • ECOG PS at baseline (0 or 1) • Prior bevacizumab administration (yes or no) • Prior anti-PD-1/PD-(L)1 therapy administration (yes or no) • Histology (SCC and adenosquamous carcinoma, adenocarcinoma) • Number of prior r/m CC systemic regimens (1, 2)

Abbreviations: CC: cervical cancer; C1D1: cycle 1 day 1; DoR: duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL: health related quality of life; MMAE: monomethyl auristatin E; ORR: overall response rate; OS: overall survival; PD-(L)1: programmed cell death-ligand 1; PFS: progression free survival; RECIST: Response Evaluation Criteria in Solid Tumour; r/m CC: recurrent or metastatic cervical cancer; SCC: squamous cell carcinoma; TF: tumour factor; TTR: time to response.

Notes: Table information relates to the InnovaTV 301 data cutoff date on 24 July 2023. ^aFollowing the European approval of pembrolizumab combination therapy in 1L r/m CC in April 2022, patients were required to have received prior anti-PD-(L)1 therapy, if eligible and available.

Sources: Vergote et al. (2024) (70), InnovaTV 301 Trial Protocol (2024) (81), InnovaTV 301 CSR (2023) (82), and ClinicalTrials.gov (72).

2.3.1.2. InnovaTV 204

InnovaTV 204 was a multicentre, phase 2, single-arm, open-label study of tisotumab vedotin in patients with previously treated r/m CC who experienced disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards) (77, 78).

Eligible patients received 2.0 mg/kg (up to a maximum of 200 mg) tisotumab vedotin intravenously Q3W until independent review committee (IRC)-verified progressive disease as per RECIST v1.1 or unacceptable toxicity. A total of 102 participants were enrolled; of these, 101 received at least one dose of tisotumab vedotin.

The primary efficacy endpoint was confirmed ORR based on RECIST v1.1, as assessed by the IRC. The key secondary efficacy endpoints included PFS, defined as the time from the first dose of the study drug to the first documentation of disease progression or death from any cause, whichever occurred first; and confirmed ORR (CR+PR), assessed by the investigator. Other secondary efficacy endpoints included TTR, DoR, safety (side-effect profile), and health economics and outcomes research endpoints.

Tumour responses were assessed by the IRC and investigators using CT or MRI scans, which were performed at baseline (≤ 28 days before cycle 1, day 1), every 6 weeks for the first 30 weeks, and every 12 weeks thereafter. To confirm responses, repeat imaging was conducted 4 weeks or more after the initial response assessment (78).

A summary of the InnovaTV 204 trial methodology is provided in Table 8.

Table 8: Summary of InnovaTV 204 trial methodology

Trial	InnovaTV 204 (NCT03438396)
Location	Conducted across 35 sites in the US and Europe.
Trial design	A Phase 2, single-arm, multicentre study to evaluate the efficacy and safety of tisotumab vedotin in patients with r/m CC who experienced disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards).
Eligibility criteria for participants	<u>Key Inclusion Criteria</u> • Age ≥18 years, or considered an adult by local regulations, at time of consent • Recurrent or metastatic CC with squamous cell, adenocarcinoma, or adenosquamous histology • Experienced disease progression during or after doublet chemotherapy (paclitaxel plus either platinum or topotecan) plus bevacizumab, if eligible • Received ≤2 prior systemic therapy regimens for r/m CC, not including adjuvant or neoadjuvant chemotherapy with or without radiotherapy • Measurable disease according to RECIST v1.1 as assessed by the IRC • ECOG PS of 0 or 1 prior to randomisation • Acceptable renal and liver function • Acceptable hematological status • Life expectancy ≥3 months <u>Key Exclusion Criteria</u> • Prior treatment with MMAE-containing drugs • Radiotherapy within 21 days before first administration of study drug • Known coagulation defects or ongoing major bleeding • Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis (e.g., Wagner syndrome, atopic keratoconjunctivitis, autoimmune disease affecting the eyes), ocular Stevens-Johnson

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	syndrome or toxic epidermal necrolysis, mucus pemphigoid, and participants with penetrating ocular transplants. Cataracts alone is not an exclusion criterion. Peripheral neuropathy Grade ≥ 2
Settings and locations where the data were collected	Academic centres, hospitals and community practices.
Trial drugs	Intervention: - Tisotumab vedotin 2.0 mg/kg IV Q3W Comparator: - Not applicable
Permitted and disallowed concomitant medication	Permitted concomitant medication: - Anti-coagulation therapy. Disallowed concomitant medication: - Chronic prophylactic treatment with acetylsalicylic acid (e.g., aspirin) in combination with any other anti-coagulation therapy. - Radiotherapy (note: radiation therapy of a symptomatic solitary non-target lesion <u>was allowed</u>). - Small molecules, chemotherapy, immunotherapy, monoclonal antibodies, other MMAE-derived drugs or any experimental agents not specified in the trial protocol. Note: Participants were instructed not to take any medications, including over-the-counter products, without consulting first with the investigator.
Primary outcomes	The primary endpoint was confirmed ORR, defined as the proportion of CRs and PRs by RECIST v1.1, as assessed by the IRC.

Other outcomes used in the economic model/specified in the scope	• PFS • Confirmed ORR (CR+PR) assessed by the investigator • TTR • DoR • Incidence of AE
Pre-planned subgroups	• TF expression • Histology subtype • Prior therapy (including cisplatin plus radiation, or doublet chemotherapy plus bevacizumab in the 1L setting)

Abbreviations: AE: adverse event; CC: cervical cancer; CR: complete response; C1D1: cycle 1 day 1; DoR: duration of response; MMAE: monomethyl auristatin E; ORR: overall response rate; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumour; r/m CC: recurrent or metastatic cervical cancer; TF: tissue factor; TTR: time to response.

Sources: Coleman et al. (including Supplementary Material) (2021) and ClinicalTrials.gov (77, 78, 80).

2.3.2. Baseline characteristics

2.3.2.1. InnovaTV 301

A total of 502 participants underwent randomisation in InnovaTV 301 globally (Figure 11). Of these, 253 participants were assigned to receive tisotumab vedotin, and 249 participants received at least one dose of tisotumab vedotin. Demographics and clinical characteristics at baseline were balanced between the treatment groups. The InnovaTV 301 trial enrolled individuals from 25 countries, and represents a geographically diverse patient population, reflective of real-world patients receiving 2L+ therapy for r/m CC. The number of UK patients enrolled in the tisotumab vedotin and chemotherapy arms was 11 (4.3%) and 11 (4.4%), respectively (70, 71).

Participants in InnovaTV 301 were primarily White or Asian, with a median age of 50 years (Table 9). The majority (84%) of participants were 65 years of age or younger. Among randomised participants, 308 (61.4%) had received 1 prior line of systemic therapy and 193 (38.4%) had received 2 prior lines of therapy. A total of 28% of participants received prior PD-(L)1 therapy. Participants were balanced across pre-specified stratification groups, including ECOG performance status, prior bevacizumab, geographic region, and prior anti-PD-(L)1 therapy (Table 10) (70, 71).

Table 9: Participant demographics at baseline in InnovaTV 301 (ITT population)

Patient Demographics	Tisotumab vedotin (N=253)	Chemotherapy (N=249)	Overall (N=502)
Age			
Median – years	51.0 (26-80)	50.0 (27-78)	50.0 (26-80)
<65 years – no. (%)	211 (83.4)	208 (83.5)	419 (83.5)
Race – no. (%)			
American Indian or Alaska Native	7 (2.8)	7 (2.8)	14 (2.8)
Asian	90 (35.6)	90 (36.1)	180 (35.9)
Black/African American	4 (1.6)	6 (2.4)	10 (2.0)
Native Hawaiian/Other Pacific Islander	1 (0.4)	0	1 (0.2)
White	122 (48.2)	122 (49.0)	244 (48.6)
Unknown/Other/Not	29 (11.5)	24 (9.6)	53 (10.6)

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Reportable			
Hispanic or Latino Ethnicity, n (%)	52 (20.6)	50 (20.1)	102 (20.3)
Region – no. (%)			
US	16 (6.3)	14 (5.6)	30 (6.0)
Europe	106 (41.9)	104 (41.8)	210 (41.8)
Asia	85 (33.6)	88 (35.3)	173 (34.5)
Other	46 (18.2)	43 (17.3)	89 (17.7)
ECOG performance status – no. (%)			
0	137 (54.2)	136 (54.6)	273 (54.4)
1	116 (45.8)	113 (45.4)	229 (45.6)

Abbreviations: CC, cervical cancer; ECOG, Eastern Cooperative Oncology Group; LOT, line of therapy; PD-(L)1, programmed death-ligand 1; r/m CC, relapsed or metastatic cervical cancer; SCC, squamous cell carcinoma; TF, tissue factor; US, United States.

Source: Vergote et al. (2024) and InnovaTV 301 CSR (2023) (70, 71).

Table 10: Clinical characteristics at baseline in InnovaTV 301 (ITT population)

Clinical Demographics	Tisotumab vedotin (N=253)	Chemotherapy (N=249)	Overall (N=502)
Median time from DX – months	24.5 (3-204)	25.1 (5-154)	25.1 (3-204)
TF membrane expression ≥1% - n (%) ^a	194 (92.4)	183 (94.3)	377 (93.3)
Histologic type – no. (%)			
SCC	160 (63.2)	157 (63.1)	317 (63.1)
Adenocarcinoma	85 (33.6)	75 (30.1)	160 (31.9)
Adenosquamous carcinoma	8 (3.2)	17 (6.8)	25 (5.0)
Extent of CC – no. (%)			
Metastatic (stage IVB) at diagnosis	61 (24.1)	56 (22.5)	117 (23.3)
Recurrent or persistent at baseline ^b	27 (10.7)	24 (9.6)	51 (10.2)
Metastatic (stage IVB) at baseline ^b	226 (89.3)	225 (90.4)	451 (89.8)
Treatment History			
Prior LOT for r/m CC – no. (%)			
One	159 (62.8)	149 (59.8)	308 (61.4)
Two	93 (36.8)	100 (40.2)	13 (38.4)
Any prior radiation	205 (81.0)	203 (81.5)	408 (81.3)

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Clinical Demographics	Tisotumab vedotin (N=253)	Chemotherapy (N=249)	Overall (N=502)
therapy – no. (%)			
Prior taxane use – no. (%) ^c	253 (100)	238 (99.6)	-
Prior 1L platinum use – no. (%)	249 (98.8)	244 (98.4)	-
Prior bevacizumab use – no. (%)	164 (64.8)	157 (63.1)	321 (63.9)
Prior anti-PD-(L)1 use – no. (%)	71 (28.1)	67 (26.9)	138 (27.5)
Distribution of investigator's choice CT – no. (%)			
Pemetrexed	-	80 (33.5)	-
Gemcitabine	-	109 (45.6)	-
Topotecan	-	19 (7.9)	-
Irinotecan	-	14 (5.9)	-
Vinorelbine	-	17 (7.1)	-

Abbreviations: CC, cervical cancer; CT, chemotherapy; DX, diagnosis; ECOG, Eastern Cooperative Oncology Group; LOT, line of therapy; PD-(L)1, programmed death-ligand 1; r/m CC, relapsed or metastatic cervical cancer; SCC, squamous cell carcinoma; TF, tissue factor; US, United States

^aTF expression was evaluable in 404 patients (80.5%) with 210 (83.0%) in the TIVDAK arm and 194 (77.9%) in the CT arm.

^bRecurrent CC refers to those patients with recurrent disease only and no history of metastasis. Metastatic CC includes those with either *de novo* metastatic disease at diagnosis or any history of metastasis during the course of disease.

^cData are from the Summary of Clinical Safety and reflect the Safety Analysis Set.

Source: Vergote et al. (2024) and InnovaTV 301 CSR (2023) (70, 71).

Lastly, at baseline, 33.2% of patients in the tisotumab vedotin arm had pre-existing peripheral neuropathies at study entry, compared with 27.2% in the chemotherapy arm (for more detail refer to Section 2.11.1) (83).

2.3.2.2. InnovaTV 204

A total of 102 participants were enrolled in InnovaTV 204 across 36 sites in Europe and the US (Table 11) (84). Of these, 101 participants received at least one dose of tisotumab vedotin. The remaining participant experienced a serious adverse event (spinal cord injury cauda equina) prior to the scheduled first dose and therefore did not receive tisotumab vedotin (77, 78).

Demographics and clinical characteristics at baseline are summarised below for the trial population in InnovaTV 204 (Table 12 and Table 13) (77, 78).

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Table 11: Trial sites and number of enrolled participants by country

Country	Number of Sites	Number of Participants (%)
Belgium	9	19 (18.6%)
Czech Republic	3	11 (10.8%)
Germany	3 ^a	5 (4.9%)
Denmark	2	9 (8.8%)
Spain	4	16 (15.7%)
Italy	5	24 (23.5%)
Sweden	1	2 (2.0%)
US	9	16 (15.7%)

Notes: ^aOne participant who was enrolled at site DE02 was subsequently transferred to site DE01.

Source: Listing 16.02.01.02 Innova 201 CSR (84).

Table 12: Participant characteristics at baseline in InnovaTV 204 (ITT population)

Patient Demographics	Tisotumab vedotin (N=101)
Age	
Median – years	50 (43–58)
Race – no. (%)	
White	96 (95%)
Asian	2 (2%)
Black or African American	1 (1%)
Other	2 (2%)
ECOG performance status – no. (%)	
0	59 (58%)
1	42 (42%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

Source: Coleman et al. (2021) (78).

Table 13: Clinical characteristics at baseline in InnovaTV 204 (ITT population)

Clinical Demographics	Tisotumab vedotin (N=101)
Histology	
SCC	69 (68%)
Adenocarcinoma	27 (27%)
Adenosquamous carcinoma	5 (5%)
Extrapelvic metastatic disease at baseline	95 (94%)
Recurrent disease*	
Yes	61 (60%)
No	40 (40%)
Previous cisplatin plus radiotherapy	
Yes	55 (54%)
No	46 (46%)
Previous lines of systemic therapies for recurrent or metastatic disease†	
1	71 (70%)
2	30 (30%)
Previous bevacizumab plus doublet chemotherapy‡ as first-line therapy	64 (63%)
Any previous bevacizumab	70 (69%)
Response to last systemic regimen†	
Yes	38 (38%)
No	57 (56%)
Unknown	6 (6%)
Positive TF expression§	
Membrane	77/80 (96%)
Medical history of or ongoing peripheral neuropathy	20 (20%)

Abbreviations: SCC: squamous cell carcinoma; TF: tissue factor.

Notes: *First-line systemic regimen given in recurrent setting. †Systemic regimen administered in the metastatic or recurrent setting. ‡Doublet chemotherapy defined as paclitaxel–platinum or paclitaxel–topotecan. §TF-positive tumour cells were those with at least 1% expression of TF; TF expression was calculated for 80 patients who had biopsy samples.

Source: Coleman et al. (2021) (78).

2.3.3. Methods for eliciting expert opinion

Expert opinion was gathered via several routes. In May 2025, Genmab conducted a UK Cervical Cancer advisory board (in accordance with best practices) to: obtain up-to-date knowledge on the treatment landscape for CC in the UK; gain feedback on the clinical data for tisotumab vedotin in r/m CC and understand how to optimally position

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tisotumab vedotin (51). Five UK-based medical and clinical oncologists with specific expertise in gynaecological cancers were consulted, along with three experts in health economics. Ad-board slides and a summary of the discussion are available as Data on File (51).

In August 2025, an additional survey was conducted by Genmab to gather more information from clinicians regarding the distribution of second-line treatments for r/m CC. The criteria for selection of clinician experts were as follows:

- Oncologists with specific expertise in gynaecological cancers who currently treat CC patients with systemic treatments
- Oncologists with specific expertise in gynaecological cancers working in both academic and teaching hospitals in various geographical areas across England

A total of 10 oncologists were approached and asked the following questions via email; of these 8 responded.

1. Here is a list of treatment options. Can you indicate which treatments are used in your clinical practice for r/m CC patients in the second line setting?

Chemotherapy regimen	Proportion of patients receiving this regimen
Topotecan	%
Vinorelbine	%
Gemcitabine	%
Irinotecan	%
Pemetrexed	%
Paclitaxel	%

2. Are there any patients in this population who are ineligible for chemotherapy but would be considered eligible for tisotumab vedotin?

Responses which did not sum to 100% were proportionally adjusted to reach this total, and any qualitative responses were excluded. Responses referring to a combination including one of the therapies in the above table were re-allocated to that respective therapy. All other therapies were omitted, and the total % per regimen was proportionally rebalanced to sum to 100% (60, 85).

The results of the survey incorporated into the model are shown below in Table 14.

1. Here is a list of treatment options. Can you indicate which treatments are used

in your clinical practice for r/m CC patients in the second line setting?

Table 14: Summary of proportionally adjusted survey responses

Chemotherapy regimen	Proportion of patients receiving this regimen
Topotecan	4.7%
Vinorelbine	2.0%
Gemcitabine	28.4%
Irinotecan	0.3%
Pemetrexed	0.3%
Paclitaxel	64.3%

The results from Question 2 are provided as Data on File with this submission (60, 85).

2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1. InnovaTV 301

There are two data cuts available from the InnovaTV 301 trial comprising the primary analysis and an ad-hoc follow-up analysis, each of which correlate to an analysis of OS or PFS (Table 15). A further final analysis is planned when all OS events have occurred; this is expected in 2026 (70-72).

The primary analysis was conducted based on a data cutoff date of 24 July 2023 at approximately 252 OS events, or 75% of the expected total OS events. Due to regulatory queries, an ad-hoc follow-up analysis for OS and PFS was conducted in January 2024. Of note, these results are outlined below, and the OS and PFS data from the January 2024 follow-up analysis have been incorporated into the economic model (refer to Section 3 for more information) (86).

Table 15: Data cuts from the InnovaTV 301 trial

	Data Cutoff Date	Relevant Analysis
Primary Analysis	24 July 2023	OS and PFS
Follow-up Analysis	16 January 2024	OS

Abbreviations: OS: overall survival; PFS: progression-free survival.

Source: InnovaTV 301 CSR (2023) (71).

Populations analysed and sample size

Table 16 summarises the analysis sets included in the InnovaTV 301 trial. Efficacy analyses were performed using the ITT population and safety analyses using the safety analysis set.

Table 16: Analysis sets included in InnovaTV 301

Analysis Set	N	Definition	Description
ITT	502	All randomised patients	Primary efficacy analyses, demographics, baseline characteristics
Safety	████	All randomised patients who received any amount of study treatment	Treatment exposure and safety analyses
PRO FAS	████	All randomised patients who received any amount of study treatment and have completed baseline and ≥1 PRO assessment	PRO analyses
PK	████	All randomised patients who received any amount of study treatment and have ≥1 reportable value for TV, TAb or MMAE concentration	PK analyses

Abbreviations: CSR, clinical study report; FAS, full analysis set; ITT, intention to treat; MMAE, monomethyl auristatin E; PK, pharmacokinetics; PRO, patient-reported outcome; TAb, Tisotumab vedotin antibodies; TV, Tisotumab vedotin (TIVDAK).

Source: InnovaTV 301 CSR (2023) (71).

Statistical analysis

The pre-specified primary analysis was conducted based on a data cutoff date of 24 July 2023 when 252 deaths (approximately 75% of total OS events) had occurred. A summary of statistical analyses for InnovaTV 301 is presented in Table 17.

Table 17: Summary of key statistical analyses used in InnovaTV 301

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT04697628 (79)	The primary hypothesis was that tisotumab vedotin would prolong OS compared with investigator's choice of chemotherapy.	<u>OS and PFS</u> Stratified log-rank test HRs and 95% CIs estimated using a stratified Cox model <u>Confirmed ORR</u> Cochran-Mantel-Haenzel chi-squared test adjusted for stratification factors Note: OS, PFS and ORR were tested hierarchically in that order <u>DoR</u> Summarised descriptively using the KM approach	It was estimated that [REDACTED] randomised participants would be needed to give an overall power of 90% for the hypothesis testing on OS at a 2-sided 5% significance level to detect a HR $\neq$ 1 when the true HR is 0.7*.	Participants were withdrawn from the study if any of the following occurred: death, lost to follow-up, study termination by sponsor and/or participant withdrawal of consent. With the following exceptions, missing data were not imputed: - Missing AE dates were imputed for the purpose of calculating duration of events and determining the treatment-emergent status. Missing disease diagnosis date was imputed for the purpose of calculating the time from diagnosis to date of randomization or date of first dose. - Missing subsequent cancer-related therapy start date was imputed for the purpose of deriving the time-to-event endpoints as applicable. - For prior therapies start dates, if month and year were present and only day was missing, the day was imputed as the first day of the month. If month or year was missing, no imputation was performed. - For prior therapies end dates, if month and year were present and only

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				day was missing, the day was imputed as the last day of the month or 21 days before the first dose of study drug, whichever was earlier. If the imputed end date was earlier than start dates, the end day was imputed as the day after the start date. If month or year was missing, no imputation was performed

Abbreviations: CI: confidence interval; DoR, duration of response; HR, hazard ratio; KM, Kaplan Meier; ORR: overall response rate; OS: overall survival; PFS, progression-free survival.

Notes: *The following assumptions have been made: median OS of 12.9 months in the tisotumab vedotin arm; median OS of 9 months in the chemotherapy arm; drop-out rate of 5% per year; an IA at approximately 75% (252) of the total number of OS events using the Lan deMets (O'Brien Fleming) boundary; accrual duration of approximately 23 months with at least 12 months of follow-up, and 1:1 randomisation ratio.

Source: InnovaTV 301 trial protocol (2024) (82).

Participant flow

Overall, 660 patients entered screening. Of these, 502 were randomised to treatment: 253 to tisotumab vedotin and 249 to chemotherapy. Two hundred and fifty patients received at least one dose of tisotumab vedotin and 239 received at least one dose of chemotherapy. At the primary analysis data cut, 21 patients treated with tisotumab vedotin, and 16 patients treated with chemotherapy remained on treatment. Treatment had been discontinued in 229 patients in the tisotumab vedotin group and 223 in the chemotherapy group; most patients discontinued treatment due to disease progression (70.0% tisotumab vedotin vs. 77.5% chemotherapy) (71).

A CONSORT diagram for the ITT population showing the flow of participants through the study and the reasons for discontinuation is included in Appendix B: Identification, selection and synthesis of clinical evidence.

2.4.2. InnovaTV 204

There are two data cuts available from the InnovaTV 204 trial, each of which correlates to an analysis of confirmed ORR or OS (Table 18) (78, 82). In this dossier, the primary analysis data cut from February 2020 is reported, with a short summary of the final analysis results also provided for context.

Table 18: Outline of data cuts from the InnovaTV 204 trial

	Data Cutoff Date	Relevant Analysis
Primary Analysis	06 February 2020	Confirmed ORR
Final Analysis	04 October 2022	OS

Abbreviations: ORR: overall response rate; OS: overall survival.

Source: Coleman et al. (2021) (78).

Populations analysed and sample size

In InnovaTV 204, efficacy and safety analyses were performed using the ITT population which included 101 randomised patients who received ≥ 1 dose of study treatment (78).

Statistical analyses

A summary of statistical analyses for InnovaTV 204 is presented in Table 19.

Table 19: Summary of key statistical analyses used in InnovaTV 204

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT03438396 (InnovaTV 204) (77)	The primary hypothesis was to test the primary efficacy endpoint (confirmed ORR based on RECIST v1.1) for tisotumab vedotin.	Median DoR, PFS, and OS were estimated using the Kaplan-Meier method. ORR was tested using the one-sided exact binomial test at a 2.5% α level and the Clopper-Pearson method was used to calculate an exact 95% two-sided CI for ORR.	Study size was calculated assuming a confirmed ORR of 21%-25% with tisotumab vedotin. The planned sample size of 100 patients provided at least 80% power to exclude an ORR of up to 11%, which was the previously documented observed efficacy of single-agent chemotherapy in this setting.	Participants were withdrawn from the study if any of the following occurred: withdrawal of consent to participate, investigator decision, or participant lost to follow-up.

Abbreviations: CI: confidence interval; DoR: duration of response; ORR: overall response rate; OS: overall survival; PFS: progression free survival.

Source: Coleman et al. (including Supplementary Material) (2021) (78, 80).

Participant flow

At the primary analysis data cut (06 February 2020), the median follow-up was 10.0 months (IQR 6.1-13.0), with four patients still on treatment and 33 in follow-up.

2.5. Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from InnovaTV 301, a Phase 3 RCT, and InnovaTV 204, a Phase 2 single-arm trial (70-72, 77, 78). A risk of bias and quality assessment was conducted for InnovaTV 301 and InnovaTV 204, respectively, full details of which are provided in Appendix B. A summary of results from the risk of bias and quality assessments are shown in Table 20 and Table 21.

Table 20: Risk of bias assessment results for InnovaTV 301

Description of criteria	Assessment Response
Was the allocation sequence adequately generated?	Yes
Was the concealment of treatment allocation adequate?	Yes
Was knowledge of the allocated interventions adequately concealed from participants and personnel	No
Was knowledge of the allocated interventions adequately concealed from outcome assessors	No
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Not clear
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes

Table 21: Quality assessment results for InnovaTV 204

Description of criteria	Assessment Response
Is the study based on a representative sample selected from a relevant population?	Not clear
Are the criteria for inclusion explicit?	Yes
Did all individuals enter the study at a similar time in their disease	Yes

Description of criteria	Assessment Response
progression?	
Was follow-up long enough for important events to occur?	Yes
Were outcomes assessed using objective criteria or was blinding used?	Yes
If comparisons of sub-series are being made was there sufficient description of the series and the distribution of prognostic factors?	No

Note: Above table based upon the Centre for Reviews and Dissemination (CRD) case series checklist.

2.6. Clinical effectiveness results of the relevant studies

Summary of key points

- In InnovaTV 301, tisotumab vedotin significantly improved OS with a 30% reduction in the risk of death compared to investigator's choice of chemotherapy (median OS 11.5 months vs 9.5 months; HR 0.70, p=0.004) and a ■■■ improvement in OS at 12 months vs chemotherapy in 2nd and 3rd line r/mCC (Figure 12).
- PFS was superior for tisotumab vedotin compared to investigator's choice of chemotherapy, with a 33% reduction in the risk of disease progression or death (median PFS 4.2 months vs 2.9 months; HR 0.67, p<0.001) (70, 71). In InnovaTV 204, median OS and PFS were 12.1 months and 4.2 months, respectively. Notably, there was a ■■■% improvement in PFS vs chemotherapy at 6 months in 2nd and 3rd line r/mCC (Figure 13) (78).
- Confirmed ORRs were >3 times higher for tisotumab vedotin compared to investigator's choice of chemotherapy in InnovaTV 301 (17.8% vs 5.2%, respectively). The confirmed ORR for tisotumab vedotin in InnovaTV 204 was 24% (70, 71, 78).
- Treatment with tisotumab vedotin in InnovaTV 301 led to a numerically higher disease control rate (DCR, i.e. CR + PR + stable disease [SD]) compared with chemotherapy (75.9% vs. 58.2%) (70-72). In InnovaTV 204, a DCR of 72%

was observed and most responses were rapid (median TTR = 1.4 months), indicating potential antitumour activity within the first 2 cycles of treatment (78).

- The median duration of response for tisotumab vedotin was 5.3 months (79) and 8.3 months (InnovaTV 204), which indicates sustained antitumour activity (70, 71, 78).
- The percentage of patients who reported an improvement in the QLQ-C30 global health status–QoL scores of 10 points or more from baseline to cycle 5 was higher in the tisotumab vedotin group than in the chemotherapy group (13.9% vs. 3.4%) (70, 71).
- EQ-5D Visual Analogue Scale (VAS) scores in the tisotumab vedotin and chemotherapy arms were stable from baseline to Cycle 5 (70, 71).

2.6.1. InnovaTV 301

The primary analysis data cut in the InnovaTV 301 trial was in July 2023 (Table 15) (70-72).

Due to regulatory queries, an ad-hoc follow-up analysis for OS and PFS was conducted in January 2024. These results are outlined below, and the OS and PFS data from the January 2024 follow-up analysis have been incorporated into the economic model (refer to Section 3 for more information) (86).

Primary analysis (July 2023)

Overall survival

At the time of primary analysis, the primary endpoint (OS, defined as the time from randomisation to death from any cause) was met. Tisotumab vedotin demonstrated a statistically significant and clinically meaningful 30% reduction in the risk of death versus investigator's choice of chemotherapy (HR=0.70 [95% CI: 0.54, 0.89], p=0.0038). Median OS was 11.5 months in the tisotumab vedotin arm vs. 9.5 months in chemotherapy arm (95% CI: 7.9, 10.7) (Figure 12) (70-72).

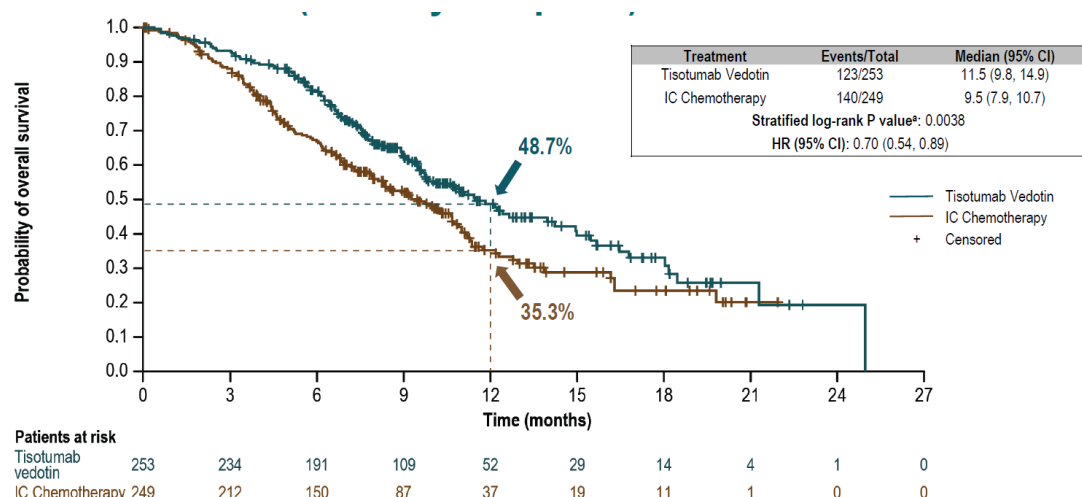
There was early and sustained separation of the OS curves, indicating a clear survival benefit for patients treated with tisotumab vedotin vs chemotherapy throughout the

study period.

In addition, the probability of OS was considerably higher at 12 months with tisotumab vedotin (48.7% [95% CI: 41.0, 55.8]) compared with the chemotherapy arm (35.3% [95% CI: 28.0, 42.7]) (Table 22) (70-72).

Notably, the Independent Data Monitoring Committee (IDMC) determined that OS crossed the pre-specified efficacy boundary during this interim analysis, and therefore this analysis is considered the final OS analysis.

Figure 12: Kaplan-Meier Estimate of Overall Survival^a with TIVDAK vs. Investigator's Choice Chemotherapy (ITT Population)



Abbreviations: CI, confidence interval; HR, hazard ratio; IC, investigator's choice; ITT, intent-to-treat

Notes: ^aDefined as the time from the date of randomisation to the date of death due to any cause.

Source: Vergote et al. (2024) (70).

Table 22: Estimated Overall Survival over Time (ITT Population)

	Tisotumab vedotin (N=253)	Chemotherapy (N=249)
Estimated OS rate (%) at ^a		
6 months (95% CI)	████ (████, █████)	████ (████, █████)
12 months (95% CI)	48.7 (41.0, 55.8)	35.3 (28.0, 42.7)
18 months (95% CI)	████ (████, █████)	████ (████, █████)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; OS, overall survival.

Notes: ^aMedian is estimated using Kaplan-Meier method and 95% CI is calculated using the complimentary log-log transformation method.

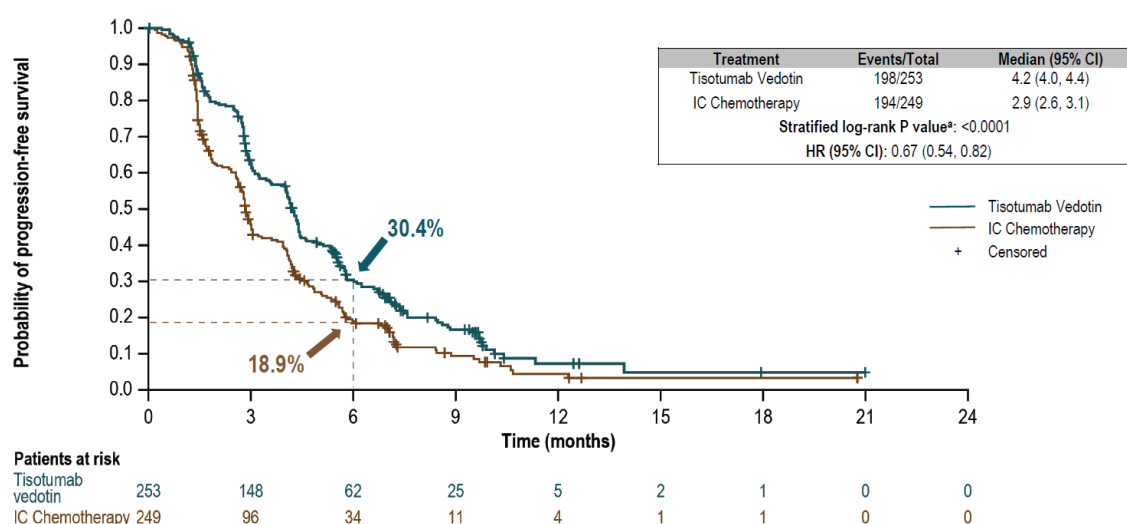
Source: InnovaTV 301 CSR (70-72).

Progression-free survival

At the time of primary analysis, tisotumab vedotin significantly reduced the risk of disease progression or death by 33% compared with investigator's choice chemotherapy (HR=0.67 [95% CI: 0.54, 0.82], $p<0.0001$) (Figure 13) (70-72).

The median PFS was 4.2 months (95% CI: 4.0, 4.4) for tisotumab vedotin compared with 2.9 months (95% CI: 2.6, 3.1) for chemotherapy (Figure 13) (70-72). Similar to the OS results, the PFS KM curves separate early, with separation maintained throughout the study. The probability of PFS was higher with tisotumab vedotin compared with the chemotherapy arm at 3, 6 and 9 months, as shown in Table 23 (70-72).

Figure 13: Kaplan-Meier Estimate of Progression-Free Survival^a with tisotumab vedotin vs. Investigator's Choice Chemotherapy (ITT Population)



Abbreviations: CI, confidence interval; HR, hazard ratio; IC, investigator's choice; ITT, intent-to-treat

Notes: ^aBased on RECIST v1.1 as assessed by investigator.

Source: Vergote et al. (2024) (70).

Table 23: Estimated Progression-Free Survival over Time (ITT Population)

	Tisotumab vedotin (N=253)	Chemotherapy (N=249)
Estimated PFS rate (%) at ^a		
3 months (95% CI)	■ (■, ■)	■ (■, ■)
6 months (95% CI)	30.4 (24.5, 36.5)	18.9 (13.8, 24.7)
9 months (95% CI)	■ (■, ■)	■ (■, ■)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; PFS, progression-free survival.

Notes: ^aMedian is estimated using Kaplan-Meier method and 95% CI is calculated using the complimentary log-log transformation method.

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Source: InnovaTV 301 CSR and Vergote et al. (2024) (70, 71).

Confirmed ORR

At the time of primary analysis, tisotumab vedotin resulted in a significantly higher confirmed ORR compared to investigator's choice of chemotherapy (17.8% vs. 5.2%; OR=4.0 [95% CI: 2.1, 7.6], $p<0.0001$) (Table 24) (70-72).

More patients who received tisotumab vedotin achieved CR or PR and fewer had PD compared with those who received investigator's choice chemotherapy. Treatment with tisotumab vedotin led to a numerically higher disease control rate (DCR) (CR + PR + stable disease [SD]) compared with chemotherapy (75.9% vs. 58.2%) (Table 24) (70-72).

Table 24: Confirmed Objective Response and Disease Control Rate with tisotumab vedotin vs. Investigator's Choice Chemotherapy (ITT Population)

	Tisotumab vedotin (N=253)	Chemotherapy (N=249)
Confirmed objective response ^a		
Confirmed ORR, n (%)	45 (17.8)	13 (5.2)
95% CI	(13.3, 23.1)	(2.8, 8.8)
Stratified odds ratio (95% CI)	4.0 (2.1, 7.6)	
Stratified CMH p-value	<0.0001	
Best confirmed overall response ^b , n (%)		
Complete response	6 (2.4)	0
Partial response		
Stable disease		
Progressive disease		
Not evaluable		
Not available		
Disease control rate		
DCR (CR + PR + SD), n (%)		
(95% CI for DCR)		

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; DCR, disease control rate; ITT, intention to treat; OR, overall response; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Notes: ^aConfirmed ORR (CR + PR) based on RECIST v1.1 as assessed by the investigator. ^bConfirmed best OR assessed per RECIST 1.1.

Source: InnovaTV 301 CSR and Vergote et al. (2024) (70, 71).

Time to response (TTR)

Time to response is defined as the time from the randomisation date to the date of the Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

first confirmed objective response (CR or PR that is subsequently confirmed) and was assessed by the investigator.

At the time of primary analysis, median TTR was 1.58 months (range 1.2 to 4.5 months) in the tisotumab vedotin arm and 1.74 months (range 1.2 to 3.9 months) in the chemotherapy arm (70).

Duration of response

Duration of response was assessed by the investigator and defined as the time from the date of the first confirmed objective response (CR or PR that is subsequently confirmed) to the date of the first documented PD per RECIST v1.1 or death from any cause, whichever occurs first.

At the time of primary analysis, the median DOR was 5.3 months (95% CI: 4.2, 8.3) with tisotumab vedotin and 5.7 months (95% CI: 2.8, not reached) in the chemotherapy arm (70-72).

Health-Related Quality of life (HRQoL)

EORTC-QLQ-C30

Between baseline and Cycle 5 (median number of cycles received per patient in the tisotumab vedotin arm), the percentage of subjects who completed the EORTC-QLQ-C30 questionnaire among those who were alive and receiving trial treatment (compliance rate) was ██████% in the tisotumab vedotin arm, and ██████% in the chemotherapy arm (70, 71).

Using a 10-point threshold to define a clinically meaningful change in score, the QLQ-C30 GHS/QoL score was maintained in the tisotumab vedotin arm from baseline to Cycle 5, whereas the chemotherapy group showed a trend toward declining quality of life. The percentage of patients who reported an improvement in the QLQ-C30 global health status–QoL scores of 10 points or more from baseline to cycle 5 was higher in the tisotumab vedotin group than in the chemotherapy group (13.9% vs. 3.4%) (70, 71).

Scores from baseline to Cycle 5 were maintained in the tisotumab vedotin and chemotherapy arms for physical, role, emotional, cognitive, and social functioning scales of the QLQ-30 (70, 71).

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EQ-5D

Between baseline and Cycle 5, the compliance rate of the EQ-5D questionnaire was ████% in the tisotumab vedotin arm, and ████% in the chemotherapy arm; completion rate was ████% in the tisotumab vedotin arm and ████% in the chemotherapy arm (70, 71).

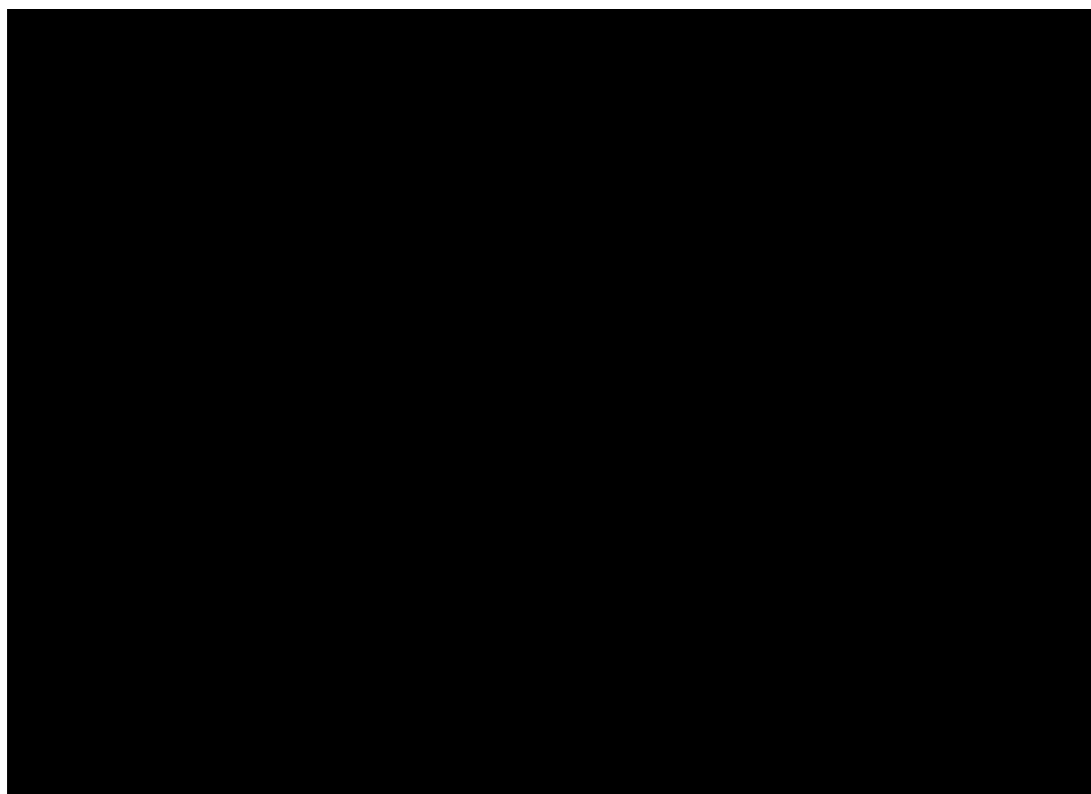
Using a 7-point threshold to define an improved, worsened, or stable score, the EQ-5D Visual Analogue Scale (VAS) scores in the tisotumab vedotin and chemotherapy arms were stable from baseline to Cycle 5 (70, 71).

Follow-up analysis (January 2024)

Overall survival

At the time of follow-up analysis, median OS was ████ months in the tisotumab vedotin arm vs ████ months in the chemotherapy arm (HR: ████, 95% CI: ████) The number of mortality events reported was ████ (tisotumab vedotin arm) and ████ (chemotherapy arm) (Figure 14) (86).

Figure 14: Overall Survival by Treatment Arm (ITT population)



Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1.

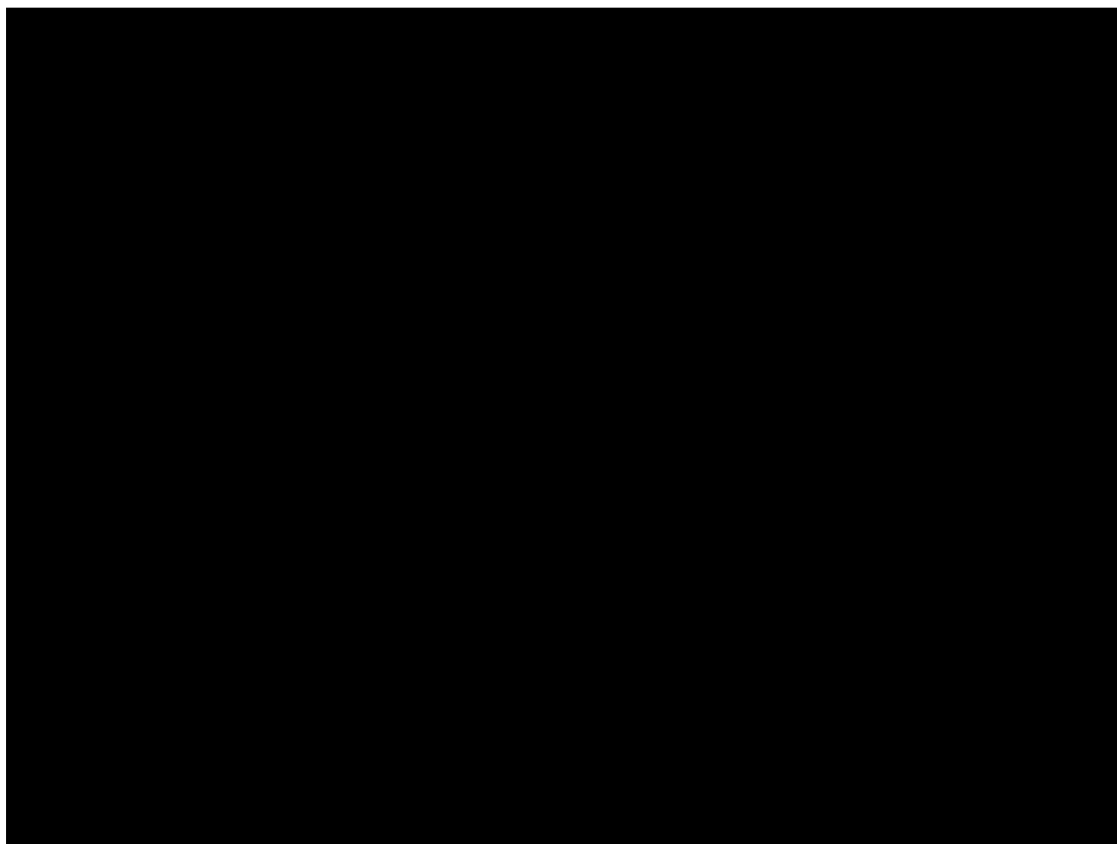
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Notes: HR is computed from the stratified Cox proportional hazards model using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomization.
Source: Genmab data on file (86).

Progression-free survival

In addition, PFS was prolonged in the tisotumab vedotin arm, with a median PFS of [REDACTED] months, compared to [REDACTED] months for chemotherapy (Figure 15) (HR: [REDACTED]) (86).

Figure 15: Kaplan-Meier Estimate of Progression-Free Survivala with tisotumab vedotin vs. Investigator's Choice Chemotherapy (ITT Population)



2.6.2. InnovaTV 204

The primary analysis data cut in the InnovaTV 204 trial is outlined below (Table 18) (78). Results from the final analysis (04 October 2022) are also briefly summarised for context.

Primary endpoint

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The primary endpoint for InnovaTV 204 was confirmed ORR per RECIST v1.1 by IRC. Patients with r/m CC who received tisotumab vedotin had a 24% ORR including 7 CRs and 17 PRs (Table 25) (78).

Table 25: Confirmed Objective Response with Tisotumab Vedotin in InnovaTV 204

	Tisotumab vedotin (N=101)
Confirmed ORR (95% CI) ^a	24 (15.9, 33.3)
Complete response, n(%)	7 (7)
Partial response, n (%)	17 (17)
Stable disease, n (%)	49 (49)
Progressive disease, n (%)	24 (24)
Not evaluable, n (%)	4 (4)

Abbreviations: CI, confidence interval; IRC, Independent Review Committee; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours

Notes: ^aConfirmed ORR based on RECIST v1.1 as assessed by IRC.

Source: Coleman et al. (2021) (78).

The final analysis results were consistent with the primary analysis. Confirmed ORR assessed by IRC was ████% (95% CI: ████%, ████%), including █ (███%) CRs and ███ (███%) PRs (84).

Secondary endpoints

Median OS with tisotumab vedotin was 12.1 months with 79% and 51% of patients alive at 6 and 12 months, respectively. A DCR of 72% was observed and most responses were rapid (median TTR = ███ months), indicating potential antitumour activity within the first 2 cycles of treatment. Additionally, the response to tisotumab vedotin was durable, with 62% of patients having an ongoing confirmed response of ≥6 months (Table 26) (78).

Table 26: Secondary Endpoints with Tisotumab Vedotin in InnovaTV 204

Endpoint	Tisotumab vedotin (N=101)
DCR, % (95% CI) ^{a,b}	72 (62.5, 80.7)
Median OS, months (95% CI)	12.1 (9.6, 13.9)
6-month OS rate, % (95% CI)	79 (69, 86)
12-month OS rate, % (95% CI)	51 (41, 61)
Median PFS rate, months (95% CI) ^a	4.2 (3.0, 4.4)
6-month PFS, % (95% CI)	30 (21, 40)

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Endpoint	Tisotumab vedotin (N=101)
Median TTR, months (IQR) ^a	1.4 (1.3, 1.5)
Median DOR, months (95% CI) ^a	8.3 (4.2, NR)
Ongoing confirmed response ≥6 months, % (95% CI)	62 (37, 80)

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; IQR, interquartile range; IRC, independent review committee; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1; SD, stable disease; TTR, time to response.

Notes: ^aBased on RECIST v1.1 as assessed by IRC. ^bDCR is the proportion of patients with CR, PR, or SD.

Source: Coleman et al. (2021) (78).

At final analysis, median OS with tisotumab vedotin was [REDACTED] months (95% CI: [REDACTED] months). A DCR of 72% was observed and most responses were rapid (median TTR=1.4 months). Additionally, the response to tisotumab vedotin was durable, with 62% of patients having an ongoing confirmed response of ≥6 months (84). Final efficacy results were therefore consistent with the primary analysis.

2.7. Subsequent treatments used in the relevant studies

Subsequent treatments used in InnovaTV 301 primary analysis data cut, InnovaTV 301 ad-hoc follow-up analysis for OS, and InnovaTV 204 are outlined in Table 27, Table 28, and Table 29, respectively.

Table 27: Summary of the subsequent lines of treatment used in InnovaTV 301 ITT (primary analysis data cut; July 2023)

Number of lines of systemic therapy in r/m CC setting	Number of lines of subsequent anti-cancer therapies	Treatment	Tisotumab vedotin (N=253), N(%)	Chemotherapy ^a (N=249), N(%)
■	■	██████████	████	████
■	■	██████████████████	████	████
■	■	██████████	████	████
■	■	██████████████████	████	████
■	■	██████████	████	████
■	■	██████████	████	████
■	■	██████████████	████	████
■	■	██████████████████	████	████
■	■	██████████	████	████

Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

Number of lines of systemic therapy in r/m CC setting	Number of lines of subsequent anti-cancer therapies	Treatment	Tisotumab vedotin (N=253), N(%)	Chemotherapy ^a (N=249), N(%)
■	■	██████████	██████	██████
■	■	██████████	██████	██████
■	■	██████████	██████	██████

Notes: Treatments with '0' patients reported for either tisotumab vedotin or chemotherapy arms were omitted. Refer to source for full details including mean time on treatment.

Source: Subsequent lines of treatment data on file (87).

Table 28: Summary of the subsequent lines of treatment used in InnovaTV 301 ITT (ad-hoc follow-up analysis for OS; January 2024)

Number of lines in systemic therapy in r/m CC	Treatment number after	Treatment	Tisotumab vedotin (N=253), N(%)	Chemotherapy ^a (N=249), N(%)
■	■	██████████	██████	██████
■	■	██████████	██████	██████
■	■	██████████	██████	██████
■	■	██	██████	██████
■	■	██████████	██████	██████
■	■	██████████	██████	██████
■	■	██████████	██████	██████

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Number of lines in systemic therapy in r/m CC	Treatment number after	Treatment	Tisotumab vedotin (N=253), N(%)	Chemotherapy ^a (N=249), N(%)
■	■	████████	████	████
■	■	████████████████████	████	████
■	■	██████████████	████	████
■	■	████████	████	████
■	■	██████████	████	████
■	■	██████████	████	████
■	■	████████	████	████
■	■	████████████████	████	████
■	■	████████	████	████
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■	■	████████	████	████
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■	■	██████████	████	████
■	■	████████	████	████
■	■	████████	████	████

Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

Number of lines in systemic therapy in r/m CC	Treatment number after	Treatment	Tisotumab vedotin (N=253), N(%)	Chemotherapy ^a (N=249), N(%)
■	■	██████████	██████	██████

Notes: Treatments with '0' patients reported for either tisotumab vedotin or chemotherapy arms were omitted. Refer to source for full details including mean time on treatment.

Source: Subsequent lines of treatment data on file (88).

Table 29: Summary of the subsequent lines of treatment used in Innova 204 FAS

Number of lines in systemic therapy in r/m CC	Treatment number after	Treatment	Tisotumab vedotin (N=101), N(%)
■	■	██████████████████	██████
■	■	██████████████████	██████
■	■	██████████	██████
■	■	██████████████████	██████
■	■	██████████████████	██████
■	■	██████████████████████████	██████
■	■	██████████	██████
■	■	██████████████	██████
■	■	██████████████████████████	██████

Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

Number of lines in systemic therapy in r/m CC	Treatment number after	Treatment	Tisotumab vedotin (N=101), N(%)
■	■	██████	████
■	■	██████	████
■	■	████████	████
■	■	██████	████
■	■	██████	████
■	■	██████	████
■	■	██████	████
■	■	██████████████	████
■	■	██████	████
■	■	██████	████
■	■	██████	████
■	■	██████	████
■	■	██████	████
■	■	████████	████
■	■	██████	████

Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

Number of lines in systemic therapy in r/m CC	Treatment number after	Treatment	Tisotumab vedotin (N=101), N(%)
■	■	██████████	██████
■	■	██████████	██████
■	■	██████████	██████
■	■	██████████	██████
■	■	██████████████████	██████
■	■	██████████████	██████
■	■	██████████████████████	██████
■	■	██████████	██████
■	■	██████████	██████
■	■	██████████	██████
■	■	██████████████	██████
■	■	██████████	██████
■	■	██████████	██████
■	■	██████████	██████

Number of lines in systemic therapy in r/m CC	Treatment number after	Treatment	Tisotumab vedotin (N=101), N(%)
■	■	██████████	██████████
■	■	████████████████████	██████████

Notes: Treatments with '0' patients reported for either tisotumab vedotin or chemotherapy arms were omitted. Refer to source for full details including mean time on treatment.

Source: Subsequent lines of treatment data on file (89).

2.8. Subgroup analysis

2.8.1. InnovaTV 301

Primary analysis (July 2023)

In InnovaTV 301, prespecified subgroup analyses were exploratory in nature and were conducted for the primary endpoint (OS) and key secondary endpoint of PFS.

Prespecified subgroups included but were not limited to the following:

- Region (US, Europe, Asia, Other)
- ECOG PS at baseline (0 or 1)
- Prior bevacizumab administration (yes or no)
- Prior anti-PD-1/PD-(L)1 therapy administration (yes or no)
- Histology (SCC and adenosquamous carcinoma, adenocarcinoma)
- Number of prior r/m CC systemic regimens (1, 2)

Analysis of OS for tisotumab vedotin–treated patients in InnovaTV 301 by prespecified subgroups demonstrated a benefit generally consistent with the overall study population, including in patients with and without prior anti-PD-(L)1 exposure.

The OS benefit with tisotumab vedotin was observed regardless of prior PD-(L)1 therapy, histology (SCC vs adenocarcinoma/adenosquamous), ECOG status, number of prior lines of therapy, race or ethnicity (refer to Appendix C Subgroup analysis for further detail) (70, 71). Similarly, consistent PFS benefit was observed with tisotumab vedotin compared to investigator’s choice chemotherapy across the prespecified patient subgroups in the ITT population (refer to Appendix C Subgroup analysis for more detail).

In addition, patients who had received bevacizumab prior to tisotumab vedotin saw greater OS benefit with tisotumab vedotin compared to those in the chemotherapy arm. However, in patients who did not receive bevacizumab, no difference in OS was observed between tisotumab vedotin and chemotherapy arms. No biologic reason is known for the differing outcomes of subsequent therapy between patients who have

received bevacizumab previously and those who have not (70, 71).

Notably, in InnovaTV 204, the subgroup of patients who did not receive prior bevacizumab therapy had a higher ORR compared to patients who had received prior bevacizumab therapy (78).

Follow-up analysis (January 2024)

Refer to Appendix C Subgroup analysis for forest plots of OS by subgroup at follow-up analysis (January 2024) (86).

2.8.2. InnovaTV 204

In InnovaTV 204, prespecified subgroup analyses included:

- Region
- Histology
- Number of previous lines of systemic therapy
- Previous radiotherapy with cisplatin
- Previous bevacizumab in combination with doublet chemotherapy as first-line treatment
- ECOG performance status

Responses were generally consistent across all prespecified subgroups (refer to Appendix C Subgroup analysis for more detail) (78).

2.9. Meta-analysis

Meta-analysis is not required for tisotumab vedotin as the InnovaTV 301 and InnovaTV 204 trials provide data on the efficacy and safety of this intervention.

2.10. Indirect and mixed treatment comparisons

An ITC was not conducted since the InnovaTV 301 trial provides data on the efficacy of tisotumab vedotin versus investigator's choice of chemotherapy.

2.11. Adverse reactions

Summary of key points

- The median duration of exposure to tisotumab vedotin in InnovaTV 301 (data cutoff: July 2023) was 3.65 months compared to 2.76 months in the chemotherapy arm (70, 71). In InnovaTV 204, the median duration of exposure to tisotumab vedotin was 4.2 months (78).
- Tisotumab vedotin had a manageable safety profile, and no unanticipated AEs were observed. In InnovaTV 301, treatment discontinuations (14.8% of patients) in the tisotumab vedotin arm were primarily driven by protocol-mandated dose modifications in response to ocular and peripheral neuropathy (70, 71). Only 12% of patients discontinued tisotumab vedotin treatment due to AEs (78).
- Rates of any TEAE were balanced between treatment arms. Grade ≥ 3 TEAEs occurred in 52% of patients treated with tisotumab vedotin versus 62% in the chemotherapy arm in InnovaTV 301, and in 28% of patients treated with tisotumab vedotin in InnovaTV 204.
- In InnovaTV 301, 132 patients (53%) treated with tisotumab vedotin reported ocular treatment-related AEs (TRAEs), and nearly all of these patients (94%) experienced complete resolution or partial improvement of symptoms. Only 4% of patients experienced a Grade 3 ocular event and all patients with Grade ≥ 3 ocular AEs had relevant medical history or preceding low grade ocular AEs (70, 71).
- In InnovaTV 204, ocular TRAEs occurred in 54 patients, with the majority (96%) of those affected experiencing either Grade 1 or 2 events. None of the ocular TRAEs in InnovaTV 204 were serious (78).
- Another known safety risk of tisotumab vedotin is peripheral neuropathy, which was reported by 96 patients (38%) following treatment with tisotumab vedotin in InnovaTV 301. Many of these patients (44%) experienced either complete resolution or partial improvement of symptoms (70, 71). In InnovaTV

204, peripheral neuropathy TRAEs occurred in 33 patients, with the majority (79%) of those affected experiencing either Grade 1 or 2 events (78).

2.11.1. InnovaTV 301

In InnovaTV 301, patients treated with tisotumab vedotin had a longer treatment exposure compared with those who received investigator's choice of chemotherapy. At the data cutoff on July 24, 2023, the median duration of exposure to tisotumab vedotin was 3.65 months (range 0.4 to 18.9) compared to 2.76 months (range 0.1 to 20.9) for chemotherapy (70, 71).

Participants in the tisotumab vedotin arm received a median of 5.0 cycles (range 1 to 26) per participant while those in the chemotherapy arm received a median of 4.0 cycles (range 1 to 30).

Treatment-emergent adverse events

Tisotumab vedotin had a manageable safety profile, and no unanticipated AEs were observed. A total of 14.8% of patients discontinued treatment with tisotumab vedotin due to AEs compared to the chemotherapy arm (3.8%). Treatment discontinuations in the tisotumab vedotin arm were primarily driven by protocol-mandated dose modifications in response to ocular and peripheral neuropathy AEs (70, 71).

Rates of any TEAE were balanced between treatment arms. The proportion of patients who experienced a treatment-emergent SAE in the tisotumab vedotin arm (32.8%) was lower than in the chemotherapy arm (39.3%) (Table 30) (70, 71).

Table 30: Summary of Treatment-Emergent Adverse Events (≥10% Either Treatment Arm) for tisotumab vedotin or chemotherapy (Safety Analysis Population)

Adverse Event	Tisotumab vedotin (N=250) n (%)	Chemotherapy (N=239) n (%)
Any TEAE ^a	246 (98.4)	237 (99.2)
Grade ≥3 TEAE	130 (52.0)	149 (62.3)
Any treatment-emergent SAE	82 (32.8)	94 (39.3)
Grade ≥5 TEAE	4 (1.6)	5 (2.1)
TEAE leading to death	4 (1.6)	5 (2.1)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Notes: ^aTEAEs are defined as events that are new or worsened on or after the first dose of study treatment (tisotumab vedotin or chemotherapy) and with onset date on or before 30 days after the last dose of study treatment.

Source: Vergote et al. (2024) and InnovaTV 301 CSR (2023) (70, 71).

The most frequently-reported TEAEs with tisotumab vedotin included nausea, conjunctivitis, peripheral sensory neuropathy, epistaxis, constipation, alopecia, decreased appetite, anaemia, and diarrhoea (Table 31) (70, 71). The most common Grade ≥3 AEs reported with tisotumab vedotin included anaemia, urinary tract infection, abdominal pain, fatigue, neutropenia, peripheral sensory neuropathy, and small intestinal obstruction (Table 31) (70, 71).

Table 31: Most common ($\geq 10\%$ either treatment arm) treatment-emergent adverse events (any grade and grade ≥ 3) for tisotumab vedotin or chemotherapy (safety analysis population)

Preferred Term, n (%)	Tisotumab vedotin (N=250)		Chemotherapy (N=239)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any event	246 (98.4)	130 (52.0)	237 (99.2)	149 (62.3)
Anaemia	58 (23.2)	21 (8.4)	125 (52.3)	66 (27.6)
Urinary tract infection	33 (13.2)	11 (4.4)	38 (15.9)	17 (7.1)
Abdominal pain	34 (13.6)	10 (4.0)	23 (9.6)	4 (1.7)
Fatigue	32 (12.8)	9 (3.6)	39 (16.3)	10 (4.2)
Neutropenia	17 (6.8)	9 (3.6)	54 (22.6)	32 (13.4)
Peripheral sensory neuropathy	71 (28.4)	7 (2.8)	6 (2.5)	0
Asthenia	40 (16.0)	5 (2.0)	38 (15.9)	5 (2.1)
Keratitis	39 (15.6)	5 (2.0)	0	0
Alanine aminotransferase increased	18 (7.2)	4 (1.6)	26 (10.9)	5 (2.1)
Nausea	83 (33.2)	1 (0.4)	96 (40.2)	5 (2.1)
Neutrophil count decreased	-	0	-	11 (4.6)

Abbreviations: TEAE, treatment-emergent adverse event.

Source: Vergote et al. (2024) and InnovaTV 301 CSR (2023) (70, 71).

Serious adverse events

The most common treatment-emergent SAEs (i.e. those occurring in $\geq 2\%$ of patients) in the tisotumab vedotin arm were urinary tract infection (4%), small intestine obstruction (2.4%), abdominal pain (2%) and sepsis (2%). In the chemotherapy arm, the most common treatment-emergent SAEs were urinary tract infection (7.1%), anaemia (4.2%), febrile neutropenia (3.3%), hydronephrosis (2.9%), and acute kidney injury (2.1%) (70, 71).

AEs that led to death occurred in 4 patients (1.6%) in the tisotumab vedotin arm and 5 patients (2.1%) in the chemotherapy arm (70). The TEAEs that led to death in the tisotumab vedotin arm were acute kidney injury, pneumonia, sepsis, and Stevens-Johnson syndrome (SJS), which were reported in 1 participant each. Of these, acute

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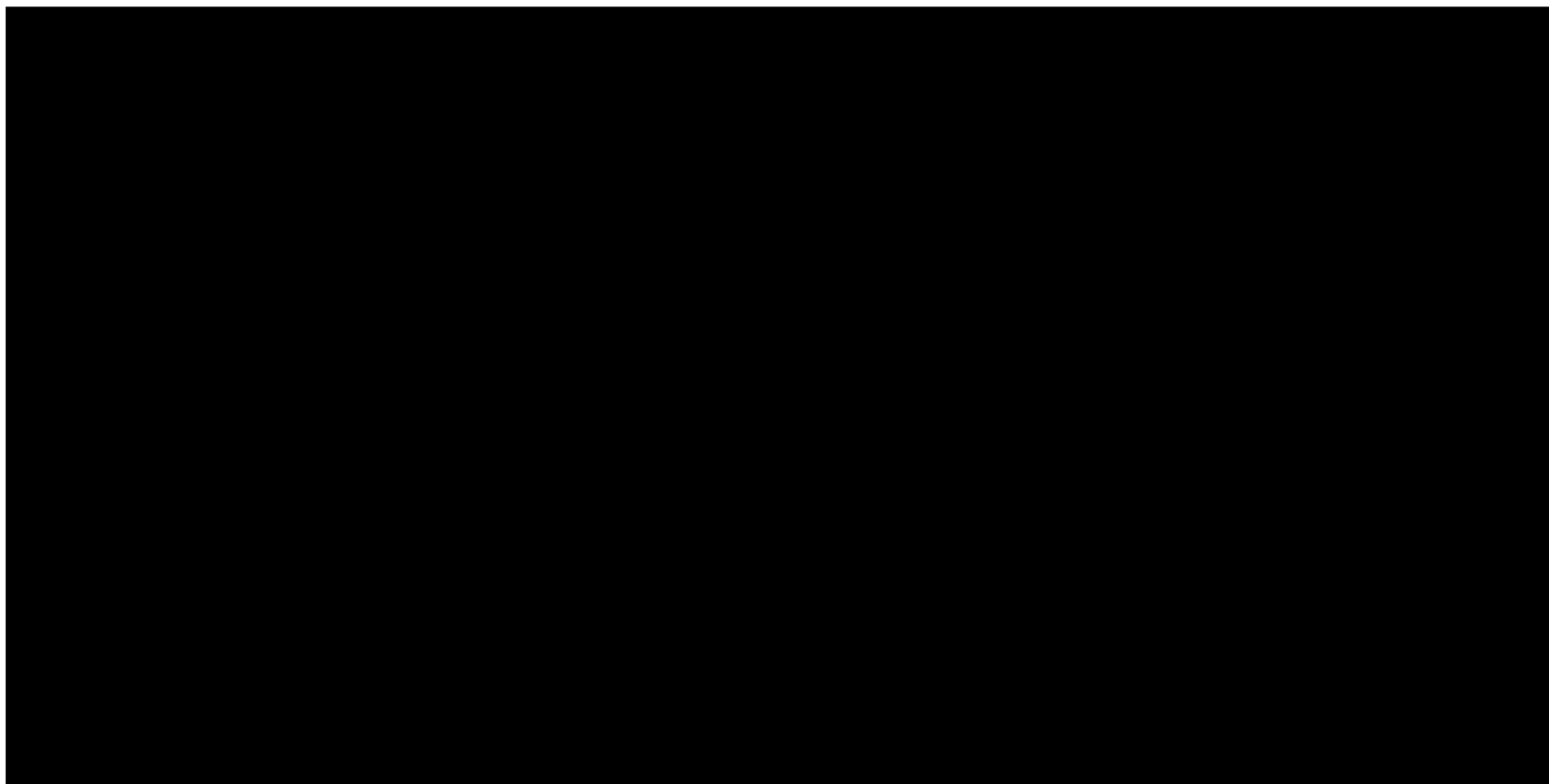
kidney injury and SJS were considered treatment-related (71). In the chemotherapy arm, the TEAEs that led to death were COVID-19, pancytopenia, pneumonia, respiratory failure, and septic shock, which were reported in 1 participant each. Of these, pancytopenia was considered treatment-related (71).

Adverse events of special interest

Ocular events

In the US, tisotumab vedotin has a black box warning for ocular toxicity, including changes in the corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss, and corneal ulceration. A well-defined mitigation and management strategy has been developed based on experience in clinical trials to help reduce the risk of ocular AEs with tisotumab vedotin. It is important to note that all patients in InnovaTV 301 underwent a baseline ophthalmic examination, and patients who received tisotumab vedotin were referred to an eye specialist if new or worsening ocular symptoms developed (70). An eye care management plan will form part of the UK management strategy for tisotumab vedotin, of which the anticipated process is highlighted below in Figure 16.

Figure 16: Eye care management plan for patients receiving tisotumab vedotin monotherapy in the UK



Abbreviations: TV, tisotumab vedotin.

Source: Genmab Eyecare Management Plan (Data on File) (90).

Of the patients treated with tisotumab vedotin, 132 (52.8%) reported ocular AEs with nearly all being Grade 1 (19.6%) or 2 (29.2%) in severity (Table 32). Only 4% of patients experienced a Grade 3 event and all patients with Grade ≥ 3 ocular AEs had relevant medical history or preceding low grade ocular AEs. The median time to onset of first ocular AE was 1.2 months with a median time to resolution of 0.59 months. Nearly all patients with ocular AEs (93.9%) experienced either complete resolution or partial improvement of symptoms. Only 5.6% of patients treated with tisotumab vedotin discontinued treatment due to ocular AEs (70, 71).

Table 32: Frequency and severity of ocular adverse events with tisotumab vedotin vs. investigators' choice chemotherapy (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)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

Notes: ^aResolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'. ^bFor 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).

Source: Vergote et al. (2024) and InnovaTV 301 CSR (2023) (70, 71).

Bleeding events

Bleeding events, including vaginal bleeding, haematuria, and rectal bleeding, have been commonly reported in studies of therapies for CC due to the disease itself or prior use of radiotherapy, which increases bleeding risk (71). Since tisotumab vedotin

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targets tissue factors, a cell surface protein expressed in cervical cancer and other solid tumours, there is a particular focus on bleeding events as outlined below.

Of the patients treated with tisotumab vedotin, 105 (42%) reported bleeding AEs. Most (39.6%) cases of bleeding AEs were Grade 1 or 2 in severity with few (2.4%) Grade ≥ 3 events. Patients treated with tisotumab vedotin reported numerically fewer bleeding SAEs than those who received chemotherapy. The median time to onset of first bleeding event was 1.9 weeks, with a median time to resolution of 1.1 weeks. The majority of tisotumab vedotin-treated patients with bleeding AEs (83.8%) experienced either complete resolution or partial improvement of symptoms by last follow-up (70, 71).

Table 33: Frequency and severity of bleeding adverse events with tisotumab vedotin vs. investigators' choice chemotherapy (Safety Analysis Population)

	Tisotumab vedotin (N=250)	Chemotherapy (N=239)
Any bleeding TEAE, n (%)	105 (42.0)	34 (14.2)
Grade 1	80 (32.0)	14 (5.9)
Grade 2	19 (7.6)	13 (5.4)
Grade 3	5 (2.0)	6 (2.5)
Grade 4	1 (0.4)	1 (0.4)
Any serious bleeding AE, n (%)	6 (2.4)	9 (3.8)
Any bleeding AE leading to permanent discontinuation, n (%)	0	0
Median time to first bleeding AE onset, months	0.43 (0.0-10.4)	0.92 (0.0-4.8)
Median time to bleeding AE resolution, months	0.26 (0.0-7.2)	0.16 (0.0-2.9)
Frequency of bleeding resolution ^a or improvement ^b , n (%)		
All events resolved or improved	77/105 (73.3)	19/34 (55.9)
Some events resolved or improved	11/105 (10.5)	2/34 (5.9)
No events resolved or improved	17/105 (16.2)	13/34 (38.2)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

Notes: ^aResolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'. ^bFor 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 the time from the first occurrence of the highest grade to the first improvement (i.e., at least one grade decrease from the highest grade and no grade increase afterward).

Source: Vergote et al. (2024) and InnovaTV 301 CSR (2023) (70, 71).

Peripheral neuropathy

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Peripheral neuropathy is a known safety risk of tisotumab vedotin, as the cytotoxic component of the ADC, MMAE, is a microtubule-disrupting agent associated with peripheral neuropathy. Peripheral neuropathy is also associated with other anticancer treatments such as taxanes and platinum compounds (including cisplatin and carboplatin), which are commonly used in CC treatment.

At baseline, 33.2% of patients in the tisotumab vedotin arm had pre-existing peripheral neuropathies at study entry, compared with 27.2% in the chemotherapy arm (Table 34) (83).

Table 34: Events of peripheral neuropathy by preferred term at baseline in InnovaTV 301 (ITT population)

Severity of PN at baseline	Tisotumab vedotin (N=250)	Chemotherapy (N=239)
Patients with pre-existing events n(%)	83 (33.2)	65 (27.2)
Patients with any PN events	36 (43.4)	3 (4.6)
Grade 1	9 (10.8)	1 (1.5)
Grade 2	22 (26.5)	2 (3.1)
Grade 3	5 (6.0) 0	0

Abbreviations: ITT: intent-to-treat; PN, peripheral neuropathy.

Source: Genmab Data on File (83).

Of the patients treated with tisotumab vedotin, 96 (38.4%) reported peripheral neuropathy (Table 35). Most (32.8%) cases of peripheral neuropathy were Grade 1 or 2 in severity with few (5.6%) Grade 3 and no Grade 4 events. The median time to onset of first peripheral neuropathy event was 2.4 months with a median time to resolution of 1.1 months (70, 71).

Many patients with peripheral neuropathy events (43.8%) experienced either complete resolution or partial improvement of symptoms. Only 5.6% of tisotumab vedotin patients discontinued treatment due to peripheral neuropathy AEs (70, 71).

Table 35: Frequency and severity of peripheral neuropathy adverse events with tisotumab vedotin vs. investigators' choice chemotherapy (Safety Analysis Population)

	Tisotumab vedotin (N=250)	Chemotherapy (N=239)
Any PN TEAE, n (%)	96 (38.4)	10 (4.2)
Grade 1	32 (12.8)	5 (2.1)
Grade 2	50 (20.0)	4 (1.7)
Grade 3	14 (5.6)	1 (0.4)
Any serious PN AE, n (%)	3 (1.2)	0
Any PN AE leading to dose interruption or reduction, n (%)	39 (15.6)	0
Any PN AE leading to permanent discontinuation, n (%)	14 (5.6)	0
Median time to first PN AE onset, months	2.38 (0.0-9.3)	1.15 (0.1-5.6)
Median time to PN AE resolution, months	1.12 (0.0-12.1)	1.31 (0.2-5.4)
Frequency of PN AE resolution ^a or improvement ^b , n (%)		
All events resolved or improved	35/96 (36.5)	5/10 (50.0)
Some events resolved or improved	7/96 (7.3)	1/10 (10.0)
No events resolved or improved	54/96 (56.3)	4/10 (40.0)

Abbreviations: AE, adverse event; CSR, clinical study report; PN, peripheral neuropathy; TEAE, treatment-emergent adverse event.

Notes: ^aResolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'. ^bFor 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 the time from the first occurrence of the highest grade to the first improvement (i.e., at least one grade decrease from the highest grade and no grade increase afterward).

Source: Vergote et al. (2024) and InnovaTV 301 CSR (2023) (70, 71).

2.11.2. InnovaTV 204

At the data cutoff on February 06, 2020, the median duration of exposure to tisotumab vedotin was 4.2 months (range: 1 – 16 months), and the median number of doses of tisotumab vedotin received was 6.0 (range: 1 – 21 months) (78).

Treatment-related adverse events

A total of 92% of patients experienced a treatment-related adverse event (TRAE) in InnovaTV 204 with most (65%) being Grade 1 or 2 in severity (Table 36). No new safety signals compared to previous studies of tisotumab vedotin were identified. Only 12% of patients discontinued treatment of tisotumab vedotin due to AEs, of which

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peripheral sensorimotor neuropathy (2 patients), peripheral sensory neuropathy (2 patients), and ulcerative keratitis (2 patients) were the most common (78, 80).

Table 36: Most common ($\geq 10\%$) treatment-related adverse events with tisotumab vedotin in InnovaTV 204

	InnovaTV 204 (n=101)	
	Grade 1-2	Grade ≥ 3
Patients with ≥ 1 AE	65 (65)	28 (28)
Alopecia	38 (38)	0
Epistaxis	30 (30)	0
Nausea	27 (27)	0
Conjunctivitis	26 (26)	0
Fatigue	24 (24)	2 (2)
Dry Eye	23 (23)	0
Myalgia	15 (15)	0
Anemia	12 (12)	1 (1)
Asthenia	12 (12)	1 (1)
Arthralgia	12 (12)	0
Decreased Appetite	11 (11)	0
Keratitis	11 (11)	0
Pruritus	10 (10)	1 (1)

Abbreviations: AE, adverse event.

Source: Coleman et al. (2021) (78).

Serious adverse events

Serious TRAEs occurred in 13 (13%) patients. The most common treatment-emergent SAEs (i.e. those occurring in $\geq 2\%$ of patients) were pneumonia (4%), constipation (3%), and pyrexia (3%) (91).

Four patients (4%) experienced a fatal non-progression TEAE, of which only one (septic shock) was considered treatment-related by the investigator. One patient died due to a non-treatment emergent non-progression AE of cardiac arrest (91).

Adverse events of special interest

Ocular events

All patients in InnovaTV 204 were assessed by an ophthalmologist at baseline and referred for additional evaluation in case of any ocular symptoms or abnormal ocular

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findings during the trial. An eye care plan was also available to reduce the risk of and manage ocular adverse events (78).

Ocular TRAEs occurred in 54 people receiving tisotumab vedotin, with the majority (96%) of affected patients experiencing Grade 1 or 2 events (Table 37). None of the ocular TRAEs were serious. The majority of events resolved with a median time to resolution of less than 1 month (78).

Table 37: Ocular adverse events with tisotumab vedotin in InnovaTV 204

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

Abbreviations: AEs, adverse events; TRAE, treatment-related adverse event.

Notes: ^aTwo events of ulcerative keratitis. ^bTwo Grade 3 events of ulcerative keratitis were reported separate from patients with keratitis. ^cResolution defined as events with status outcome of recovered/resolved or recovered/resolved with sequelae within 30 days after the last dose of tisotumab vedotin. ^dAssessments were limited by the protocol-defined follow-up period for AEs of only 30 days after the last dose.

Source: Coleman et al. (2021) (78).

Peripheral neuropathy

Peripheral neuropathy TRAEs occurred in 33 people receiving tisotumab vedotin, with the majority (79%) of affected patients experiencing Grade 1 or 2 events (Table 38). Peripheral neuropathy events resolved in 21% of the cases with a median time to resolution of 2.6 weeks (78).

Table 38: Peripheral neuropathy adverse events with tisotumab vedotin in InnovaTV 204

Preferred Term	Tisotumab vedotin (N=101)	
	Any TRAE	Grade ≥3
Any PN TRAE, n (%)	33 (33)	7 (7)
Most common (≥5%) PN TRAEs		
Neuropathy peripheral	10 (10)	2 (2)
Peripheral sensory neuropathy	9 (9)	2 (2)
Peripheral sensorimotor neuropathy	5 (5)	2 (2)
Number of total events, N		47
Median time to PN TRAE onset, months		3.1
Frequency of PN TRAE resolution ^a , n/N (%)		10/47 (21)
Median time to PN TRAE resolution ^b , months		0.6

Abbreviations: AEs, adverse events; PN, peripheral neuropathy; TRAE, treatment-related adverse event.

Notes: ^aResolution defined as events with status outcome of recovered/resolved or recovered/resolved with sequelae within 30 days after the last dose of tisotumab vedotin. ^bAssessments were limited by the protocol-defined follow-up period for AEs of only 30 days after the last dose.

Source: Coleman et al. (2021) (78).

Bleeding events

Bleeding TRAEs occurred in 39 people receiving tisotumab vedotin, with the majority (95%) of affected patients experiencing Grade 1 or 2 events (Table 39). Bleeding events resolved in 90% of the cases, with a median time to resolution of 2 weeks. There were no clinically meaningful changes in prothrombin time, international normalised ratio, or activated partial thromboplastin time observed (78).

Table 39: Bleeding adverse events with tisotumab vedotin in InnovaTV 204

Preferred Term	Tisotumab vedotin (N=101)	
	Any TRAE	Grade ≥3
Any bleeding TRAE, n (%)	39 (39)	2 (2) ^a
Most common (≥3%) bleeding TRAEs		
Epistaxis	30 (77)	0 (79)
Vaginal hemorrhage	7 (18)	0
Hematuria	3 (1)	0
Number of total events, N		57
Median time to bleeding TRAE onset, months		0.3
Frequency of bleeding TRAE resolution ^b , n/N (%)		51/57 (90)

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Preferred Term	Tisotumab vedotin (N=101)	
	Any TRAE	Grade ≥3
Median time to bleeding TRAE resolution ^c , months		0.5

Abbreviations: AEs, adverse events; TRAE, treatment-related adverse event.

Notes: ^aTwo events of vaginal hemorrhage. ^bResolution defined as events with status outcome of recovered/resolved or recovered/resolved with sequelae within 30 days after the last dose of tisotumab vedotin. ^cAssessments were limited by the protocol-defined follow-up period for AEs of only 30 days after the last dose.

Source: Coleman et al. (2021) (78).

2.12. Ongoing studies

No relevant ongoing studies are available.

2.13. Interpretation of clinical effectiveness and safety evidence

Despite recent advances in 2L+ treatment for r/m CC, there remains a significant need for therapies that:

- Are more effective than current options
- Offer an alternative option to repeated chemotherapy exposure, for patients who have progressed on or after standard first-line immunochemotherapy

The clinical evidence from the Phase 3 InnovaTV 301 and Phase 2 InnovaTV 204 trials demonstrate that tisotumab vedotin offers clinically meaningful benefits in r/m CC after prior systemic therapy.

Patients receiving 2L+ treatment for r/m CC are often offered single-agent chemotherapy, which lack well-controlled studies supporting their use in 2L and provide poor survival outcomes. In InnovaTV 301, tisotumab vedotin significantly improved mean OS (11.5 months vs 9.5 months; HR 0.70, p=0.004) and PFS (4.2 months vs 2.9 months; HR 0.67, p<0.001) compared to investigator's choice of chemotherapy (70, 71). These results are further supported by an encouraging OS (12.1 months) and PFS (4.2 months) reported in the InnovaTV 204 trial (78).

Confirmed ORRs were higher for tisotumab vedotin compared to investigator's choice of chemotherapy in InnovaTV 301 (17.8% vs 5.2%, respectively), with a substantially higher disease control rate. Similarly, the confirmed ORR for tisotumab vedotin in InnovaTV 204 was 24% (70, 71, 78). With regards to treatment durability, the median

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duration of response for tisotumab vedotin was 5.3 months (79) and 8.3 months (InnovaTV 204), which indicates sustained antitumour activity (70, 71, 78).

In terms of QoL, the percentage of patients who reported an improvement in the QLQ-C30 global health status–QoL scores of 10 points or more from baseline to cycle 5 was higher in the tisotumab vedotin group than in the chemotherapy group (13.9% vs. 3.4%) (79). EQ-5D Visual Analogue Scale (VAS) scores in the tisotumab vedotin and chemotherapy arms were also stable in InnovaTV 301 from baseline to Cycle 5 (70, 71).

AEs observed in InnovaTV 301 and InnovaTV 204 were frequent but manageable, as seen for traditional chemotherapy. In InnovaTV 301, Grade ≥ 3 AEs occurred in 52% of patients treated with tisotumab vedotin versus 62% in the chemotherapy arm, and 28% of patients treated with tisotumab vedotin in InnovaTV 204. Ocular events and peripheral neuropathy were common in both trials, although these AEs were predominantly low-grade. Lastly, trial discontinuation due to toxicity occurred in 14.8% of patients in Innova TV 301 and 12.0% of patients in InnovaTV 204, supporting the tolerability of tisotumab vedotin with protocol-guided management (70, 71, 78).

Both the InnovaTV 301 and InnovaTV 204 trials enrolled patients with r/m CC after 1-2 prior systemic regimens, which aligns with the population intended for 2L+ treatment. During the UK Cervical Cancer advisory board, clinical advisors identified weekly (Q1W) paclitaxel as a frequently used chemotherapy monotherapy regimen in the UK for the r/m CC population. Although Q1W paclitaxel was not used in the pivotal trial for tisotumab vedotin (79, 92), clinicians agreed there are no data to show that the efficacy of Q1W paclitaxel differs from other chemotherapies, therefore exclusion of Q1W paclitaxel as a comparator in this submission is not viewed as a concern (51). In addition, published real-world evidence based on retrospective UK data demonstrates that paclitaxel has comparable efficacy to the chemotherapies in the control arm of InnovaTV 301 (20).

Moreover, the InnovaTV 301 trial is the first study of its kind conducted in a contemporary patient population, since patients were enrolled having had prior treatment with anti-PD-(L)1 agents (70, 71). By including patients with prior PD-(L)1 use, InnovaTV 301 closely reflects current and anticipated clinical practice in patients

who represent the real-world r/m CC population, with clinical benefit consistently observed for tisotumab vedotin across all patients with r/m CC, including those with prior anti-PD-(L)1 use (70, 71).

Limitations of InnovaTV 301 include its open-label trial design, which can introduce the possibility of performance bias. However, the presence of objective endpoints such as OS allow for the mitigation of this risk (70, 71). The single-arm design of InnovaTV 204 limited the assessment of tisotumab vedotin's effects on patient survival and restricted comparisons with controlled studies. Comparisons with historical studies assessing chemotherapy are challenging due to differences in study populations, study conduct and procedures (e.g., RECIST criteria and response confirmation), and because historically these studies did not enroll patients treated with the current first-line standard (bevacizumab) (78).

Tisotumab vedotin is the first ADC to demonstrate clinically meaningful improvements in survival as a 2L+ treatment for r/m CC patients following progression on or after chemotherapy, as demonstrated by clinical data in the Phase 3 InnovaTV 301 and Phase 2 InnovaTV 204 trials. With proven efficacy and a unique mechanism of action, tisotumab vedotin offers an effective and durable treatment option for r/m CC patients (including those with aggressive disease), providing an alternative option for those who have progressed on or after first line systemic therapy.

3. Cost effectiveness

3.1. *Published cost-effectiveness studies*

An SLR was conducted in accordance with NICE methods and guidance to identify relevant evidence from published economic evaluations, studies eliciting utilities and those looking at cost and resource use data associated with the treatment of recurrent or metastatic cervical cancer in both previously treated or chemotherapy naïve patients.

Searches for the original review were conducted in June 2019 and updated in 2023, 2024 and 2025. The 2025 update searches were conducted between 08 May 2025 and 23 May 2025 and retrieved 14,201 records. Following deduplication (within set and against the 2019, 2023 and 2024 results) 604 records were assessed for relevance.

A total of 31 studies were identified that met the eligibility criteria for the SLR of economic evaluations, which are presented in Appendix E Published cost-effectiveness studies. Full details of the SLR including search strategy and study selection are provided in Appendix E Published cost-effectiveness studies.

3.2. *Economic analysis*

One published economic analysis compared tisotumab vedotin with chemotherapy in patients with r/m CC from the US third-party payer perspective, using data from the InnovaTV 301 trial, the pivotal trial of tisotumab vedotin. This model adopted a partitioned survival model structure with three health states (i.e., progression-free, progressed disease, death), with an estimated reconstruction of individual patient data from Kaplan-Meier (KM) curves based on the July 2023 data-cut (93). The published economic model was conducted from the US payer perspective without actual individual patient data and did not reflect UK utilities, costs, chemotherapy composition, or updated data.

Therefore, a *de novo* economic model was developed based on the most recent tisotumab vedotin January 2024 data cut to evaluate the cost-effectiveness of tisotumab vedotin with r/m CC with disease progression on or after systemic therapy

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in the UK. Chemotherapy was selected as the comparator given it is the most commonly used 2L or 3L treatment in patients with r/m CC (61, 66).

The model was conducted from the UK NHS and personal social services (PSS) perspective, using a 30-year time horizon to comprehensively capture the expected costs and health outcomes over patients' remaining lifetimes from treatment initiation.

3.2.1. Patient population

Adult patients with r/m CC with disease progression on or after systemic therapy, reflecting the InnovaTV 301 trial population and anticipated MHRA indication for tisotumab vedotin, were considered for the economic evaluation (71).

Baseline characteristics for the base case model cohort are presented in Table 40. Mean age was assumed to be the same as the InnovaTV 301 trial global population. Mean body surface area (37) and mean weight (kg), required for calculating the doses for treatments included in the model were based on data from the InnovaTV 301 global trial population (71).

Table 40: Characteristics of the model cohort

Characteristic	Parameter value	Source
Mean age (years)	51.44	InnovaTV 301 trial global population (71)
Body surface area (m2)	1.65	InnovaTV 301 trial global population (71)
Body mass (kg)	63.31	InnovaTV 301 trial global population (71)

3.2.2. Model structure

A model was developed in Microsoft Excel® 365 using the observed PFS and OS curves from InnovaTV301 first the first 12 months and a three state semi-markov model thereafter. The semi-Markov, allowed for the application of the assumption of a common post-progression mortality rate to be applied for tisotumab vedotin and chemotherapy in the model. This assumption was also supported by UK clinicians and health economist experts at the UK CC advisory board, and in the InnovaTV 301 trial (data cutoff date: January 2024), the OS Kaplan-Meier curves of tisotumab vedotin

and chemotherapy appear to converge at the tails when very few patients are at risk and very few patients are still on treatment assigned at randomization.

Notably, the clinical oncology experts specializing in gynaecological cancers and attending the UK CC advisory board uniformly considered the KM estimates of OS observed in the chemotherapy arm in the trial to be clinically implausible and overestimated when very few patients are still at risk. They considered the KM estimates with this assumption of a common post-progression mortality rate to be more clinically plausible at the tails when very few patients are still at risk. For example, at month ■■■ with only ■ patients at risk, the KM estimates for OS observed in the chemotherapy arm was approximately■■■■■and the clinicians found this to be clinically implausible, pointing out that real-world clinical experience and expectations of 2-year OS on chemotherapy is closer to 10%.

To address this uncertainty and ensure external validity, a semi-Markov model was therefore considered more appropriate than a partitioned survival model, as it allows an explicit structural link between intermediate health state (i.e., post-progression) and death. In contrast, partitioned survival models estimate health state occupancy solely by extrapolating trial-reported OS and progression-free survival (PFS) curves. Additionally, Markov models have been used in prior HTA appraisals of pembrolizumab in recurrent, persistent or metastatic CC (94, 95). The economic model thus uses KM estimates for OS and PFS for the first 12 months and predicted estimates thereafter. The model comprised of three mutually exclusive health states: (i) Progression-free (PF), (ii) Progressed disease (PD) and (iii) death (Figure 17).

All patients entered the model in the PF health state. In each weekly model cycle, the following transitions were allowed,

- Patients in the PF state could remain in the PF state, transition into the PD state based on time to progression (TTP), or transition directly into the death state based on time from PF to death
- Patients in the PD state could remain in the PD state or transition into the death state based on post-progression survival (PPS)

- Patients in the death state always remained in that state, as it was an absorbing state

Figure 17: Model structure

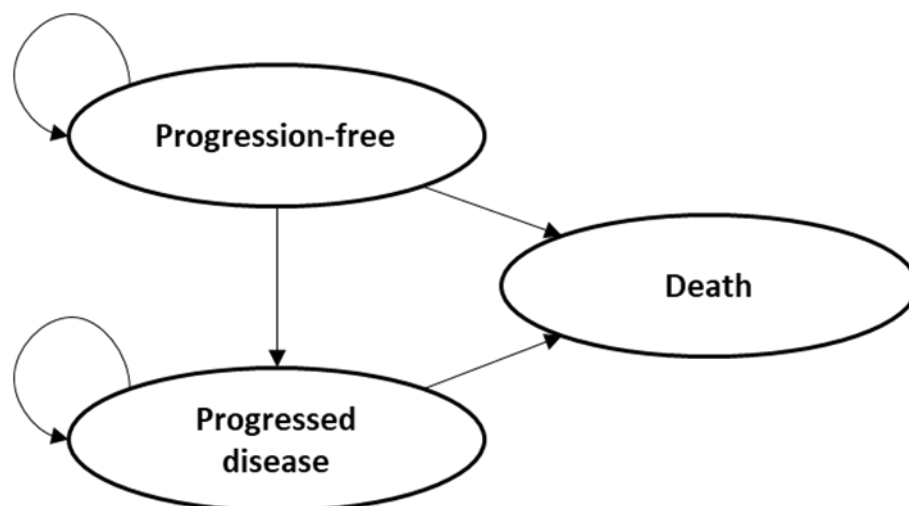


Table 41 Features of the de novo economic analysis

Features	Description	Justification
Target population	Adult patients with r/m CC with disease progression on or after systemic therapy	Aligned with the anticipated MHRA indication (if approved), and consistent with the study population in the InnovaTV 301 trial (86)
Perspective	UK NHS and PSS perspective	In line with NICE guidelines (96)
Time horizon	Lifetime (30 years)	Long enough to capture relevant differences in costs and outcomes associated with the intervention and comparator
Cycle length	1 week	Allow for precise calculation of costs and outcomes
Model structure	Semi-Markov model with three health states (progression-free, progressed disease and death)	Allows for an explicit structural linkage between intermediate health states and death, particularly when post-progression mortality by treatment is subject to uncertainty, as in InnovaTV301 situation

Features	Description	Justification
		Previously used in the HTA appraisals of pembrolizumab (NICE TA939 and CDA-AMC appraisal) (94, 95)
Discount rate	3.5% for both costs and outcomes	As per NICE guidelines (96)
Intervention	Tisotumab vedotin	Treatment being appraised
Comparators	Single agent chemotherapy	Chemotherapy agents from InnovaTV 301 were used, also consistent with efficacy of commonly used single agent chemotherapy in the UK. Best supportive care is not considered because patients initiating single agent chemotherapy or tisotumab vedotin are typically those with adequate performance status to initiate and tolerate an active treatment. In contrast, as per treatment guidelines, best supportive care is generally reserved for patients who have ECOG>2, or are unfit for or have declined further active therapy.
Efficacy inputs	• Time to progression • Time from progression free (PF) to death • Post progression survival (PPS)	Disease progression and survival were assessed in the InnovaTV 301 trial (86)
Utility inputs	• Utilities by health state • Disutilities associated with AEs • Age-adjusted disutility	Reflect health-related quality-of-life associated with health states, AEs, and age. Adjusting for treatment arm (pooled chemotherapy vs. tisotumab vedotin), with or without interactions with health state, did not yield a significant association between treatment and utility values, therefore treatment-specific utilities are not applied (see section 3.4.1).
Cost inputs	• Pre-progression treatment costs • Post-progression treatment	Reflect costs incurred by patients with r/m CC and relevant to the UK NHS and PSS perspective.

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Features	Description	Justification
	costs • AE costs for pre-progression treatments • Pre-progression disease management costs • Post-progression disease management costs • Costs associated with management of ocular toxicity for tisotumab vedotin • Terminal care costs	
Outputs	• Total costs • Total LYs • Total QALYs • Incremental cost per LY gained • Incremental cost per QALY gained	In line with NICE guideline (96)

Abbreviations: AE, adverse event; HTA, Health Technology Assessment; LY, life year; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PF, progression-free; PFS, progression-free survival; PPS, post-progression survival; PSS, Personal Social Service; QALY, quality-adjusted life year; r/m CC, recurrent or metastasis cervical cancer; TV, tisotumab vedotin; UK, United Kingdom.

3.2.3. Intervention technology and comparators

The intervention and comparator assessed in the model were tisotumab vedotin and single agent chemotherapy, respectively.

3.2.3.1. Intervention – TV

Tisotumab vedotin is an antibody-drug conjugate composed of a human monoclonal antibody G1 chemically conjugated via a protease cleavable valine citrulline linker to the drug microtubule-disrupting agent monomethyl auristatin E. Based on the analyses of InnovaTV 301 trial data (data cutoff date: January 2024), tisotumab vedotin significantly prolonged PFS, with a median PFS of █ months, as opposed to █ months for chemotherapy (hazard ratio [HR]: █ 95% confidence interval [CI]: █); tisotumab vedotin was also associated with significant survival benefits, with a median OS of █ months, as opposed to █ months for chemotherapy (HR: █, 95% CI: █) (86).

3.2.3.2. Comparators – chemotherapy

Outside of the UK, chemotherapy agents, including topoisomerase I inhibitors (e.g., irinotecan, topotecan), multitargeted anti-folate (pemetrexed), antimitotic agents (e.g., vinorelbine), and antimetabolite agents (e.g., gemcitabine), are the most commonly used agents for r/m CC (61, 66). The comparators to tisotumab vedotin in the global InnovaTV 301 trial comprised topoisomerase I inhibitors (e.g., irinotecan, topotecan), multitargeted anti-folate (pemetrexed), antimitotic agents (e.g., vinorelbine), and antimetabolite agents (e.g., gemcitabine) (71) (see Section 2.3.1.1). In contrast, clinical oncologists specializing in gynaecological cancers and participating in a UK CC advisory board conducted by Genmab indicated that topotecan, gemcitabine, and weekly paclitaxel are the most common single agent chemotherapy considerations in 2L/3L r/m CC in the UK. This was also supported by findings from the subsequent Genmab survey of the distribution of commonly used chemotherapies in 2L/3L r/m CC by HCPs from England. The clinical advisors at the UK CC advisory board unanimously pointed out that current evidence indicates that single agent chemotherapies provide comparable efficacy in 2L/3L r/m CC patients (51). Specifically, there are no data indicating the efficacy of weekly paclitaxel differs from other single agent chemotherapies included in the InnovaTV 301 trial (51). This is supported by a UK real-world retrospective study at the Royal Marsden Hospital (2004–2014) which demonstrated that chemotherapy regimens used in the second line treatment setting provided comparable efficacy outcomes with very poor response rates and poor survival outcomes. This included weekly paclitaxel, which was used in 28% of the patients (20), which is consistent with the response rates observed with the single agent chemotherapies included in the InnovaTV 301 trial.

Essentially, as long as the efficacy of the single agent chemotherapies used in 2L/3L r/m CC is comparable and is the same as among chemotherapies used in UK clinical practice as those used in the InnovaTV 301 trial, cost-effectiveness results most relevant to the UK would be generated using pooled efficacy data from the chemotherapies in control arm of InnovaTV 301 and costs based on the distributions of the chemotherapies representative of UK clinical practice. We therefore apply pooled efficacy data from InnovaTV 301 and comparator chemotherapy costs based

on the distribution that is aligned with single-agent chemotherapy use in UK clinical practice, as well as a scenario based on the InnovaTV 301 trial distribution (see Table 42).

Although some HCPs participating in the Genmab survey indicated use of or rechallenge with platinum doublet chemotherapy, there is no RCT data supporting any assumption of differentiated efficacy of this strategy in this setting. These have, therefore, been conservatively excluded from the model even though the associated costs would result in higher acquisition and administration costs in the chemotherapy arm of the model.

The distribution of chemotherapies applied in the model and shown in Table 42, were obtained via a survey of 8 UK clinicians involved in the management of r/m CC in the UK. Full details of the survey methods can be found in Section 2.3.3.

Table 42: Comparator chemotherapy distribution applied in the cost-effectiveness analysis

Chemotherapy agent	UK clinician survey (base case)	InnovaTV 301 trial (scenario analysis)
Topotecan	4.7%	7.90%
Vinorelbine	2.0%	7.10%
Gemcitabine	28.4%	45.60%
Irinotecan	0.3%	5.90%
Pemetrexed	0.3%	33.50%
Paclitaxel	64.3%	0.00%

3.3. Clinical parameters and variables

Clinical parameters in this model were obtained from the InnovaTV 301 trial (data cutoff date: January 2024) for tisotumab vedotin and chemotherapy (86, 97). The key patient characteristics of the data sources for tisotumab vedotin and comparators were summarised in Section 2.3.2.

3.3.1. Base case – Semi-Markov model with transition probabilities

In the base case, transition probabilities used in the semi-Markov model were

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estimated using individual patient data for TTP, PFS and PPS.

- Transition probabilities from PF to PD were informed by TTP data in each arm.
- Transition probabilities from PF to death were informed by time from PF to death in each arm.
- Transition probabilities from PD to death were informed by pooled PPS data of both arms.

Transition probabilities were estimated using individual patient-level data (IPD) from the InnovaTV301 trial. For transitions from PF (i.e., PF→PD and PF→Death), standard parametric models were fitted to TTP and time from PF to death separately for each treatment arm. For transitions from PD (i.e., PD→Death), an exponential model was fitted to pooled PPS data from both arms. This pooled approach was used beyond month 12, while treatment-specific observed OS was applied during the first 12 months.

3.3.2. Estimation of transition probabilities from the PF state (i.e., PF to PD and PF to death)

Transition probabilities starting from the PF state were estimated using the parametric multistate modelling approach described by Williams et al. (98, 99). Parametric models were used to estimate the cause-specific hazards of PF to PD and PF to death. Seven different parametric distributions were considered, including exponential, Weibull, Gompertz, log-logistic, lognormal, generalised gamma, and gamma distributions. Within each weekly cycle of the model, the probability of each of these transitions was calculated as a function of these two cause-specific hazards. Of note, this parametric multistate modelling approach is equivalent to a poly-hazard modelling approach, a type of flexible parametric model described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 21 (100). Under this approach, an overall hazard function (in this case, the overall hazard of PFS failure) is modelled as the sum of different cause-specific hazards (in this case, the cause-specific hazards of PF to PD and PF to death), each of which can be modelled using different distributions; the resulting overall hazard function is far more flexible than if standard parametric distributions were fitted to the overall hazard (see Section 3.2.5 of NICE DSU TSD 21

(100).

For transitions from PF to PD and from PF to death, the base-case parametric models were selected using the following criteria:

- Visual fit to the observed KM data within the trial period of InnovaTV 301 for PFS and OS
- Clinical plausibility of the long-term extrapolations
- Statistical goodness of fit to the observed data (TTP and time from PF to death), as indicated by Akaike information criterion and Bayesian information criterion values
- Assessment of the underlying hazard functions over time and clinical plausibility of hazard assumptions (including validity of proportional hazards assumption)

The most appropriate and clinically plausible models were used in the base-case analysis, with alternative models tested in scenario analyses.

The overlay of the observed KM and predicted curves of TTP and goodness of fit (i.e., AIC and BIC) are presented in Figure 18 and Table 43 (79) and Figure 19 and Table 43 (chemotherapy). The generalised gamma models were selected for both tisotumab vedotin and chemotherapy arms based on both statistical goodness of fit (i.e., smallest AIC) and visual inspection for the estimation of transition probabilities from PF to PD. This choice was further supported by the non-monotonic shapes observed in the hazard plots over time (Appendix K: Supplementary modelling analyses, Section 1.2).

Figure 18: Overlay of observed Kaplan-Meier and predicted curves of TTP for tisotumab vedotin

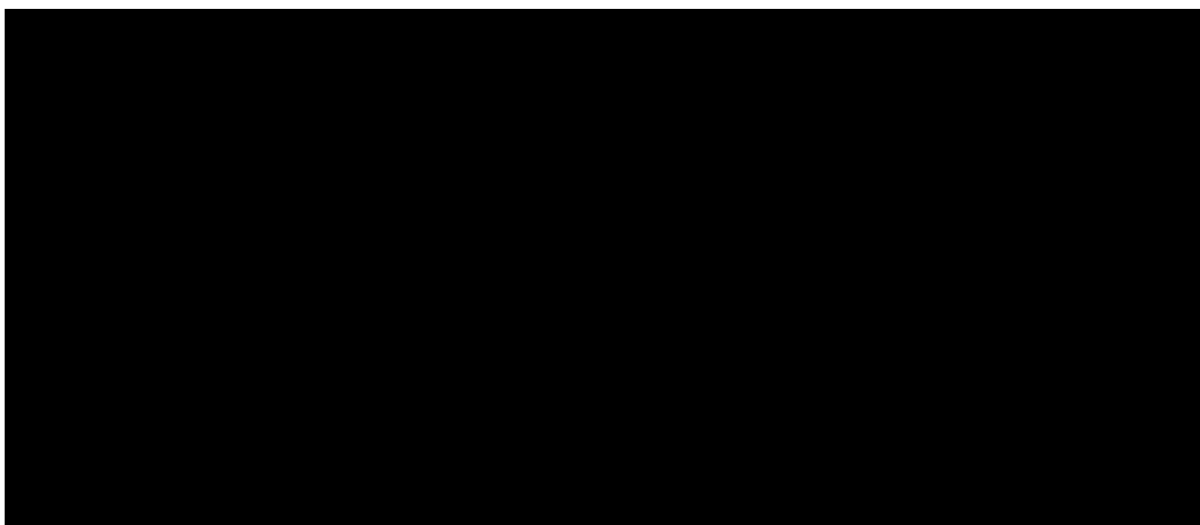


Table 43: Goodness of fit (AIC and BIC) of TTP for tisotumab vedotin

Functional Form	AIC	BIC
Exponential	1669.3	1672.9
Weibull	1649.8	1656.9
Log-Logistic	1611.7	1618.8
Lognormal	1608.1	1615.2
Gompertz	1670.4	1677.5
Gamma	1636.8	1643.9
Generalised Gamma	1604.1	1614.7

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; TTP, time to progression; TV, tisotumab vedotin.

Figure 19: Overlay of observed Kaplan-Meier and predicted curves of TTP for chemotherapy

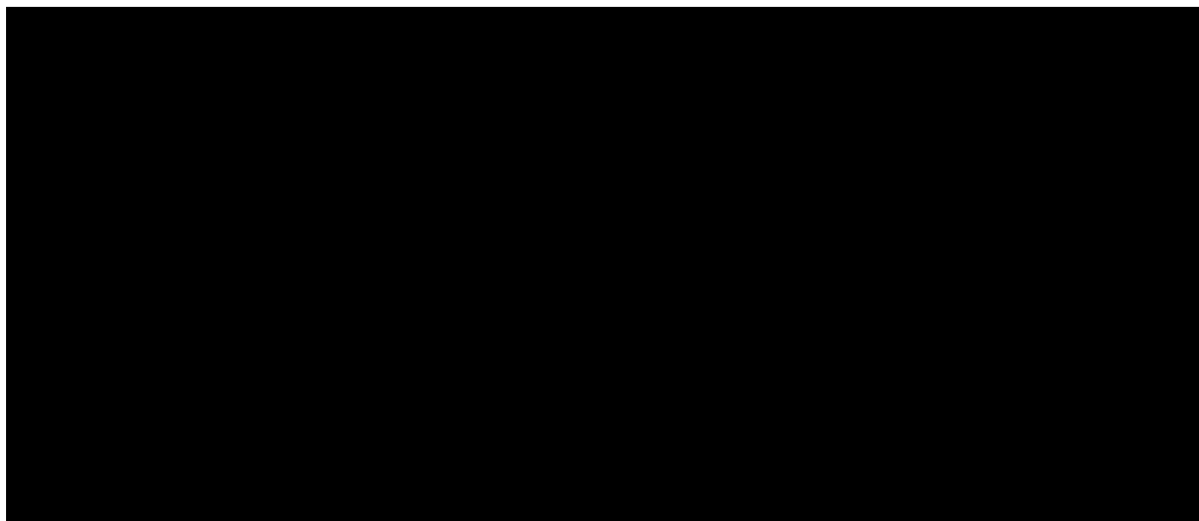


Table 44: Goodness of fit (AIC and BIC) of TTP for chemotherapy

Functional Form	AIC	BIC
Exponential	1455.6	1459.1
Weibull	1442.6	1449.7
Log-Logistic	1400.8	1407.9
Lognormal	1397.8	1404.8
Gompertz	1457.6	1464.7
Gamma	1430.0	1437.1
Generalised Gamma	1394.6	1405.2

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; TTP, time to progression; TV, tisotumab vedotin.

Similarly, parametric models for the estimation of transition probabilities from PF to death were selected based on both statistical goodness of fit (i.e., smallest AIC) (Table 45 and

Table 46) and visual inspection (Figure 20 and Figure 21) for tisotumab vedotin and chemotherapy, respectively. The Gompertz model was selected for tisotumab vedotin and the lognormal model was selected for chemotherapy. Proportional hazards

approach was not supported based on the hazard plots over time (Appendix K: Supplementary modelling analyses, Section 1.2). The overlay of the observed KM and predicted curves of PF survival are presented in Figure 22 (tisotumab vedotin) and Figure 23 (chemotherapy).

Figure 20: Overlay of observed Kaplan-Meier and predicted curves of time from PF to death for tisotumab vedotin

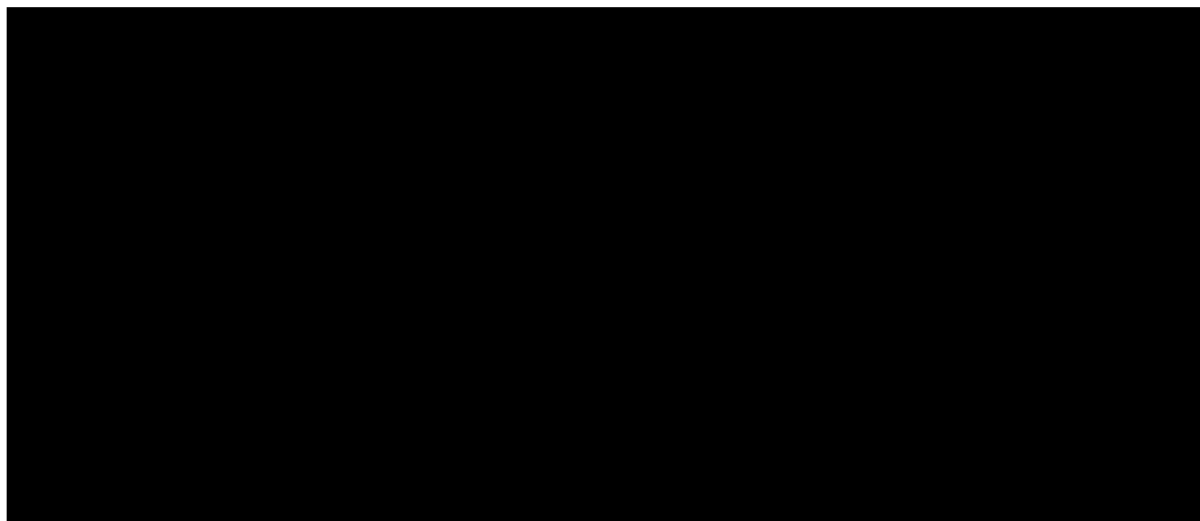


Table 45: Goodness of fit (AIC and BIC) for tisotumab vedotin

Functional Form	AIC	BIC
Exponential	291.3	294.7
Weibull	292.6	299.6
Log-Logistic	292.0	299.0
Lognormal	290.0	296.9
Gompertz	289.8	296.8
Gamma	292.8	299.7
Generalised Gamma	289.9	300.4

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; TTP, time to progression; TV, tisotumab vedotin.

Figure 21: Overlay of observed Kaplan-Meier and predicted curves of time from PF to death for chemotherapy

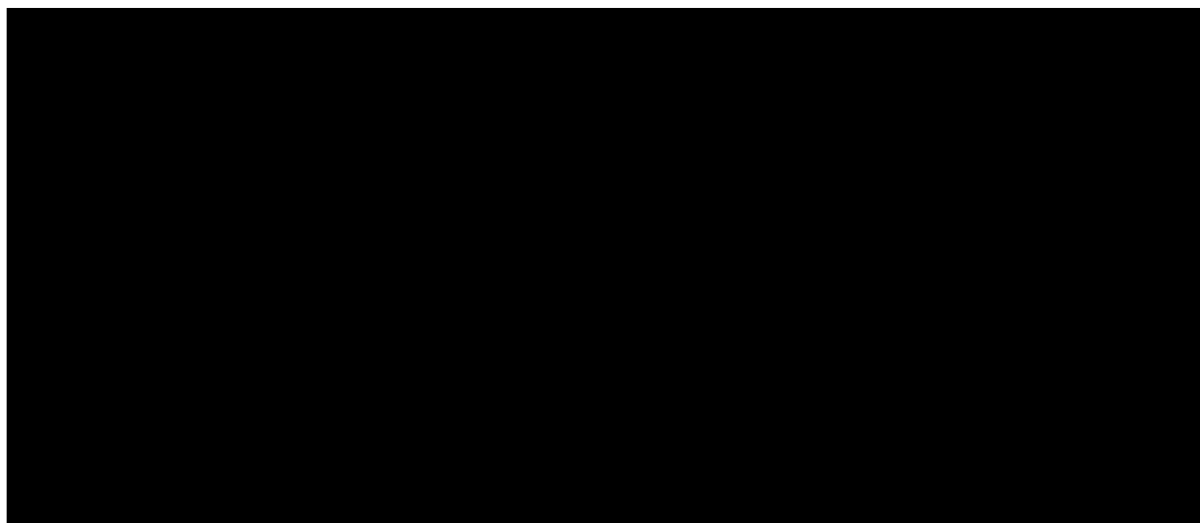


Table 46: Goodness of fit (AIC and BIC) for chemotherapy

Functional Form	AIC	BIC
Exponential	268.9	272.3
Weibull	270.4	277.3
Log-Logistic	269.8	276.7
Lognormal	268.4	275.2
Gompertz	268.8	275.7
Gamma	270.5	277.4
Generalised Gamma	270.0	280.3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; TTP, time to progression; TV, tisotumab vedotin.

Figure 22: Overlay of the observed KM and predicted curves of PF survival (tisotumab vedotin)

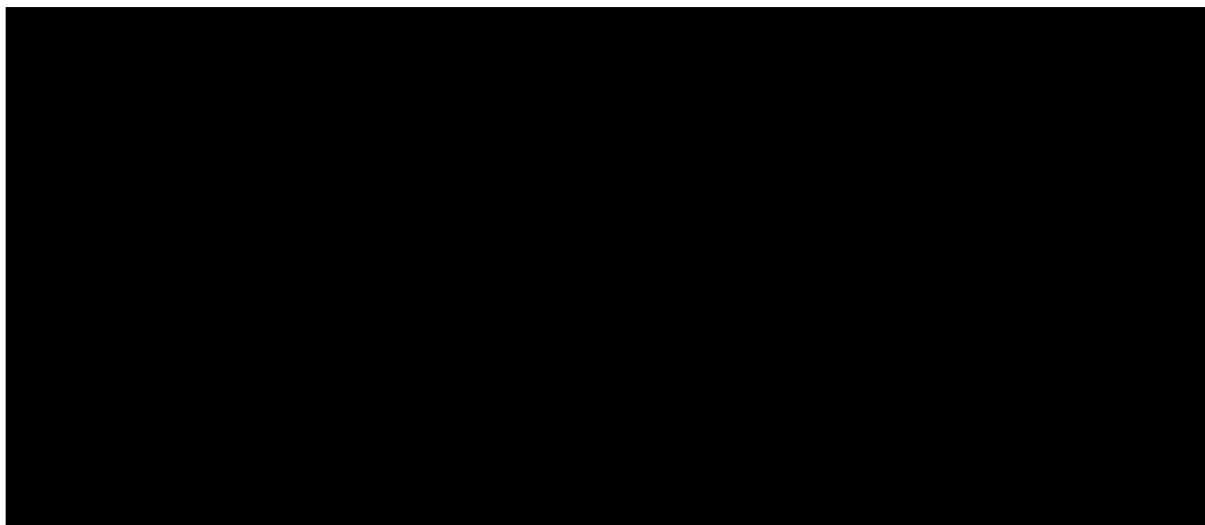
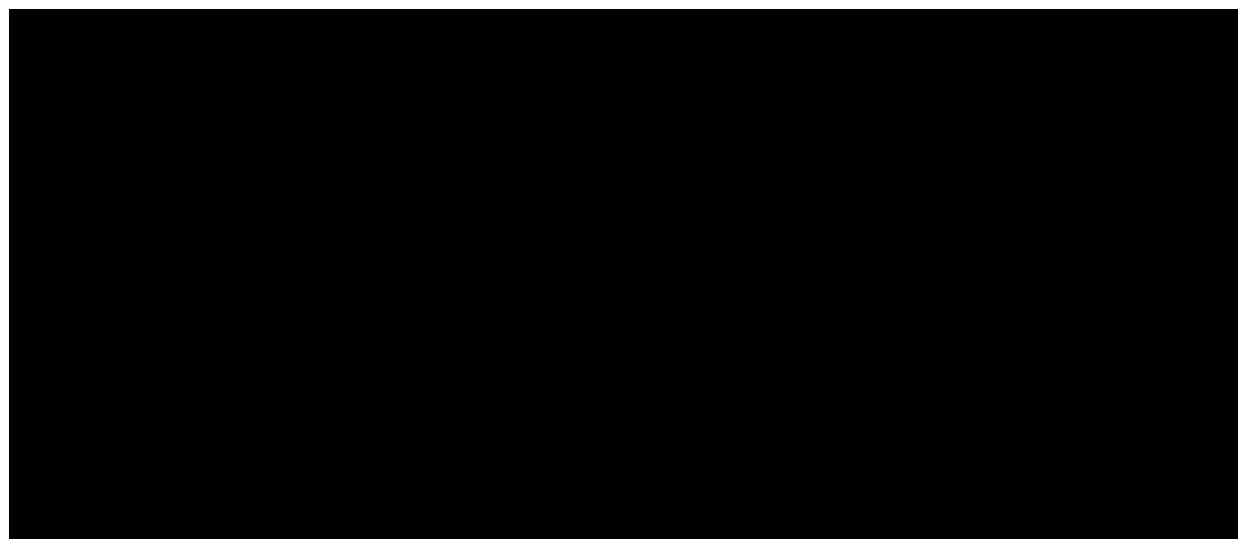


Figure 23: Overlay of the observed KM and predicted curves of PF survival (chemotherapy)



3.3.3. Estimation of transition probabilities from the PD state (i.e., PD to death)

For transitions from PD (i.e., PD→Death), an exponential model was fitted to pooled PPS data from both arms. Exponential distribution was considered to model transition from PD to death based on pooled data from tisotumab vedotin and chemotherapy

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arms in InnovaTV 301 trial, as the hazard rate under an exponential distribution does not depend on time since entry into the health state and is thus compatible with the memoryless property of Markov models (101). In contrast, alternative parametric distributions would require tracking the time since progression for each patient, which is not compatible with Markov model structure. The exponential model also demonstrated good fit (Figure 24), and the Cox-Snell residual plots showed the residual curve of the exponential model is closely aligned with the 45 degree curve (Appendix K: Supplementary modelling analyses, Section 1.2), further supporting the good fit of the exponential model.

The estimated mortality rate from the exponential model, common to both arms, was used beyond month 12, while treatment-specific observed OS from InnovaTV 301 was applied during the first 12 months. The 12-month cutoff was selected because by that point, more than 95% of patients had discontinued randomised treatment—only ■■■% in the tisotumab vedotin arm and ■■■% in the chemotherapy arm remained on study therapy. This timing coincided with the convergence of the log cumulative hazard (with time in log scale) between the two arms (Figure 25), supporting this implementation beyond this period. This approach is supported by clinician input suggesting that once patients transition to available subsequent therapeutic options, their survival trajectories are comparable and no longer influenced by the initial treatment assigned at randomisation. This approach enhanced model stability and model validation with clinical expectations (Section 3.13.1).

Figure 24: Overlay of observed Kaplan-Meier and predicted curves of post-progression survival

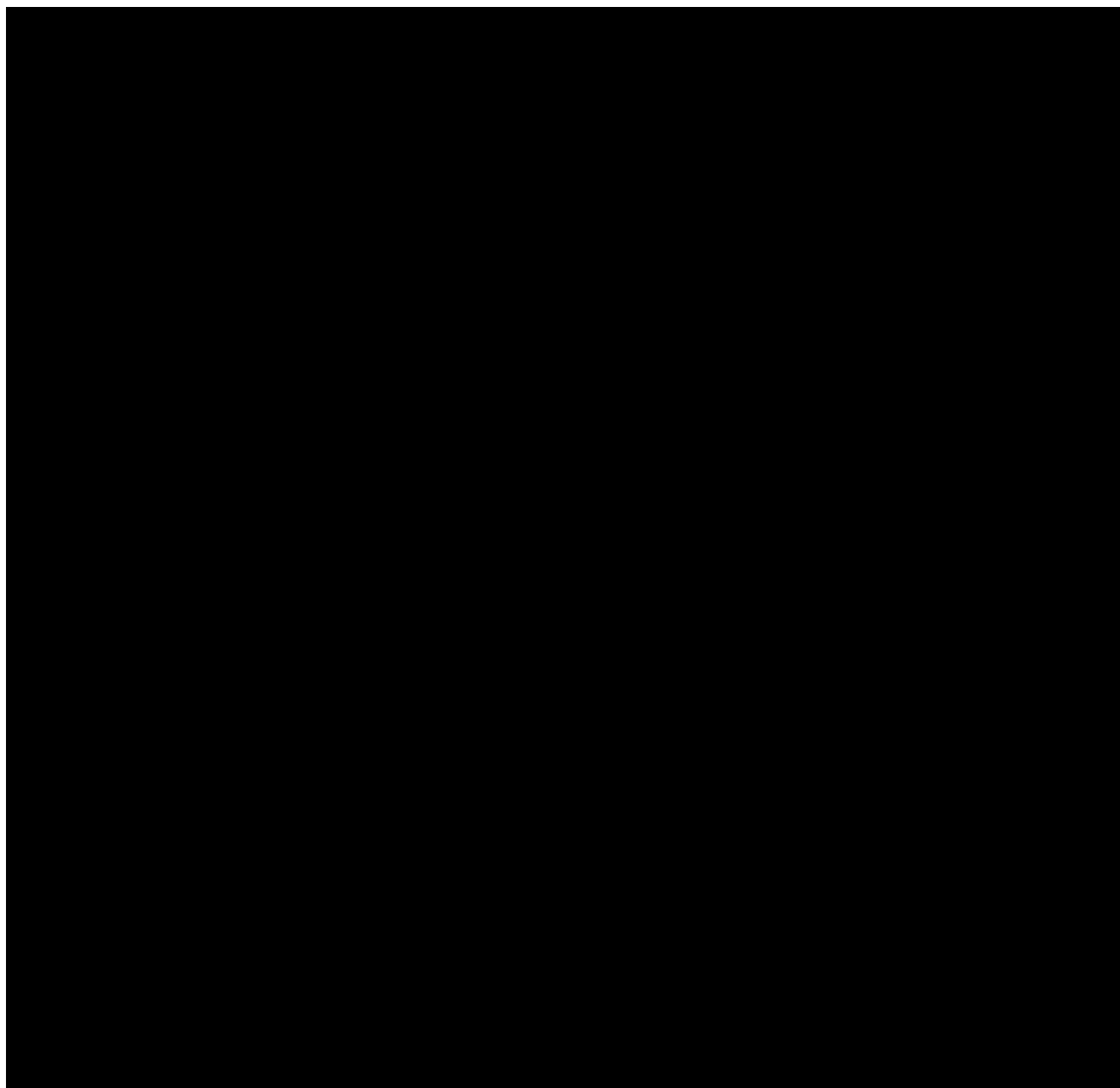
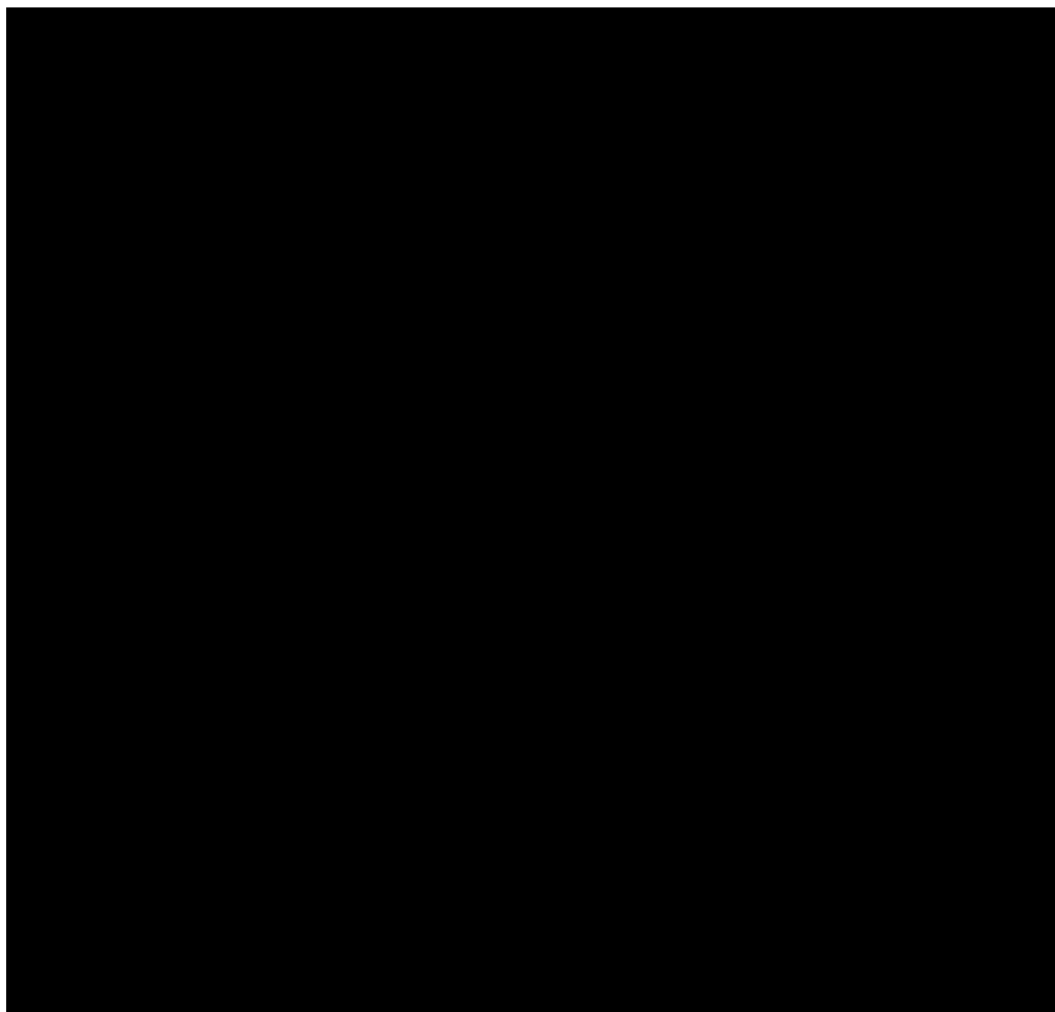


Figure 25: Log cumulative hazard plot for post-progression survival



Abbreviations: Chemo, chemotherapy; TV, tisotumab vedotin.

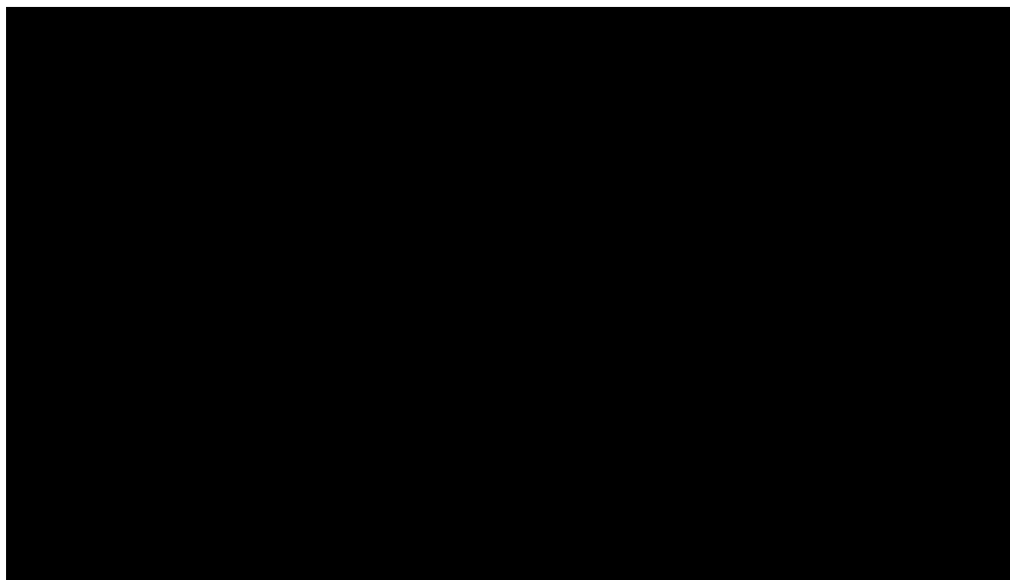
3.3.4. Overall survival and progression-free survival in the base case

Using the transition probabilities estimated based on the selected parametric models, OS and PFS for tisotumab vedotin and chemotherapy were predicted. The mortality rates of tisotumab vedotin and chemotherapy in each cycle were bounded by the age-specific mortality rates of the general female population (Appendix K: Supplementary modelling analyses, Section 1.3; the PFS curves of tisotumab vedotin and chemotherapy were capped by the corresponding OS curves.

Figure 26 and Figure 27 present the predicted OS and PFS curves for tisotumab vedotin and chemotherapy. The internal and external validations of the predicted OS and PFS curves are described in Section 3.13.1.

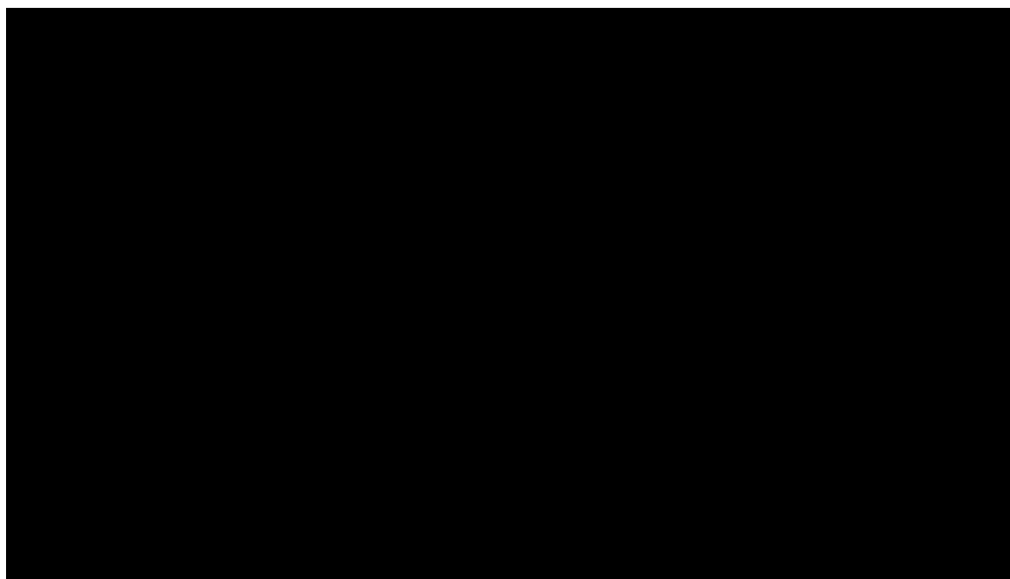
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Figure 26 Predicted OS curves in the base case



Abbreviation: OS, overall survival.

Figure 27 Predicted PFS curves in the base case



Abbreviation: PFS, progression-free survival.

3.3.5. Adverse events related to treatment

In the base case, the AEs used in the model were estimated using rates derived from the InnovaTV 301 trial (data cutoff date: Jul 2023) (71). In the analysis Grade 3/4 AEs

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with $\geq 5\%$ rate in either tisotumab vedotin or chemotherapy arm were considered (Table 47). The rates of AEs are applied as a one-off incidence at model entry before application of consequent disutilities (Section 3.4.2) and costs (Section 3.5.1.3).

Table 47: AEs rate related to treatment

Grade 3+ AE	AE rate	
	Tisotumab vedotin	Chemotherapy
Anemia	8.4%	27.6%
Urinary tract infection	4.4%	7.1%
Neutropenia	3.6%	13.4%
Peripheral neuropathy	5.6%	0.0%
Ocular event	52.8%	0.0%
Source	InnovaTV 301 trial (71)	

Abbreviations: AE; adverse event.

3.4. Measurement and valuation of health effects

The utility and disutility inputs consisted of utilities of health states (pre-progression and post-progression), age-related utility adjustment, and disutilities due to AEs. The health-state utilities were obtained from the InnovaTV 301 trial (data cutoff date: January 2024) in the base-case analysis (22), while age-related utility adjustment and AE disutilities were based on published literature (52, 102, 103).

3.4.1. Health-related quality-of-life data from clinical trials

The health-state utilities were estimated based on the patient-level EuroQol-5 Dimension-5 Level Instrument (EQ-5D-5L) data collected in the InnovaTV 301 trial (data cutoff date: January 2024) (22, 71). EQ-5D-5L assessments were conducted at screening/baseline, on day one of each treatment cycle, at the end of treatment visit (30 days after the last dose), and during the follow-up (every 60 days after the last dose of TV). Observations from tisotumab vedotin and chemotherapy were pooled for analysis.

In line with the current NICE guideline, a mapping function developed by the NICE Decision Support Unit, was applied to map the EQ-5D-5L data to the EQ-5D-3L value set, using the 'EEPRU dataset' (96, 104-106). The UK-specific EQ-5D-3L value set was then used to derive utility values for use in the model (107). The utilities were estimated for the progression-free state and the progressed disease state, separately:

- **EQ-5D measures for the progression-free health state:** any EQ-5D assessments corresponding to patients in the PFS state were used. This included all data collected from screening up to the date of the first documented progression, death due to any cause, or censoring date based on PFS definition per InnovaTV 301 trial protocol.
- **EQ-5D measures for the progressed disease health state:** any EQ-5D assessments corresponding to patients in the progressed disease state were used. This included all data collected on or after the first documented progression event. For patients who were censored for PFS, EQ-5D assessments occurring after the censor date were excluded for the analyses.

All available EQ-5D measures from the InnovaTV 301 trial, collected at baseline, on day one of each treatment cycle, at the end of treatment visit, and each follow-up visits, were used in the utility analysis. This utility analysis did not impute values for missing evaluations. The utility scores were measured repeatedly over time, which resulted in correlation of observations across different time points for the same patient. To account for the repeated and longitudinal nature of the data, a mixed effect model using generalised estimating equation (GEE) was developed to estimate the health-state utility values at population-level with a robust variance estimator to account for correlation within patients' repeated assessments. An exchangeable working correlation structure was specified, which assumes a constant correlation among all time points within each patient. The dependent variable of the model was EQ-5D utility score and the independent variable was health state status. One patient can contribute to multiple utility values in the GEE model. The death state was assumed to have 0 utility. The GEE models did not include additional covariates, as the InnovaTV 301 trial population is representative of the target population for tisotumab vedotin. Therefore, the resulting utility estimates reflect the average values for this population, stratified by health states. In the model, health-state utilities were further adjusted by age.

The impact of baseline covariates on utility values was tested in a series of GEE models and was deemed to have limited impact. A series of exploratory analyses were conducted to assess the impact of treatment arm and key baseline characteristics (Table 48). Adjusting for treatment arm (pooled chemotherapy vs. tisotumab vedotin), with or without interactions with health state, did not yield a significant association between treatment and utility values, suggesting that health state utilities are not treatment specific. Further analyses explored the inclusion of key baseline covariates, including region, ECOG performance status at baseline, disease diagnostic stage, metastatic/recurrent disease at study entry, number of prior systemic therapies, and prior use of bevacizumab or anti-PD-1/L1 agents. Of these, only baseline ECOG score was statistically significant. However, the inclusion of ECOG in the model had minimal impact on the estimated health state utility difference (-0.148 vs. -0.147), and the resulting health state-specific utility values remained similar to those from the unadjusted model. Given this limited impact and the fact the CEA model does not incorporate utility values stratified by baseline ECOG status, the simpler specification

with health state as the sole independent variable was retained for the base case utility analysis.

The base-case utilities of pre-progression and post-progression states based on GEE model were [REDACTED] and [REDACTED], respectively (Table 48).

Table 48: GEE-model estimates on EQ-5D utilities in the InnovaTV 301 trial

Health States	N patients ^a	N assessments	Mean	SE
Pre-progression	430	[REDACTED]	[REDACTED]	[REDACTED]
Post-progression	284	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: GEE, generalised estimating equation; N, number; SE, standard error.

Note: ^a The same patient can have multiple health states at different visits. The statistics presented here reflect the number of patients with at least one assessment with the specified health state.

Health-state utilities were further adjusted by age using a multiplicative approach, in which health-state values were multiplied by an adjustment index derived from UK-specific population norms for EQ-5D-3L, as reported by McNamara et al. (2022) (Table 50) (103). In each model cycle, a relative utility modifier was calculated as the ratio of the population norm utility at the patient's current age to that at the starting age in the model (i.e., 51.4 years based on median age of patients in the InnovaTV 301 trial). This modifier reflects the natural decline in health-related quality life with age. The calculated modifiers were applied to the estimated health-state utility values at each cycle, ensuring that QALY estimates reflected the impact of ageing on background health status over time.

Table 49: Exploratory Analyses in the GEE model

GEE model	Health State				Added covariate(s)			
	Variable Level	Estimate	Standard Error	P-value	Variable Level	Estimate	Standard Error	P-value
Health State (final model)	Progressed disease	██████	██████	██████				
Health State + Treatment	Progressed disease	██████	██████	██████	Tisotumab vedotin	██████	██████	██████
Health State + Treatment + Health State * Treatment	Progressed disease	██████	██████	██████	Tisotumab vedotin	██████	██████	██████
					Progressed disease; tisotumab vedotin	██████	██████	██████
Health State + Region	Progressed disease	██████	██████	██████	Asia	██████	██████	██████
					Europe	██████	██████	██████
					US	██████	██████	██████
Health State + ECOG at Baseline	Progressed disease	██████	██████	██████	1	██████	██████	██████
Health State + Disease Stage at Diagnosis	Progressed disease	██████	██████	██████	Stage III	██████	██████	██████
					Stage IV	██████	██████	██████
					Unknown	██████	██████	██████

Health State + Metastatic/Recurrent Disease at Study Entry	Progressed disease	██████	██████	██████	Metastatic	██████	██████	██████
Health State + Number of Prior Systemic Therapies	Progressed disease	██████	██████	██████	2	██████	██████	██████
					3-4	██████	██████	██████
Health State + Prior Use of Bevacizumab	Progressed disease	██████	██████	██████	Y	██████	██████	██████
Health State + Prior Use of Anti-PD-1/L1	Progressed disease	██████	██████	██████	Y	██████	██████	██████

Abbreviations: Eastern Cooperative Oncology Group; GEE, generalised estimating equation.

Table 50: Age-related utility adjustment

Age group	Female	Source
50-54	0.798	McNamara 2022 (103)
55-59	0.791	
60-64	0.776	
65-69	0.775	
70-74	0.784	
75-79	0.730	
80-84	0.710	
85-89	0.666	
90+	0.666	

3.4.2. Adverse event-related disutilities in the base case

The model considered disutilities associated with AEs. Additionally, ocular events of grade 3 or > were considered for tisotumab vedotin arm only, as these were events of special interest. Total QALY decrement due to AEs was calculated as the sum of AE disutilities weighted by corresponding AE rates (Table 47) and duration (Table 51). This weighted disutility was -0.0020 and -0.0011 for tisotumab vedotin and chemotherapy, respectively. Disutility associated with AEs for either treatment were applied as a one-off at the start of each treatment in the model.

Table 51: AE disutilities and AE duration

Adverse event	AE disutility	AE duration (weeks)	Source
Anemia	-0.073	2.13	Liu 2023 (108) for disutility, Shah 2022 for duration (109)
Urinary tract infection	-0.019	0.57	Birmingham 2012 for disutility (102), Shah 2022 for duration (109)
Neutropenia	-0.050	1.89	Liu 2023 (108) for disutility, Shah 2022 for duration (109)
Peripheral neuropathy event	-0.121	4.87	Niño-de-Guzmán 2023 for disutility (110), InnovaTV 301 trial for duration (70, 71)
Ocular event (any grade)	-0.040	2.57	Brown 2009 for disutility (111), InnovaTV 301 trial for duration (70, 71)

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Abbreviations: AE, adverse event.

3.4.3. Utility and disutility data in scenario analyses

An alternative approach using the mixed effects model was used to derive health-state utilities from InnovaTV 301. Utilities were estimated considering both the between-patient variation and the within-patient variation (pre-progression vs. post-progression). That is, random intercept and random slope were both included in the regression. In addition, health-state utilities were also identified from published cost-effectiveness studies in r/m CC. Health-state utilities based on the mixed effects model and from the literature are presented in Table 52, and they were considered in the scenario analyses.

Table 52: Health-state utility values in scenario analyses

Variable	Utility value	Source
Scenario – mixed effects model		InnovaTV 301 trial (mixed effects model) (71)
Pre-progression	██████	
Post-progression	██████	
Scenario – Zheng 2023		Zheng 2023 (112)
Pre-progression	0.850	
Post-progression	0.520	

3.4.4. Mapping

As EQ-5D-5L data were collected as part of the InnovaTV 301 trial, mapping from a disease-specific measure to a generic outcome measure was not necessary. The conversion of the EQ-5D-5L data to the requested NICE reference case (104), 3L, was undertaken and is described in Section 3.4.1.

3.4.5. Health-related quality of life studies

An SLR was conducted to identify published sources for HRQoL data in CC. Relevant evidence was sought including data available in economic evaluations and studies eliciting utilities associated with the treatment of previously treated, recurrent or metastatic cervical cancer. A detailed description of the SLR including search strategy and study selection is provided in Appendix E.

The original search was conducted in June 2019 and was subsequently updated in April 2023. The search covered a global geographical scope. A recent update, in May 2025, also covering a global geographical scope. A summary of the identified studies and full details of methods of the SLR are provided in Appendix E.

3.4.6. Health-related quality-of-life data used in the cost-effectiveness analysis

The NICE methods guide states that the preferred source of utility values should come from clinical studies. Therefore, utilities generated from the InnovaTV 301 trials (71) were applied in the model as a base case. The methods for deriving these estimates are described previously (Section 3.4.1). Methods of elicitation, valuation and collection time points are described in Section 3.4.1. Table 53 provides a summary of the values applied in the model.

Table 53: Summary of utility values for cost-effectiveness analysis

Health State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Pre progression			Section 3.4.1	Based on InnovaTV 301 trial data relevant to the treatment population
Post progression			Section 3.4.1	Based on InnovaTV 301 trial data relevant to the treatment population
Disutility for AE for tisotumab vedotin	-0.0020	-0.00180 - - 0.00220	Section 3.4.2	Liu 2023 (108); Bermingham 2012 (102); Niño-de-Guzmán 2023 (110); Brown 2009 (111)
Disutility for AE for chemotherapy	-0.0011	-0.00098 - - 0.0012	Section 3.4.2	A weighted

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				average disutility was applied which was varied by 10% in the DSA and PSA.
Anaemia	-0.073	NA	Section 3.4.2	Liu 2023 (108); Birmingham 2012 (102); Niño-de-Guzmán 2023 (110); Brown 2009 (111)
Urinary tract infection	-0.019	NA	Section 3.4.2	
Neutropenia	-0.050	NA	Section 3.4.2	
Peripheral neuropathy event	-0.121	NA	Section 3.4.2	
Ocular event (any grade)	-0.040	NA	Section 3.4.2	

Abbreviations: AE, adverse event; DSA, deterministic sensitivity analysis; PSA; probabilistic sensitivity analysis.

3.5. Cost and healthcare resource use identification, measurement and valuation

The model was based on United Kingdom (England) healthcare payer perspective; hence, the base-case analysis considers all costs incurred within the health care sector. The model considered the following cost components: pre-progression treatment costs, pre-medication costs for tisotumab vedotin, post-progression treatment costs, AE costs, disease management costs and terminal care costs.

A systematic literature review was conducted to identify any healthcare resource utilisation (HRU) and costs in CC. Relevant evidence was sought including data available in economic evaluations and studies looking at resource use associated with the treatment of previously treated, recurrent or metastatic CC. A detailed description of the SLR including search strategy and study selection is provided in Appendix G: Cost and healthcare resource identification, measurement and valuation.

All costs were reported in 2024 Pound Sterling. Published estimates based on prior years were adjusted to 2024 Pound Sterling using the Personal Social Services Research Unit (PSSRU) Inflation Index (113, 114).

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3.5.1. Intervention and comparators' costs and resource use

3.5.1.1. Pre-progression treatment costs

Pre-progression treatment costs consisted of drug acquisition costs and administration costs for tisotumab vedotin and chemotherapy. Patients were assumed to incur pre-progression treatment costs while remaining on treatment and progression-free.

Drug acquisition costs were calculated as a function of unit drug costs, dosing, relative dose intensity (RDI), duration of treatment (DoT) and weight and BSA distributions based on the InnovaTV 301 trial (71). Drug wastage (i.e., no vial sharing) was considered in the base-case model. The distribution of chemotherapies applied in the model was obtained via a UK survey of 8 oncologists with specific expertise in gynaecological cancers, who are involved in the management of r/m CC (Table 42). Full details of the survey methods can be found in Section 2.3.3.

The dosing schedules and RDIs of tisotumab vedotin and chemotherapy were based on the InnovaTV 301 trial (71, 81). Unit drug acquisition costs of individual drug agents in chemotherapy were obtained from eMIT (Table 54) (71, 81, 115-120). The unit drug acquisition cost of [REDACTED] for tisotumab vedotin is based on a [REDACTED] PAS discount on the UK list price of [REDACTED]. Table 54 presents the drug acquisition costs for both tisotumab vedotin and chemotherapy.

Drug administration costs associated with tisotumab vedotin and chemotherapy are provided in Table 55 and are based on NHS reference costs (121). Associated costs per administration were calculated as a function of unit administration costs. Both tisotumab vedotin and chemotherapy were assumed to be administered in the outpatient setting. Duration of administration for each chemotherapy associated treatment was determined based on the open-label phase III trial of tisotumab vedotin vs. investigators choice of chemotherapy in 2nd and 3rd line r/m CC study protocol (81). Table 55 and Table 56 present treatment administration and dispensing costs.

Table 54: Dosing schedules and drug acquisition costs for tisotumab vedotin and chemotherapy

Drug	Dosing schedule (descriptive)	Proportion of each drug within the arm	RDI	Unit cost (2024)	Unit strength (mg)	Units per day	Dosing Reference
Tisotumab vedotin	2.0 mg/kg Q3W	100%	██████	██████	40	3	- Dosing schedule: InnovaTV 301 trial protocol (81) - Genmab UK - RDI: InnovaTV 301 trial TLF (71)
Chemotherapy							
Topotecan	1 or 1.25 mg/m ² on days 1 to 5, Q3W	5.0%	██████	£41.64	4	1	- Dosing schedule: InnovaTV 301 trial protocol (81) - Drug cost: eMIT (115) - RDI: InnovaTV 301 trial TLF (71)
Vinorelbine	30 mg/m ² on days 1 and 8, Q3W	2.0%	██████	£17.55	50	1	
Gemcitabine	1000 mg/m ² on Days 1 and 8, Q3W	28.0%	██████	£19.74	2000	1	
Irinotecan	100 or 125 mg/m ² weekly for 28 days, Q6W	0.0%	██████	£16.59	500	1	
Pemetrexed	500 mg/m ² on day 1, Q3W	0.0%	██████	£47.25	850	1	
Paclitaxel	80 mg/m ² on day 1, QW	64.0%	██████	£19.46	150	1	

Abbreviations: eMIT Drugs and pharmaceutical electronic market information tool; Q3W, every 3 weeks; Q6W, every 6 weeks; RDI, relative dose intensity; TLF, tables, listings, and figures; TV, tisotumab vedotin, mg, milligram, ml, milliliters.

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Table 55: Treatment administration and dispensing costs (tisotumab vedotin and chemotherapy)

Activity	HRG code	Unit cost (£)	Source
Deliver Simple Parenteral Chemotherapy at First Attendance	SB12Z	£152	NHS reference costs (121)
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	£352	NHS reference costs (121)
Topical	-	£0	Assumption
Oral	-	£0	Assumption

Abbreviation: HRG, healthcare resource group.

Table 56: Administration resource use and cost per administration for tisotumab vedotin and chemotherapy (base case)

Drug	Admin route	Proportion of each drug within the arm	Cost per admin (£) (2024)	Source
Tisotumab vedotin	IV	100%	152.00	Proportions: InnovaTV 301 trial (71) (data cutoff date: Jul 2023)
Chemotherapy				
Topotecan	IV	5.0%	7.14	
Vinorelbine	IV	2.0%	3.04	
Gemcitabine	IV	28.0%	43.17	
Irinotecan	IV	0.0%	0.46	
Pemetrexed	IV	0.0%	0.46	
Paclitaxel	IV	64.0%	226.34	

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Abbreviations: IV, intravenous; TV, tisotumab vedotin.

3.5.1.1.1. Additional Pre-progression disease management costs for ocular events for tisotumab vedotin

At treatment initiation, patients allocated to tisotumab vedotin treatment are given an ocular assessment which includes a full eye exam by an eye care professional which includes a visual acuity and slit lamp exam (Table 61, Section 3.5.2.1). For tisotumab vedotin, patients also received pre-medications of dexamethasone 0.1% (one drop [assuming 0.05 ml per drop] in each eye, three times daily on days 1-4, Q3W) and brimonidine tartrate 0.2% (three drops in each eye on day 1, Q3W) to reduce the incidence and severity of ocular AEs. Pre-medication costs are presented in Table 57, with no cost being associated with administration of the treatments. After treatment initiation, subsequent treatment with tisotumab vedotin also involves an eye examination before each treatment administration (once every three weeks; 0.33), for those who experienced a grade 3/4 AE in prior treatment cycles (4%; Table 61, Section 3.5.2.1).

Table 57: Pre-medication costs for tisotumab vedotin

Drug	Unit cost for acquisition (2024)	Unit strength	Unit cost for admin (2024)	Source
Dexamethasone 0.1%	£11.92	0.5 ml	0	Drug costs: BNF (122, 123) Dosing: InnovaTV 301 trial protocol (81)
Brimonidine tartrate 0.2%	£1.97	5 ml	0	

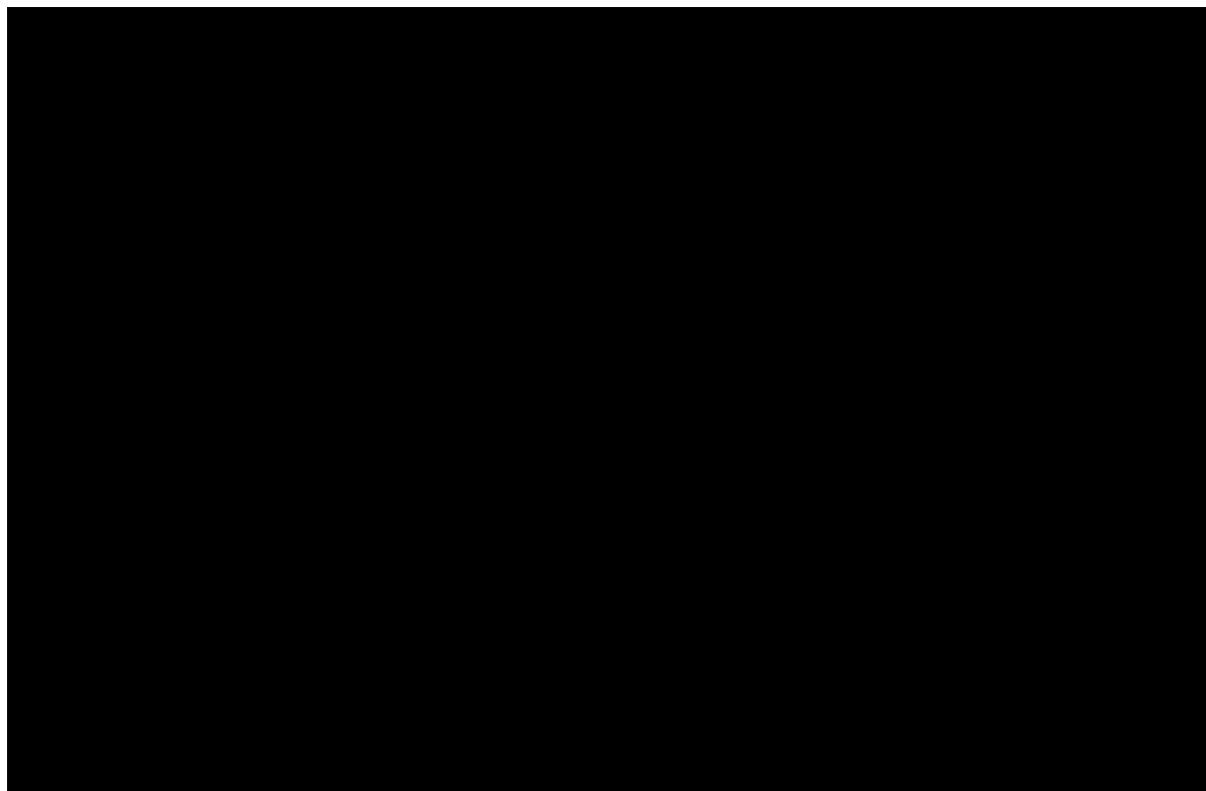
Abbreviations: BNF, British National Formulary; eMIT Drugs and pharmaceutical electronic market information tool.

3.5.1.1.2. Pre progression treatment duration

The DoT for tisotumab vedotin and chemotherapy was obtained from the IPD from the InnovaTV 301 trial (71) (Figure 28 and Figure 29). Standard parametric models (i.e., exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalised gamma) were fitted to the tisotumab vedotin and chemotherapy DoT curves independently and best fit models were selected for base-case (Figure 30). Specifically, generalised gamma for tisotumab vedotin and log-logistic for chemotherapy were selected. For chemotherapy this was based on best fit by AIC/BIC (i.e., smallest). For TV, the log-logistic curve overestimates the DOT from month 6. As

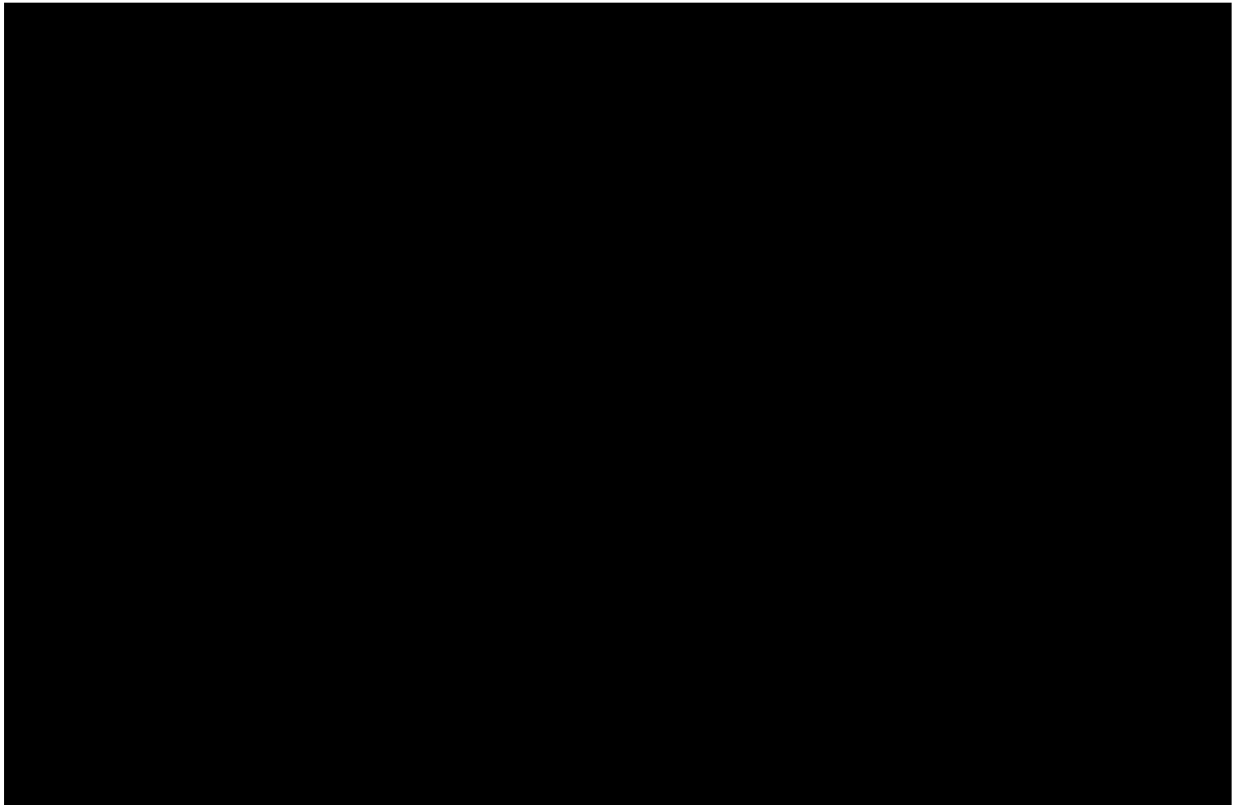
a result, generalised gamma curve was selected based on visual inspection. DoT was bounded by corresponding PFS at all time points.

Figure 28: DOT and PFS (chemotherapy)



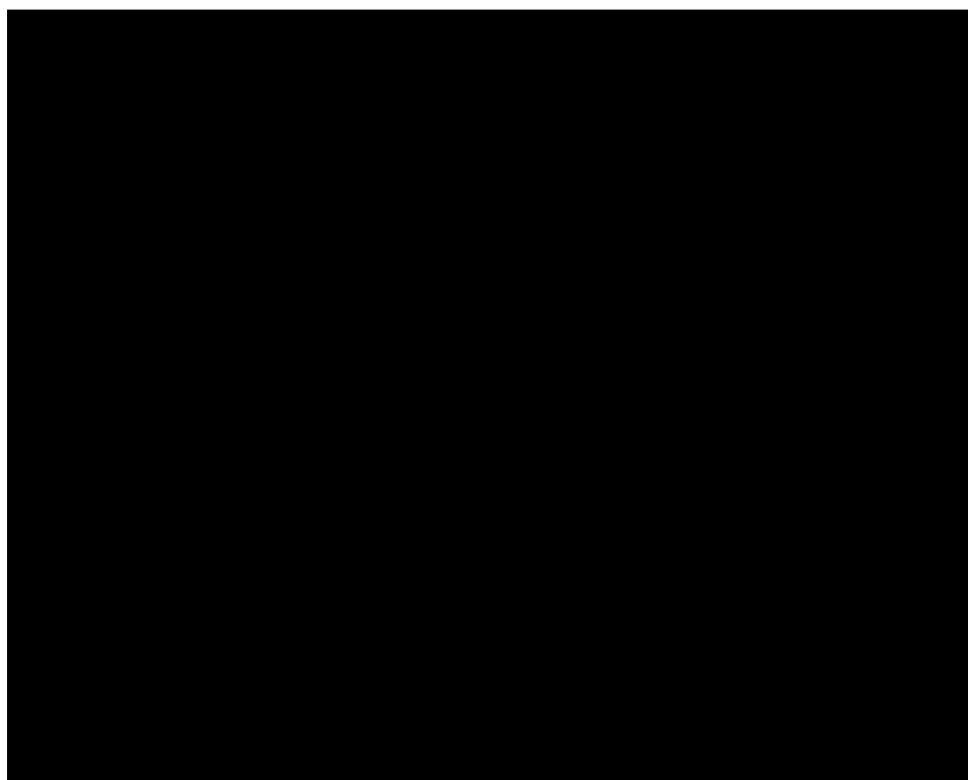
Abbreviations: DoT, duration of treatment; PFS Progression free survival.

Figure 29: DOT and PFS (tisotumab vedotin)



Abbreviations: DoT, duration of treatment; TV, tisotumab vedotin; PFS Progression free survival.

Figure 30: Predicted DoT curves for tisotumab vedotin and chemotherapy



Abbreviations: DoT, duration of treatment; TV, tisotumab vedotin.

3.5.1.2. Post-progression treatment costs

Post-progression treatment options included chemotherapy of topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed and paclitaxel. A lump sum post-progression treatment cost for each treatment regimen was estimated based on treatment costs (including drug acquisition and administration costs) per week and mean DoT as observed in the InnovaTV 301 trial (Table 58) (71).

The proportion of patients that received post-progression treatment among those who progressed (██████) was estimated based on pooled data of tisotumab vedotin and chemotherapy from the InnovaTV 301 trial (71). Among those receiving post-progression treatments, the proportion of patients who receive post-progression treatment was assumed to be: topotecan (33%), vinorelbine (0%), gemcitabine (33%), irinotecan (0%), pemetrexed (0%), and paclitaxel (33%) in both arms.

To sum up, a total post-progression treatment cost of £2,273.58 was included for each patient who progressed from tisotumab vedotin or chemotherapy.

Table 58: Post-progression treatment costs

Treatment	Drug Acquisition and Administration Costs per Week (2024)	DoT (weeks)	Lump treatment cost (2024)	Proportion of patients who received post-progression treatment	Source
Topotecan	£322.73	████	████████	33.0%	- Drug acquisition and admin cost: same as pre-progression treatment costs - DoT: InnovaTV 301 trial (71)
Vinorelbine	£113.03	████	████████	0.0%	
Gemcitabine	£114.50	████	████████	33.0%	
Irinotecan	£112.39	████	████████	0.0%	
Pemetrexed	£66.42	████	████████	0.0%	
Paclitaxel	£371.46	████	████████	33.0%	

Abbreviations: DoT, duration of treatment.

3.5.1.3. Adverse reaction unit costs and resource use

Grade 3/4 AEs reported in ≥5% of patients for at least one of the treatment arms were included. AE costs were calculated for each treatment arm based on rates of AEs (Table 47) and unit costs per AE (Table 59). It was assumed no proportion of AE were treated in an inpatient setting. The AE cost per event in the outpatient setting were obtained from NHS reference costs (121) and NICE technology appraisal of pembrolizumab in r/m CC population (ID3798) (124), respectively. A weighted average cost was calculated based on rates of AE and their associated costs for tisotumab vedotin and chemotherapy (Table 60). Costs associated with AEs for either treatment were applied as a one-off cost at the start of each treatment in the model.

Table 59: AE rates and costs

Grade 3+ AE	Cost per event (2024)	% Inpatient
Anemia	£3,177.71	0
Urinary tract infection	£2,428.68	0
Neutropenia	£735.64	0

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Peripheral neuropathy	£2,220.07	0
Ocular event (any grade)	-*	0
Source	- NICE STA (ID3798) (65) - NHS reference costs (2023-2024) (125) - AE costs: (121, 126) - % inpatient: assumption	

Abbreviations: AE, adverse event, STA, single technology appraisal; TV, tisotumab vedotin.

Note: *Cost is considered in disease management costs and eye drops (Section 3.5.2.1.).

Table 60: Weighted cost for AEs, for tisotumab vedotin and Chemotherapy

Treatment	Tisotumab vedotin	Chemotherapy
Total AE Cost (2024)	£524.60	£1,148.77

Abbreviations: AE, adverse event, TV, tisotumab vedotin.

3.5.2. Health-state unit costs and resource use

3.5.2.1. Disease management costs

Patients all received regular disease management resource use before and after disease progression. Due to lack of state-specific resource use data, resource use and corresponding frequencies were assumed the same in progression-free and progressed disease states. Additionally, ocular assessment was received by all patients in tisotumab vedotin arm at treatment initiation and eye examination was received by patients with ocular events (4% of patients in tisotumab vedotin arm) before each treatment administration. Treatment monitoring with eye examinations was considered for tisotumab vedotin in the progression-free state. Resource use services with unit costs and weekly frequencies are presented in Table 61.

Table 61: Unit costs and weekly frequencies and resource use for disease management costs

Service	Unit cost (2024)	Weekly frequency			Source
		Year 1-2	Year 3-5	Year 6+	
Regular disease management in progression-free and progressed disease states					
Oncologist visit	£193.02	0.06	0.03	0.02	- Unit cost: NHS reference costs (121) - Resource use: Cancer research UK- follow up after cervical cancer treatment (127)
Complete blood count	£1.46	0.06	0.03	0.02	
Chemistry panel	£4.89	0.06	0.03	0.02	
Colposcopy	£246.46	0.02	0.02	0.02	
Chest X-ray	£101.10	0.06	0.03	0.02	
PET-CT scans	£638.03	0.03	0.01	0.01	
MRI	£171.08	0.03	0.01	0.01	
Additional treatment monitoring for tisotumab vedotin in progression-free state					
Ocular assessment	£169.00	1.00*	1.00*	1.00*	- Unit cost: NHS reference costs (121)
Eye examination	£107.00	0.33	0.33	0.33	- Resource use: InnovaTV 301 trial protocol (81)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Note*: Ocular assessment was received once at treatment initiation.

3.5.2.2. Terminal care costs

The model considered a one-time terminal care cost before death of £5,490.14 for each patient who died (128).

3.6. Severity

QALY weightings for disease severity were considered to align with the NICE Method Manual (PMG36) to calculate the absolute and proportional QALY shortfalls (96). The utility data used to calculate the QALY absolute or relative shortfall was taken from McNamara et al. (103) but using the 2021-2023 UK life tables. The key features of the QALY shortfall analysis are provided in Table 63

Table 63 which presents the QALYs and life years gained from chemotherapy treatment. An overall summary of QALY shortfall analysis is provided in Table 64.

The analysis resulted in an absolute shortfall of [REDACTED] QALYs, corresponding to a proportional QALY shortfall of [REDACTED]. According to PMG36, this translates to a QALY modifier of 1.7 for tisotumab vedotin versus chemotherapy (96). Notably, patients with r/m CC represent a population with considerable unmet need, with a median OS observed at [REDACTED] months for tisotumab vedotin and [REDACTED] months for chemotherapy in the InnovaTV 301 trial (70). As such, the application of a 1.7x QALY modifier for tisotumab vedotin versus chemotherapy was considered appropriate and applied in the cost-effectiveness analysis results.

Table 62: Summary features of QALY shortfall analysis

Factor	Values	Reference to section in submission
Sex distribution	100% female	Section 1.3.2
Starting age	[REDACTED]	Section 3.2.1
QALY weight	1.7	N/A

Table 63: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Pre-progression	██████████	0.38
Post-progression	██████████	0.61

Table 64: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with chemotherapy	QALY shortfall	Relative shortfall (%)
14.45	██████████	██████████	██████████

Abbreviation: QALY, quality adjusted life year.

3.7. *Uncertainty*

Overall survival data for tisotumab vedotin in the InnovaTV 301 trial are relatively mature. Only █ and █ people each in the tisotumab vedotin and chemotherapy arms, respectively, (████ and █████, respectively) remained at risk at 24 months in the January 16th, 2024, data-cut. Furthermore, there were █████ OS events (████ and █████ events in the tisotumab vedotin and chemotherapy arms, respectively), with only █ patients in each arm remaining on treatment since initial randomisation in the January 2024 data-cut. These data are further complemented by longer follow-up data from InnovaTV 204 trial which shows that a similar small proportion, █████ of those treated with tisotumab vedotin were at risk at 24 months. Therefore, we consider the uncertainty to be low in this appraisal.

3.8. *Managed access proposal*

Genmab is open to considering managed access if indicated by NICE during the submission process.

3.9. Summary of base-case analysis inputs and assumptions

3.9.1. Summary of base-case analysis inputs

A tabulated summary of the base-case analysis inputs is provided in Appendix J.

3.9.2. Assumptions

Table 65 provides a list of all assumptions in the economics model as well as justification for each assumption.

Table 65: Assumptions applied in the model

Assumption	Justification
Treatment efficacy for tisotumab vedotin and chemotherapy	Efficacy observed in the InnovaTV 301 clinical trial are generalisable to the target population in England and Wales.
Chemotherapy comparator proportions	Chemotherapy consisted of a mixture of different chemotherapy agents, i.e., topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed and paclitaxel. Proportion of patients using each agent was informed by a survey of 8 UK clinicians involved in the management of r/m CC in the UK.
Efficacy and safety of chemotherapy	Efficacy and safety for all chemotherapy agents were assumed to be the same based on the InnovaTV 301 trial chemotherapy arm. Efficacy of chemotherapy agents did not differ much from each other; therefore, only costs and treatment duration differed between the individual chemotherapy agents. Although weekly paclitaxel is a common regimen used in the UK, there are no efficacy data available to support different efficacy of this regimen. This assumption of comparable efficacy of all single agent chemotherapies, including weekly paclitaxel, was also supported by oncologists specializing in gynaecological cancers that participated in the UK CC advisory board conducted by Genmab.
Health state transitions	For transitions from PD to death, the model assumed there was no difference in post-progression mortality after month 12. The 12-month cutoff was selected because by that point, more than [REDACTED] of patients had discontinued randomised treatment—only [REDACTED] in the tisotumab vedotin arm and [REDACTED] in the chemotherapy arm remained on study therapy. This approach is supported by clinical insights suggesting that once patients transition to subsequent therapies or palliative care, their survival trajectories are no longer influenced by the initial treatment received.

Health state utilities	Health-state utilities were dependent only on health states and independent of treatment arms. Health state utilities were further adjusted by age.
Adverse events	Grade 3/4 AEs that happen in more than 5% of any intervention or comparator arm, plus all ocular events of grade 3/4, were considered in the model for costs and disutilities.
Disutilities	Only patients with severe AEs (grade 3+) would experience meaningful disutilities.
Relevant costs	In addition to drug acquisition costs, drug administration costs and AE-related costs, patients in progression-free and progressed disease states would incur disease management costs which are independent of treatments.
Premedication costs	Only patients receiving tisotumab vedotin would receive pre-medication with eye drops and treatment monitoring with eye examinations.
Costs associated with mortality	All patients would incur terminal care costs before death.

Abbreviations: TV, Tisotumab vedotin; AEs, adverse events.

3.10. Base-case results

3.10.1. Base-case incremental cost-effectiveness analysis results

Over a lifetime horizon, the total discounted QALYs and costs for tisotumab vedotin were estimated to be [REDACTED] and [REDACTED], respectively. Relative to chemotherapy, tisotumab vedotin resulted in [REDACTED] incremental QALYs and £[REDACTED] incremental costs (Table 66) without the application of a severity modifier. Based on the QALY shortfall analysis, tisotumab vedotin was eligible for a QALY modifier of 1.7 (see Section 3.6). Based on the application of the severity modifier, relative to chemotherapy, tisotumab vedotin results in [REDACTED] adjusted incremental QALYs. The discounted costs per QALY gained of tisotumab vedotin relative to chemotherapy, with and without the application of a severity modifier of 1.7, were estimated to be £47,046 and £79,978, respectively. Disaggregated results are provided in Appendix H: Clinical outcomes and disaggregated results from the model.

The results from the net-health benefit (NHB) analysis are presented in Table 67, which shows the impact of tisotumab vedotin on the modelled population when compared to the use of chemotherapy, at a willingness to pay (WTP) of both £20,000 and £30,000. The NHB for those being treated with tisotumab vedotin would be [REDACTED] and [REDACTED] without the severity modifier and [REDACTED] and [REDACTED] with the 1.7 QALY modifier,

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at a WTP of £20,000 and £30,000, respectively.

Table 66: Base-case results of costs, effectiveness, and incremental outcomes

	Total			Incremental			ICER
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Tisotumab vedotin	██████	1.18	██████	██████	0.21	██████	79,978
Chemotherapy	██████	0.96	██████				
Severity-weighted results					QALY weight	Incremental QALYs	Weighted ICER
					1.7	██████	£47,046

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

Table 67: Net health benefit

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

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

A probabilistic sensitivity analysis (PSA) was conducted to simultaneously vary multiple parameters, based on their distributions, and re-estimate model outputs. A Monte-Carlo simulation with 200 iterations was conducted, with 150 iterations deemed sufficient to lead to convergence in the ICER. In each iteration, input values were randomly drawn from the specified distributions to inform the possible range of the input values. The results were presented as a cost-effectiveness scatter plot and a plot of cost-effectiveness acceptability curves comparing tisotumab vedotin with chemotherapy. The severity modifier applied in the PSA is based on the median of the modifiers generated from the simulations in the chemotherapy arm, which ensures that the weight is either 1, 1.2 or 1.7 and not an average. All the model parameters that were varied in the PSA and their associated distributions are summarised in Table 68, with details of uncertainty parameters provided in Table 21 (Appendix J: Summary of model inputs). Whenever available, the standard error (SE) of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability, the SE for each parameter was assumed as 10% of the mean value.

Table 68: PSA parameters

Parameter	Description
Demographics	
Age, BSA, body weight	Patient age, BSA and weight were varied using normal distributions. Means and SEs were obtained from the InnovaTV 301 trial (71).
Efficacy	
Parametric estimates for OS and PFS	Parametric estimates used in the base-case were varied using multivariate normal distributions. The SEs of the OS and PFS parameters were estimated using variance-covariance matrix from the same source for the base-case input.
DoT	
Parametric estimates for DoT of tisotumab vedotin and chemotherapy	Parametric estimates for DoT of tisotumab vedotin and chemotherapy used in the base-case were varied using multivariate normal distributions. The SEs of the DoT

Parameter	Description
	parameters were estimated using variance-covariance matrix from the same source for the base-case input.
Cost	
Pre-progression treatment costs	Costs were varied using gamma distributions, with mean values as specified in the base-case model. SEs were assumed to be 10% of the mean.
Administration unit costs	
Post-progression treatment costs	
AE costs	
Disease management costs	
Terminal care costs	
RDI	
Pre-progression treatment RDI for tisotumab vedotin and comparators	Pre- and post-progression treatment RDIs were varied using beta distributions. Means and SEs were obtained from the InnovaTV 301 trial.
Utility and disutility	
Health-state utilities	Health-state utilities and QALY decrement due to AE were varied using beta distributions. SEs of health-state utilities were obtained from InnovaTV 301 trial. SEs of QALY decrement due to AEs were assumed to be 10% of the mean.
QALY decrement due to AEs	

Abbreviations: AE, adverse event; BSA, body surface area; DoT, duration of treatment; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; SE: standard error; TV, tisotumab vedotin.

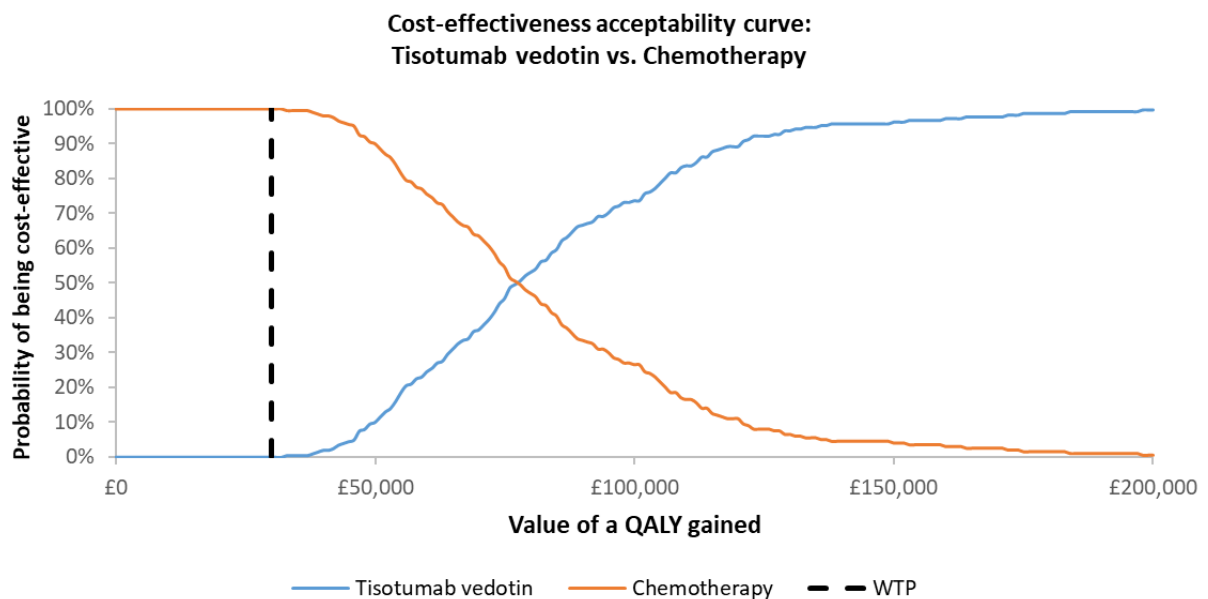
Table 69 shows the PSA results. The probabilistic ICER per QALY gained for tisotumab vedotin versus chemotherapy is comparable with the base-case deterministic results (Table 66). Cost-effectiveness acceptability curves and cost-effectiveness scatterplots, including the application of the severity modifier, are shown in Figure 31 and Figure 32, respectively. The cost-effectiveness acceptability curve suggested a 0% probability of tisotumab vedotin being cost-effective relative to chemotherapy at WTP thresholds of £20,000-£30,000/QALY, with the severity modifier.

Table 69: 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	██████	1.19	██████							
Chemotherapy	██████	0.96	██████	██████	0.23	██████	██████	██████	75,921	46,660

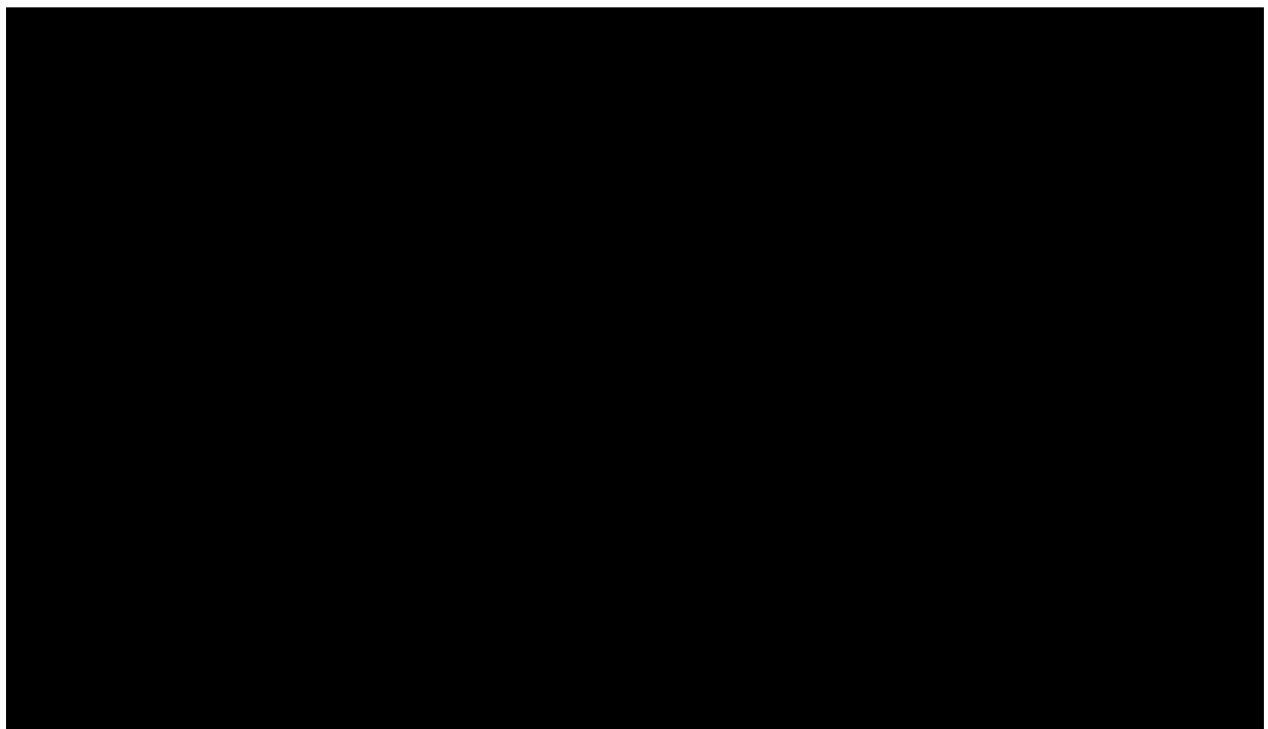
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; TV, tisotumab vedotin.

Figure 31: Cost-effectiveness acceptability curves (tisotumab vedotin vs. chemotherapy)



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

Figure 32: Cost-effectiveness scatterplot (tisotumab vedotin vs. chemotherapy)



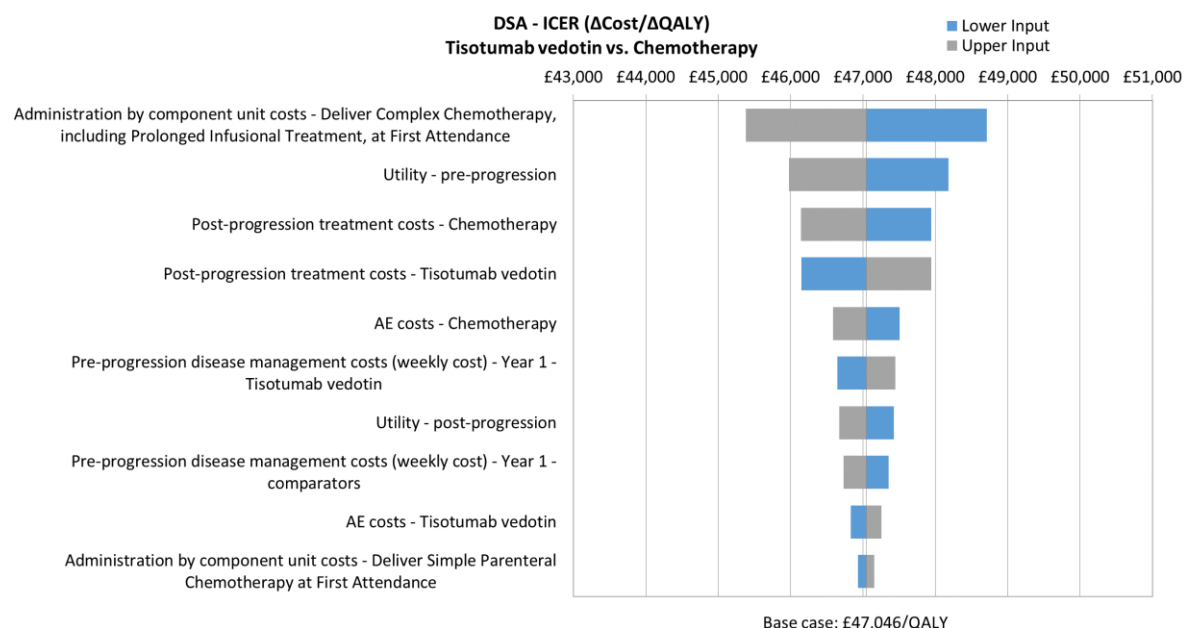
Abbreviations: QALY, quality-adjusted life year; WTP: willingness-to-pay.

3.11.2. *Deterministic sensitivity analysis*

The robustness of the CEA model was tested by a set of deterministic sensitivity analyses (DSAs). One parameter was varied at a time while holding the other parameters at base-case values. The parameters were varied according to their 95% CI. If such information was not available, the parameters were varied by $\pm 10\%$ from the base-case values. The detailed list of parameters and assumptions tested in the DSAs is included in Appendix J: Summary of model inputs.

The tornado diagram presenting the top 10 DSA results are shown in Figure 33. The DSA results indicated that the model was robust to most parameter changes. The top three key drivers of the ICERs per QALY gained include administration costs for chemotherapy, pre-progression utility and post progression treatment costs for chemotherapy.

Figure 33: 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

Scenario analyses were performed in the model to understand the impact of key assumptions on the cost-effectiveness of tisotumab vedotin by replacing the base case data with plausible alternative scenarios for treatment efficacy, chemotherapy treatment distribution, AE costs, utility and disutility of AEs (Table 70). Relative to chemotherapy, the ICER per QALY gained (weighted) of tisotumab vedotin ranged from £35,936 to £62,028. The top drivers include applying the global trial-based chemotherapy treatment distribution, modelling of PD survival and alternative PF to PD and PF to death parametric curve distributions.

Table 70: Scenario analysis results

Scenarios	Scenario analysis setting	Base case setting	Incremental QALYs (weighted*)	Incremental Costs (£)	ICER/QALY (£)
Base case	-	-	■	■	47,046
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	■	■	59,667
InnovaTV 301 trial – mixed effects model utilities	pre-progression: 0.711, post-progression: 0.566	InnovaTV 301 trial (GEE) utilities	■	■	47,127
Literature - Zheng 2023 utilities	pre-progression: 0.850, post-progression: 0.520	InnovaTV 301 trial (GEE) utilities	■	■	40,917
Literature – Liu 2023 utilities	pre-progression: 0.817, post-progression: 0.779	InnovaTV 301 trial (GEE) utilities	■	■	56,333
Exclude AE disutility	Exclude AE disutilities	Include AE distuility	■	■	47,060
Exclude AE costs	Exclude AE costs	Include AE costs	■	■	49,552
Use dependent models for tisotumab vedotin and chemotherapy (proportional	PFS: Generalised gamma, OS: Lognormal	Apply the same risk of death after progression for tisotumab vedotin and	■	■	34,471

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Scenarios	Scenario analysis setting	Base case setting	Incremental QALYs (weighted*)	Incremental Costs (£)	ICER/QALY (£)
hazards approach)		chemotherapy			
Tisotumab vedotin/chemotherapy PF to PD parametric curve distribution – Lognormal (based on second lowest AIC and BIC)	Tisotumab vedotin/chemotherapy PF to PD parametric curve distribution - Lognormal	Tisotumab vedotin/chemotherapy PF to PD parametric curve distribution - Generalised Gamma			58,955
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			52,894

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.

3.12. *Benefits not captured in the QALY calculation*

To align with the STA reference case the HRQoL of family members has been excluded. However, cervical cancer often affects young women often with children and at the age when they are raising families, even small improvements in survival would allow them to spend more time with their families.

3.13. Validation

3.13.1. *Validation of cost-effectiveness analysis*

3.13.1.1. Internal validity

Internal quality control procedures were undertaken by Analysis Group, Inc., who developed the model on behalf of the manufacturers (Genmab). The quality control included a line-by-line audit of the Visual Basic for Applications code used in the model. In addition, all source inputs and calculations in the Excel model were generated by one researcher and verified by another researcher to ensure accuracy. Further, the model structure, setting, assumptions, input, and data were internally reviewed by health economists who have extensive experience in model construction.

To assess the validity of survival extrapolation, comparisons were made between the predicted and observed OS and PFS curves from the InnovaTV 301 trial for tisotumab vedotin and chemotherapy (Appendix H: Section 1.1). Comparisons of OS and PFS with landmark comparison of PFS and OS rates are also summarised in Appendix H: Section 1.1.

The model demonstrated a strong fit to the observed OS for tisotumab vedotin, accurately capturing the survival trend. While some divergence was noted for chemotherapy at the tail end of the curve, this likely reflects uncertainty due to the small number of patients remaining in that time frame. This interpretation is supported by clinical expert input, which estimates 2-year survival for chemotherapy at approximately 10%, rather than the 20% observed in the data. The model's predicted OS at 24 months was [REDACTED], aligning closely with clinical expectations.

PFS predictions showed a good fit for both tisotumab vedotin and chemotherapy. The

model slightly underestimated PFS for tisotumab vedotin starting around month 16, but this deviation was not observed for chemotherapy.

3.13.1.2. External validity

External validation was conducted by comparing model predicted OS and PFS curves of tisotumab vedotin with the KM curves of tisotumab vedotin from the InnovaTV 204 trial and comparing predicted OS and PFS curves of chemotherapy with the KM curves of chemotherapy from the EMPOWER CERVICAL-1 trial (data cutoff date: January 4th, 2021, for both PFS and OS).

In addition, the estimated LYs and QALYs from published cost-effectiveness studies of tisotumab vedotin and cemiplimab were also used to validate the estimated LYs and QALYs (93).

Validation for the predicted OS and PFS of tisotumab vedotin

Longer-term follow-up data are available for tisotumab vedotin from the phase 2 InnovaTV 204 trial (Section 2.3.2). The InnovaTV 204 trial is a single-arm phase 2 trial of tisotumab vedotin among patients with previously treated r/m CC and it has a longer follow-up than in the InnovaTV 301 (median follow-up: █████ months) (84). Characteristics of patients in InnovaTV 204 and InnovaTV 301 are comparable (see Section 2.3.2). Therefore, InnovaTV 204 was considered as a valid source to validate the predicted efficacy for tisotumab vedotin.

Figure 15 and Figure 16 in the Appendix present the comparisons of OS and PFS for tisotumab vedotin, with landmark comparison of PFS and OS rates summarised in Appendix H: Clinical outcomes and disaggregated results from the model, Section 1.1). The model-predicted PFS and OS curve aligned well with estimates from the InnovaTV 204 trial data. Although the predicted OS and PFS rates at the tail end were slightly lower than those observed in KM curves with InnovaTV 204 trial data, they were still within the 95% CIs. These supported the validity of the model predictions for tisotumab vedotin.

Validation for the predicted OS and PFS of chemotherapy

Chemotherapy data from the EMPOWER CERVICAL-1 trial were used to validate the OS and PFS data for chemotherapy. EMPOWER CERVICAL-1 was an open-label,

multicentre, phase 3 trial which enrolled 608 women with r/m CC who progressed after receiving platinum containing therapy. Of the 608, an equal split of 304 were randomised to the chemotherapy and cemiplimab arm. Both disease characteristics and demographics were balanced between both treatment groups. The median duration of treatment for the chemotherapy arm was 10.1 weeks. The median follow-up period in EMPOWER CERVICAL-1 is 18.2 months for PFS and 30.2 months for OS (129, 130), longer than that for InnovaTV 301. Therefore, EMPOWER CERVICAL-1 was considered a valid source to validate the predicted efficacy for chemotherapy.

Figure 17 and Figure 18 in the Appendix present the comparisons of OS and PFS of chemotherapy, with landmark comparison of PFS and OS rates (summarised in Appendix H, Section 1.1). Although patients in the EMPOWER CERVICAL-1 trial was conducted among patients without prior anti-PD-(L)1 use in the 2L+ setting, the efficacy of chemotherapy is not expected to substantially differ based on patients' prior use of anti-PD-(L)1, making EMPOWER CERVICAL-1 a valid data source for external validation. The model-predicted OS and PFS aligned well with the observed OS and PFS from the EMPOWER CERVICAL-1. Notably, the 24-months OS from EMPOWER was 11.3%, supporting the interpretation that the 24-month OS observed in the InnovaTV 301 chemotherapy arm (approximately 20%) may be overestimated, likely due to uncertainty stemming from the small number of patients at risk (n=7) at that time point.

Validation for the estimated QALYs for tisotumab vedotin and chemotherapy

A cost-effectiveness study of tisotumab vedotin vs. chemotherapy which was published recently, was identified during the literature search for model validation (93). In this study, OS and PFS for tisotumab vedotin and chemotherapy were extrapolated based on log-logistic models per InnovaTV 301 data. The estimated discounted QALYs of tisotumab vedotin and chemotherapy were 1.15 and 0.90, respectively. LYs were not reported in the study. The comparison with our estimated discounted QALYs is presented in Table 71. If the same discount rate and utilities were applied, the model estimated discounted QALYs were comparable to those in the publication.

Table 71: Comparison of estimated discounted QALYs in published cost-effectiveness study vs. the current model

	Discount rate	Utility values	Discounted QALYs
Tisotumab vedotin			
Current model – base-case	3.5%	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]
Current model – same discount rate and utilities as in the published study (Huo 2024) (93)	3.0%	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]
Tisotumab vedotin CEA publication (Huo 2024) (93)	3.0%	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]	1.15
Chemotherapy			
Current model – base-case	3.5%	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]
Current model – same discount rate and utilities as in the published study	3.0%	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]
Tisotumab vedotin CEA publication (Huo 2024) (93)	3.0%	• Pre-progression: [REDACTED] • Post-progression: [REDACTED]	0.90

Abbreviations: CEA, cost-effectiveness analysis; QALYs, quality-adjusted life years; TV, tisotumab vedotin.

3.14. Interpretation and conclusions of economic evidence

Recurrent/ metastatic cervical cancer affects young women in their productive, child-bearing/ family-raising years of their lives. The disease is associated with a substantial burden of disease and current therapies confer very poor survival and responses, with no clear standard of care in the 2L setting. Tisotumab vedotin is the first-in-class ADC that has demonstrated significantly better efficacy than single agent chemotherapy in the 2L/3L setting. The InnovaTV 301 trial demonstrated that in r/m CC patients treated in the 2L/3L setting, tisotumab vedotin significantly reduces the risk of disease progression by █% vs. chemotherapy (median PFS of █ vs. █ months; HR: █ [95% CI: █]) and significantly reduces the risk of mortality by █% vs. chemotherapy (median OS of █ vs. █ months; HR: █ [95% CI: █] based on the January 2024 datacut) (86). With these survival benefits and a 4-fold increase in response rates and 30% improvement in the disease control rate, tisotumab vedotin presents an attractive alternative treatment option for a very limited patient population with high unmet needs.

The economic value of tisotumab vedotin in 2L/3L r/m CC was evaluated using a semi-Markov model. Internal and external validations support the selected modelling approach and model results.

The current base-case provided a reasonably long-term estimate for clinical and health economic impact of tisotumab vedotin. The model estimated undiscounted LY benefit of 0.23 with a discounted QALY benefit of █ and █ for tisotumab vedotin compared to chemotherapy, with and without a 1.7 severity modifier based on a █% severity shortfall. The total discounted cost difference was estimated at around █ and a discounted ICER of £47,046. Sensitivity analyses and scenario analyses supported these findings albeit with the QALY failing to capture the benefits of extending lives of young women at a stage in their lives when they are often most productive and raising families. These results suggest a meaningful extension in both the quantity and quality of life for this very limited patient population with significant unmet need, highlighting the potential value of tisotumab vedotin from a public health perspective.

3.15. Conclusion

In the base-case model, the ICER for tisotumab vedotin compared with chemotherapy was £47,046 per QALY gained as a treatment for adult patients with r/m CC with disease progression on or after systemic chemotherapy, from the UK NHS and PSS perspective. The model demonstrates a strong internal and external validity through, comparisons of observed and predicted OS and PFS curves of both TV and chemotherapy from the innovaTV 301, innovaTV 204 and EMPOWER CERVICAL-1 trials, respectively. Additional validation of model outcomes through comparison against existing literature (Huo et al. (93)) demonstrates comparable findings. The results from this economic evaluation demonstrate the value of tisotumab vedotin at an ICER of £47,046 per QALY gained as an attractive alternative treatment option in a population which is currently conferred very poor survival and treatment response from currently available therapies.

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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

January 2026

File name	Version	Contains confidential information	Date
ID3753 Tisotumab vedotin Evidence Submission_Addendum_30012026 [REDACTED]	1.0	Yes	30 January 2026

3. Cost effectiveness

The results in this addendum are generated using the updated Patient Access Scheme (PAS) price of ■■■ per vial. This represents a ■■■ discount off the list price of ■■■ 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), updated only with the new PAS and generated using the EAG’s model.

3.10. Base-case results

3.10.1. Base-case incremental cost-effectiveness analysis results

Table 1: Base-case results of costs, effectiveness, and incremental outcomes

	Total			Incremental			ICER
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Tisotumab vedotin	████	1.18	████	████	0.21	████	59,552
Chemotherapy	████	0.96	████				
Severity-weighted results					QALY weight	Incremental QALYs	Weighted ICER
					1.7	████	£35,030

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

Table 2: Net health benefit

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

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*

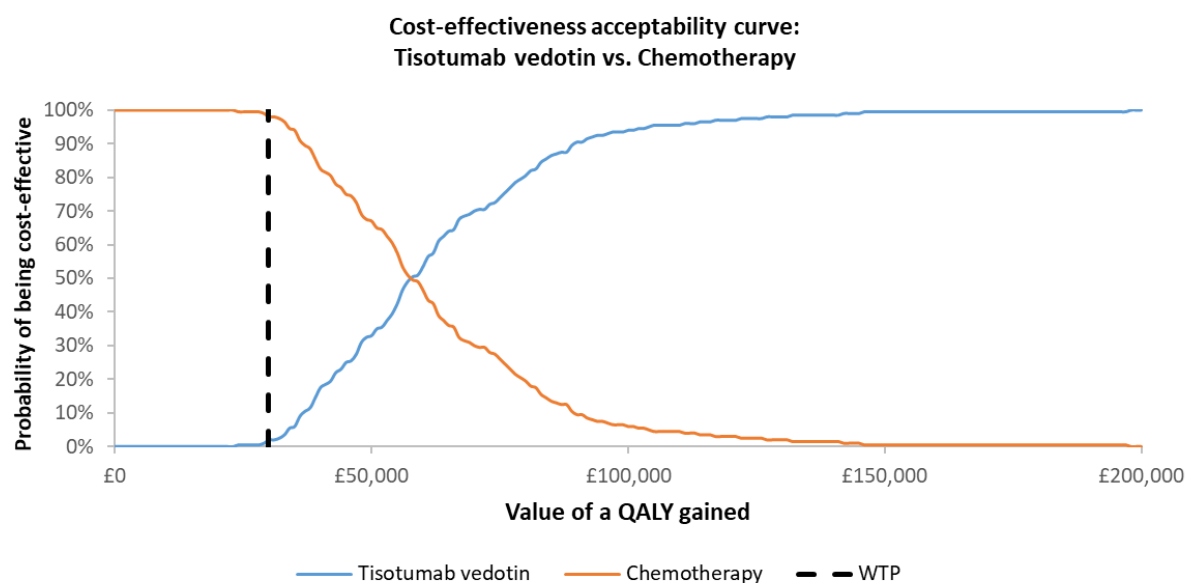
Table 3 shows the PSA results. The probabilistic ICER per QALY gained for tisotumab vedotin versus chemotherapy is slightly lower than the base-case deterministic results (Table 1). Cost-effectiveness acceptability curves and cost-effectiveness scatterplots, including the application of the severity modifier, are shown in Figures 31 and 32, respectively. The cost-effectiveness acceptability curve suggested a 0.5% and 6% 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 3: 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	■	1.19	■							
Chemotherapy	■	0.96	■	■	0.23	■	■	■	56,824	33,426

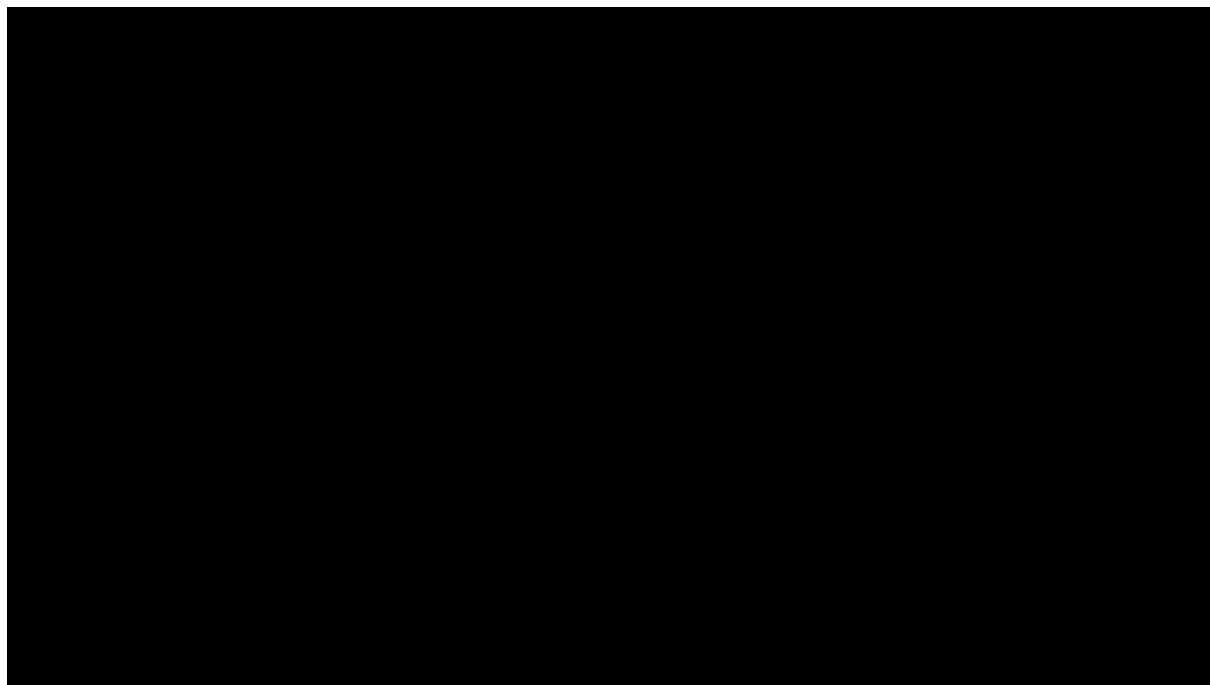
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; TV, tisotumab vedotin.

Figure 31: Cost-effectiveness acceptability curves (tisotumab vedotin vs. chemotherapy)



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

Figure 32: Cost-effectiveness scatterplot (tisotumab vedotin vs. chemotherapy)

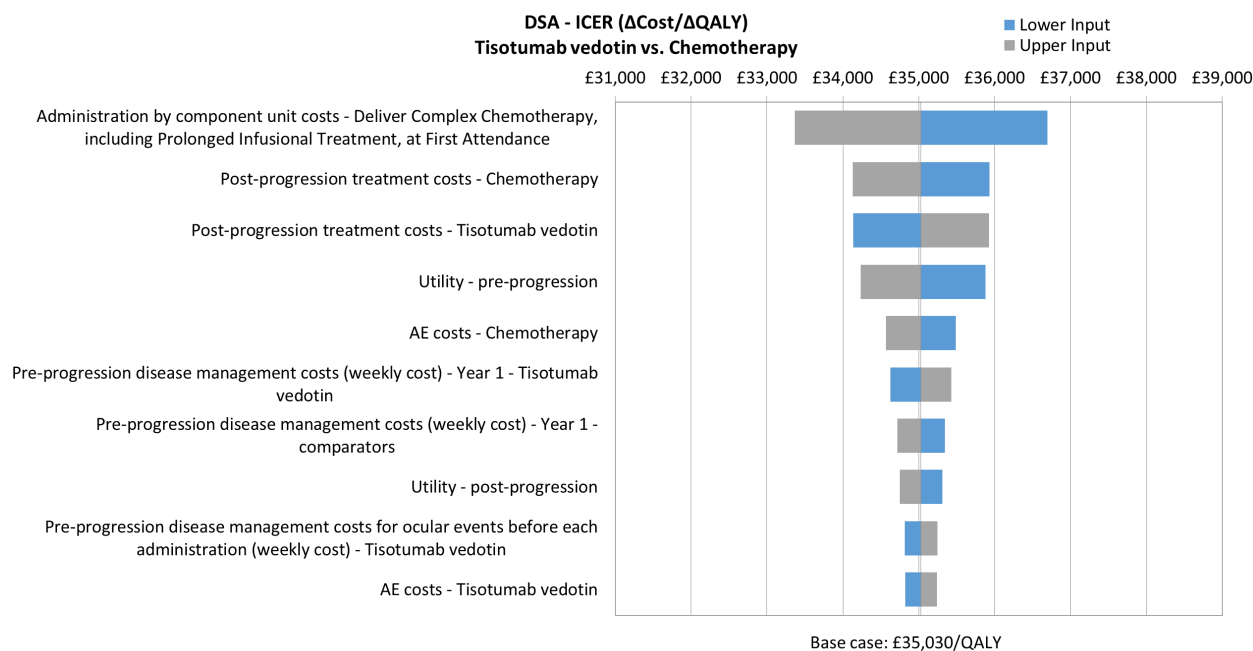


Abbreviations: QALY, quality-adjusted life year; WTP: willingness-to-pay.

3.11.2. Deterministic sensitivity analysis

Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer with disease progression on or after systemic therapy

Figure 33: 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 4: Scenario analysis results

Scenarios	Scenario analysis setting	Base case setting	Incremental QALYs (weighted*)	Incremental Costs (£)	ICER/QALY (£)
Base case	-	-	■	■	35,030
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	■	■	47,652
InnovaTV 301 trial – mixed effects model utilities	pre-progression: 0.711, post-progression: 0.566	InnovaTV 301 trial (GEE) utilities	■	■	35,091
Literature - Zheng 2023 utilities	pre-progression: 0.850, post-progression: 0.520	InnovaTV 301 trial (GEE) utilities	■	■	30,467
Literature – Liu 2023 utilities	pre-progression: 0.817, post-progression: 0.779	InnovaTV 301 trial (GEE) utilities	■	■	41,946
Exclude AE disutility	Exclude AE disutilities	Include AE distuility	■	■	35,041
Exclude AE costs	Exclude AE costs	Include AE costs	■	■	37,537
Use dependent models for tisotumab vedotin and chemotherapy (proportional	PFS: Generalised gamma, OS: Lognormal	Apply the same risk of death after progression for tisotumab vedotin and	■	■	27,377

Company evidence submission template for tisotumab vedotin for treating recurrent or metastatic cervical cancer with disease progression on or after systemic therapy

Scenarios	Scenario analysis setting	Base case setting	Incremental QALYs (weighted*)	Incremental Costs (£)	ICER/QALY (£)
hazards approach)		chemotherapy			
Tisotumab vedotin/chemotherapy PF to PD parametric curve distribution – Lognormal (based on second lowest AIC and BIC)	Tisotumab vedotin/chemotherapy PF to PD parametric curve distribution - Lognormal	Tisotumab vedotin/chemotherapy PF to PD parametric curve distribution - Generalised Gamma	■	■	49,258
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	■	■	39,261

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 modifi

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

October 2025

File name	Version	Contains confidential information	Date
ID3753_Tisotumab vedotin Genmab_SIP_Final_17102025	1.1	No	17 October 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Tisotumab vedotin (Tivdak®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Tisotumab vedotin is a prescription medicine used to treat adults with cervical cancer (CC):

- that has returned (recurrent) or has spread to other parts of the body (metastatic), **and**
- who have received therapy that has not worked or is no longer working.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Tisotumab vedotin monotherapy was approved for use in relapsed or metastatic cervical cancer by the European Medicines Agency (the organisation that gives companies the legal right to sell medicines in the European Union) on the 28th of March 2025.

In the UK, approval from the Medicines and Healthcare products Regulatory Authority (MHRA) is currently pending. Please see Section 1.2 of the company evidence submission for further details.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Not applicable.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

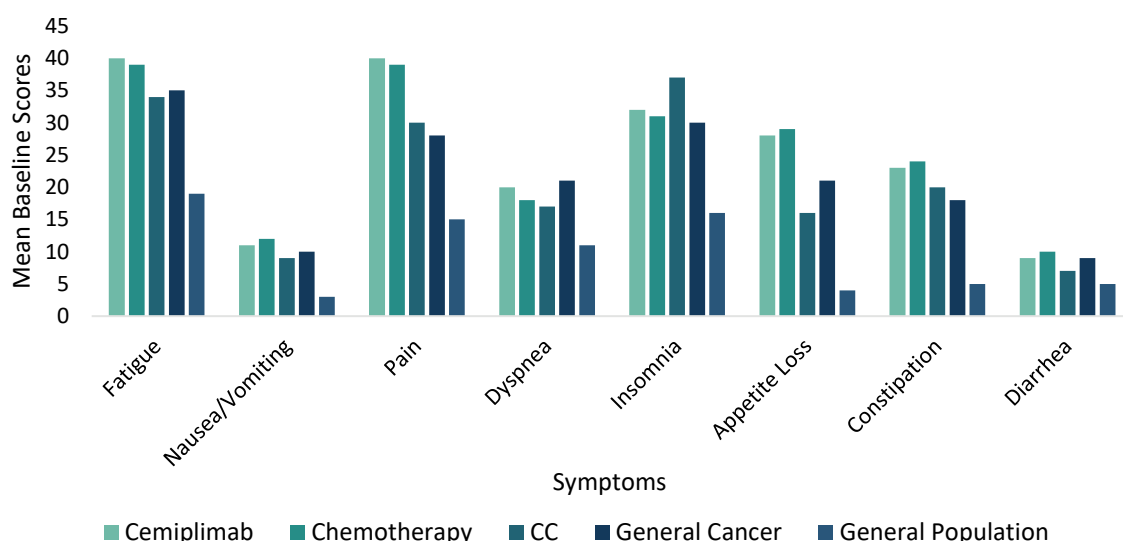
Recurrent or metastatic cervical cancer (r/m CC) refers to cervical cancer that has either spread to distant parts of the body at the time of diagnosis (stage IVB) or has come back and spread following treatment. Cervical cancer often spreads to nearby lymph nodes, lungs, liver and/or bones. Clinical outcomes of patients diagnosed with r/m CC depend on the status of the tumour, how much it has spread, and where it has spread or returned to¹.

In the UK, cervical cancer (CC) is the 14th most common cancer in women, making up about 2% of all new cancer cases between 2017 and 2019². In England, there is an estimated 2,342 patients living with CC, of which approximately 117 patients have r/m CC who have previously received therapy which has not worked or is no longer working³⁻⁶. Refer to Section 1.3.2 in the company evidence submission for further details.

Burden of disease

CC often does not cause symptoms at first. When symptoms begin to appear, they can include: bleeding between periods, after sex, or after menopause; pain during sex; pelvic pain; heavier or longer periods than usual; or unusual vaginal discharge. In patients with r/m CC, symptoms can include extreme tiredness, swelling or pain in the legs, lower back or stomach pain, coughing or trouble urinating^{1,7}. A study of patients with r/m CC showed these patients had more severe symptoms (except trouble sleeping) compared with CC in general, other types of cancer, and the general European population⁸ (Figure 1).

Figure 1: Symptom scores for women with r/mCC versus all CC, other types of cancer and the general population



Notes: Data has been estimated from published figures in the source paper.

Source: Oaknin et al. (2022)⁸,

Patients with r/m CC have a poor outlook, and the disease has a large impact on young women, who are in the most productive time of their lives in terms of family and careers⁹⁻¹². Women with

metastatic CC have much lower survival rates compared to those with early-stage disease¹³⁻¹⁵. A study of 75 women in the UK who started first-line treatment for r/m CC between 2004 and 2014 at one hospital showed that only 30% were still alive after 5-years¹⁶⁻¹⁸. This shows that as r/m CC patients go through more lines of treatment, their chance of survival generally decreases.

There is currently no standard of care (SOC) treatment for women with r/m CC after first-line treatment. As a result, chemotherapy is often used, however it has limited benefits and can cause serious side effects (i.e., toxicity) resulting in reduced quality of life (QoL) for patients. Women with CC report significantly worse health-related quality of life (HRQoL) compared with individuals without CC¹⁹⁻²⁰. Figure 2 shows r/m CC patients reported worse HRQoL and functioning as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) compared with CC in general, other types of cancer, and the general European population⁸.

Figure 2: EORTC QLQ-C30 scores for women with r/mCC vs. all CC, other types of cancer and the general population



Notes: Data has been estimated from published figures in the source paper.

Source: Oaknin et al. (2022)⁸.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The UK primarily relies on cervical screening to detect Human papillomavirus (HPV) and abnormal cervical cells as part of its approach to diagnosing cervical cancer. When abnormalities are identified, further diagnostic procedures like colposcopy and biopsy are used to confirm the presence of cancer and assess its severity²¹⁻²².

Tisotumab vedotin does not require any additional diagnostic tests for the treatment of adults with recurrent or metastatic cervical cancer.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:

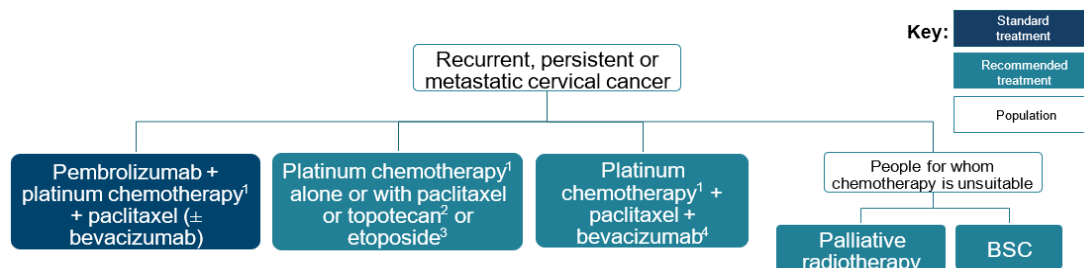
- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Clinical decisions on treatment options for r/m CC are primarily directed by the National Institute for Health & Care Excellence (NICE) in the UK, who provide guidance on treatment approvals and drug availability. Alternative clinical guidelines published for r/m CC are detailed in Section 1.3.4 of the company evidence submission.

NICE Guidance (2022)²³

The first line treatment recommendations outlined by NICE for r/m CC patients are shown below in Figure 3.

Figure 3: First-line treatment recommendations for r/mCC from NICE



Abbreviations: BSC: best supportive care.

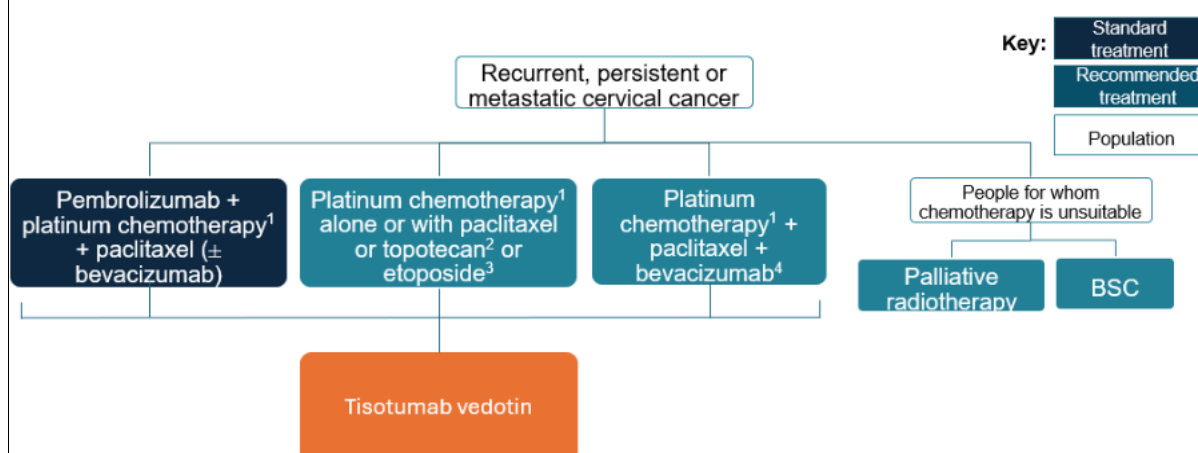
Notes: ¹Cisplatin or carboplatin. ²NICE recommends topotecan with cisplatin as an option for treating recurrent or stage 4B cervical cancer in people who have not previously received cisplatin (TA183), ³Source: Cancer Research UK and NHS chemotherapy protocol (indicated for small cell gynaecological cancers including those affecting the cervix, endometrium and ovaries). ⁴Bevacizumab with paclitaxel and platinum chemotherapy¹ available in routine commissioning for untreated recurrent or metastatic cervical cancer

Source: Adapted from NICE Public Committee Slides ACM1 - TA885²³.

Despite published guidance for r/m CC, there remains a significant unmet need in r/m CC for second-line treatments which are more effective than current therapies, which offer an alternative option to repeated chemotherapy exposure, and which are suitable for patients who have progressed on or after standard first-line pembrolizumab treatment (Figure 3).

Therefore, the proposed positioning of tisotumab vedotin is for the treatment of adult patients with r/m CC with disease progression on or after systemic therapy (Figure 4).

Figure 4: Proposed positioning of tisotumab vedotin for r/mCC in current treatment pathway



Abbreviations: BSC: best supportive care.

Notes: ¹Cisplatin or carboplatin. ²NICE recommends topotecan with cisplatin as an option for treating recurrent or stage 4B cervical cancer in people who have not previously received cisplatin (TA183), ³Source: Cancer Research UK and NHS chemotherapy protocol (indicated for small cell gynaecological cancers including those affecting the cervix, endometrium and ovaries). ⁴Bevacizumab with paclitaxel and platinum chemotherapy¹ available in routine commissioning for untreated recurrent or metastatic cervical cancer

Source: Adapted from NICE Public Committee Slides ACM1 - TA885²³.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Not applicable.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The active substance in Tivdak, tisotumab vedotin, is an antibody (a type of protein) combined with another substance known as MMAE (a chemotherapy medicine). The antibody first attaches to tissue factor (TF), a protein found on the surface of certain cancer cells, to enter these cells.

Once inside the cells, MMAE disrupts the cells' internal skeleton, causing cell death and helping to prevent the cancer from getting worse or spreading²⁴.

The summary of product characteristics from the European Medicines Agency for tisotumab vedotin is available here:

https://www.ema.europa.eu/en/documents/product-information/tivdak-epar-product-information_en.pdf

As mentioned, tisotumab vedotin is pending approval by the MHRA in the UK so the summary of product characteristics provided is from the European Medicines Agency.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, tisotumab vedotin is not intended to be used in combination with other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Tisotumab vedotin can only be obtained with a prescription. Treatment should be started and supervised by a doctor experienced in the use of cancer treatments²⁴.

Tisotumab vedotin is given by infusion (drip) into a vein over 30 minutes, every 3 weeks. This dosing schedule is less frequent than traditional chemotherapy options such as gemcitabine and paclitaxel, which is administered weekly. Treatment should be continued until the disease gets worse or the patient gets unacceptable side effects. The doctor may decide to reduce the dose or interrupt treatment if certain side effects occur. The recommended dose of tisotumab vedotin is 2 mg/kg (up to a maximum of 200mg)²⁴.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The table below summarises the two main clinical trials upon which the evidence for Tisotumab vedotin is based (InnovaTV 301 and InnovaTV 204):

Study	InnovaTV 301 (NCT04697628) ²⁵⁻²⁶	InnovaTV 204 (NCT03438396) ²⁷⁻²⁸
Study design	Phase 3, randomised, open-label study.	Phase 2, single-arm, global, multicentre study.
Population	Patients with r/mCC who have received 1 or 2 prior lines of systemic therapy.	Patients with previously treated r/mCC who experienced disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards).
Intervention(s)	Tisotumab vedotin (TIVDAK)	Tisotumab vedotin (TIVDAK)
Comparator	Investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed)	Not applicable
Number of patients	502 participants underwent randomisation.	101 participants.
Study completion date	Ongoing; expected completion date in May 2026.	August 2022.
Main Reported outcomes	Overall survival (OS) Progression-free survival (PFS) based on RECIST v1.1 Confirmed ORR based on RECIST v1.1 Time to response (TTR) DoR per RECIST v1.1 Adverse effects of treatment Health-related quality of life (HRQoL)	Overall response rate (ORR) PFS TTR Duration of response Adverse effects of treatment
Key Inclusion/ Exclusion Criteria (refer to section 2.3.1 in company submission for more detail)	Key inclusion criteria: • Age ≥18 years. • Recurrent or metastatic CC • Experienced disease progression during or after treatment with a chemotherapy, or platinum-based therapy (if eligible) • Received 1 or 2 prior therapy regimens for r/mCC • Measurable disease according to the Response	Key inclusion criteria: • Age ≥18 years. • Recurrent or metastatic CC • Experienced disease progression during or after treatment with a chemotherapy, or

	Evaluation Criteria in Solid Tumours (RECIST). • An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (assessed on a 5-point scale, with higher scores indicating greater disability) • Life expectancy ≥ 3 months Key exclusion criteria: • Patients with cancer that had specific features known as primary neuroendocrine, lymphoid, or sarcomatoid • Patients with serious bleeding problems, heart or blood vessel conditions/ risks	platinum-based therapy (if eligible) • Received ≤ 2 prior therapy regimens for r/mCC • Measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST). • An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (assessed on a 5-point scale, with higher scores indicating greater disability) • Life expectancy ≥ 3 months Key exclusion criteria: • Previously treated with drugs containing a substance called MMAE • Had radiation treatment within 21 days before starting the study drug • Patients with serious bleeding problems, active eye surface disease or a history of serious eye conditions • Have moderate to severe (Grade ≥ 2) nerve damage

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

InnovaTV 301:

Tisotumab vedotin was studied in a (Phase 3) clinical trial of 502 people with cervical cancer that has returned or has spread, and who had received chemotherapy that did not work or was no longer working.

In this trial (InnovaTV 301), about half of the patients were treated with tisotumab vedotin (N=253), and about half of the patients were treated with chemotherapy (N=249). The clinical effectiveness of tisotumab vedotin compared with chemotherapy is outlined below²⁶.

Overall survival:

During InnovaTV 301, tisotumab vedotin improved median overall survival compared to chemotherapy (11.5 months vs. 9.5 months), representing a 30% lower risk of death in patients who received tisotumab vedotin²⁶.

Progression-free survival:

The median progression-free survival was also significantly longer with tisotumab vedotin (4.2 months) than with chemotherapy (2.9 months)²⁶.

Objective response rate:

The confirmed objective response rate (ORR) was higher with tisotumab vedotin (17.8%) compared to chemotherapy (5.2%), which indicates a greater likelihood of tumor shrinkage²⁶.

InnovaTV 204:

Tisotumab vedotin was also studied in another (Phase 2) clinical trial of 101 people with r/m CC, and who had received chemotherapy that did not work or was no longer working. Results from this trial (InnovaTV 204) are outlined below²⁸.

Overall survival:

During InnovaTV 204, tisotumab vedotin demonstrated a median overall survival of 12.1 months²⁸.

Progression-free survival:

The median progression-free survival shown by tisotumab vedotin was 4.2 months²⁸.

Objective response rate:

The confirmed objective response rate (ORR) for tisotumab vedotin was 24%²⁸.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality-of-life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

All patients enrolled in the InnovaTV 301 study (n=502) had the option to complete a quality-of-life (QoL) survey (called the EORTC QLQ-C30) at the start. By the fifth treatment cycle, patients who were still in the study and receiving study treatment completed the survey again; 93% of patients remained in the tisotumab vedotin group and 88.6% of patients remained in the chemotherapy group²⁶.

Patient QoL stayed mostly the same in both groups from the trial start to fifth treatment cycle, with only small changes in scores (less than 10 points on the EORTC QLQ-C30 QoL scales). The average change was -1.1 in the tisotumab vedotin group and -5.0 in the chemotherapy group, with the chemotherapy group showing a slight trend toward declining QoL. In addition, more patients in the tisotumab vedotin group reported a noticeable improvement in their QoL (13.9%) compared to the chemotherapy group (3.4%)²⁶.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The most common side effects (which may affect more than 1 in 10 people) of tisotumab vedotin include²⁴:

- Decreased red blood cell counts
- Numbness or tingling in your hands or feet
- Eye problems (conjunctival disorders)
- Nausea
- Tiredness
- Changes in liver function blood tests
- Nosebleed
- Hair loss (alopecia)
- Bleeding (hemorrhage)

Serious side effects of tisotumab vedotin may include²⁴:

Eye problems are common with tisotumab vedotin and can be severe. Tisotumab vedotin can cause changes to the surface of your eye that can lead to dry eyes, eye redness, eye irritation, corneal ulcers, blurred vision, and severe vision loss.

Nerve problems (peripheral neuropathy) are common with tisotumab vedotin and can be serious. Patients are advised to tell their healthcare provider right away if they have new or worsening numbness or tingling in their hands or feet or muscle weakness.

Bleeding problems (hemorrhage) are common with tisotumab vedotin and can be serious. Patients are advised to tell their healthcare provider or get medical help right away if they have signs or symptoms of bleeding during treatment with tisotumab vedotin, including blood in their stools or black stools (looks like tar), blood in their urine, cough up or vomit blood, unusual vaginal bleeding, or any unusual or heavy bleeding.

Lung problems. Tisotumab vedotin may cause severe or life-threatening inflammation of the lungs that can lead to death. Patients are advised to tell their healthcare provider right away if they have new or worsening symptoms, including trouble breathing, shortness of breath, or cough.

Severe skin reactions. Tisotumab vedotin may cause severe or life-threatening skin reactions that can lead to death. Patients are advised to tell their healthcare provider or get medical help right away if they have signs or symptoms of a severe skin reaction during treatment with tisotumab vedotin, including:

- Skin reactions that look like rings (target lesions)
- Rash or itching that continues to get worse
- Blistering or peeling of the skin
- Painful sores or ulcers in their mouth, nose, throat, or genital area
- Fever or flu-like symptoms
- Swollen lymph nodes

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There are few treatment choices for patients with r/m CC, of which tisotumab vedotin offers an alternative option for these patients. Unlike traditional chemotherapy, tisotumab vedotin is an antibody drug conjugate, a different type of drug which is intended to target cancer cells whilst sparing healthy cells.

The benefits of tisotumab vedotin were evaluated in a study involving 502 patients with cervical cancer which had come back or was metastatic, after one or two systemic treatments, including one chemotherapy. In this study, tisotumab vedotin was compared with chemotherapy, as chosen by the doctor for each patient. Patients who received tisotumab vedotin lived on average for 11.5 months while those who received chemotherapy lived for an average of 9.5 months. In addition, patients who received tisotumab vedotin lived on average for around 4 months without their disease getting worse, compared to around 3 months for those given chemotherapy²⁵⁻²⁶.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Regarding safety, tisotumab vedotin's side effects differ from those seen with chemotherapy. They can be serious and life-threatening, and include:

- Eye problems, which can be common and severe.
- Nerve problems known as peripheral neuropathy are common and can be serious.
- Bleeding problems are common and can be serious.

Of note, the European Medicines Agency (EMA) (regulatory body in Europe) have considered the side effects of tisotumab vedotin to be manageable, with measures in place to minimise the risks. Therefore, the EMA have concluded tisotumab vedotin's benefits to be greater than its risks and have authorised its use in the European Union²⁴.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Genmab, the manufacturer of TIVDAK® (tisotumab vedotin) built an economic model in Microsoft®Excel® to assess the cost effectiveness of TIVDAK® vs. physician's choice of chemotherapy in adult patients with r/m CC who had progressed during or after systemic chemotherapy doublet or platinum-based therapy. The model is informed by efficacy observed from the InnovaTV 301 trial²⁶, which is applied to the target population in the UK. Long term disease progression is modelled over a lifetime (30 year) horizon.

How the model reflects the condition:

The economic model structure comprises three health states, progression free (PF) disease, progressive disease (PD) and death. These health states are key markers of disease status which capture the consequences of disease progression. The purpose of the health states is to model the treatment response via improvements in duration of PF disease and overall survival (OS) in a response to TIVDAK® or chemotherapy.

The model structure aims to capture the value of TIVDAK® through the inclusion of PF and PD disease health states, tracing the patient's journey for the rest of the patient's life, and capturing improvements in disease status and the associated health-related quality of life (HRQoL) (referred to in cost-effectiveness models as utility) and cost inputs. Furthermore, the side effects associated with TIVDAK® vs. chemotherapy treatment are captured through a reduction in HRQoL decrements (disutilities) and their associated costs.

Modelling how much a treatment extends life:

Clinical parameters in this model were obtained from the innovaTV 301 trial for TV and chemotherapy²⁶. Disease progression in the model were estimated using individual patient data for time to progression (TTP), time from PF to death, and post progression survival (PPS). Progression from PF to PD was informed by TTP data in each arm. Transition from PF to death was informed by time from PF to death in each arm. Transition from PD to death was informed by pooled PPS data of both arms.

Statistical models were fitted to TTP and time from PF to death separately for each treatment arm and to pooled PPS data from both arms. The pooled approach for PPS was used beyond 12 months, while treatment specific observed overall survival (OS) was applied during the first 12 months.

Benefits from treatment with TIVDAK® versus chemotherapy are captured via a difference in the proportion of individuals experiencing progression free and overall survival over time. Additional benefits are reflected in the difference in the treatment related AEs.

Modelling how much a treatment improves quality of life:

HRQoL data is incorporated into the model by assigning different utility/ quality values for each health state and adjusting that utility for the age of the patients and taking into consideration the disutility due to any side effects of treatment. The health-state utilities were obtained from a questionnaire that was administered in the innovaTV 301 trial (data cutoff date: January 2024) in

the base-case analysis²⁶ and age-related utility adjustment and AE disutilities were based on published literature²⁹⁻³¹.

Improvements in HRQoL associated with TIVDAK[®] are modelled through, improvements associated with the transition through the PF and PD health states and reduction in disutilities associated with adverse events related to either treatment (TIVDAK[®] vs. chemotherapy).

Modelling how the costs of treatment differ with the new treatment:

The increase in PF disease from treatment with TIVDAK[®] results in a longer duration of treatment, which increases both pre-progression treatment costs and disease management costs. Although subsequent post progression treatment costs decrease due to increases in PF survival and OS, there is an increase in post progression disease management costs. Lastly, there is a reduction of costs associated with AE and terminal care (related to improved OS).

Administration cost for TIVDAK[®] does not differ compared to existing treatments except paclitaxel which is administered as a complex weekly chemotherapy regimen involving prolonged treatment infusion.

Uncertainty:

In the model an equal post-progression risk of mortality was assumed across treatment arms. This assumption was both data-driven and clinically validated. Clinical experts confirmed that post-progression survival is unlikely to differ significantly between trial arms. This assumption was necessary due to limitations associated with small number of patients at the tails of the survival curves for the trial.

A series of scenario analyses were conducted using alternative assumption and data. Treatment efficacy-related scenarios had the most substantial impact on the model outcomes/cost-effectiveness estimates.

Additional factors:

A case for inclusion of a severity modifier has been made due to the considerable unmet need in the population being modelled.

Based on a 100% female population, starting age of 51, total QALYs of 0.6 for the current treatment population vs. an expected total QALYs of 14.45 for the general population. This results in a 96% relative and 13.85 QALY shortfall. As such an application of a 1.7x QALY modifier for TIVDAK[®] vs. chemotherapy is warranted.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Tisotumab vedotin is new and unique treatment known as an antibody-drug conjugate (ADC) which targets a protein called tissue factor found on cancer cells. It works by delivering a toxic agent directly to cancerous cells, helping reduce damage to healthy cells, compared to traditional chemotherapy options which work systemically (across the whole body).

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues [here](#)

In England, cervical cancer incidence is 65% higher among women in the most deprived quintile compared to those in the least deprived³². CC screening rates are known to be lower among women in deprived populations and while studies examining HPV vaccine uptake by ethnicity and/or socioeconomic status are scarce, evidence suggests uptake is lower among both more deprived, and non-white ethnic populations³³⁻³⁵.

These disparities highlight the inequalities which exist in CC patients, which should be taken into consideration during the evaluation of tisotumab vedotin.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

European Medicines Agency website:

<https://www.ema.europa.eu/en/medicines/human/EPAR/tivdak>

Summary of Product Characteristics: https://www.ema.europa.eu/en/documents/product-information/tivdak-epar-product-information_en.pdf

InnovaTV301 trial & publication (open access):

- <https://www.nejm.org/doi/pdf/10.1056/NEJMoa2313811>
- <https://clinicaltrials.gov/study/NCT04697628>

InnovaTV204 trial & publication (restricted access):

- [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(21\)00056-5/abstract](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00056-5/abstract)
- <https://clinicaltrials.gov/study/NCT03438396>

NICE guidance: <https://cks.nice.org.uk/topics/cervical-cancer-hpv/management/management/>

Educational materials:

- Patient info: <https://patient.info/cancer/gynaecological-cancer/cervical-cancer>
- Cancer Research UK: <https://www.cancerresearchuk.org/about-cancer/cervical-cancer>
- NHS: <https://www.nhs.uk/conditions/cervical-cancer/treatment/>
- Macmillan Cancer Support: <https://www.macmillan.org.uk/cancer-information-and-support/cervical-cancer>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Antibody drug conjugate** – Targeted cancer therapy which delivers chemotherapy directly to cancerous cells.
- **European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30** – Widely used outcome measure for assessing the quality of life in clinical trials involving patients with cancer (includes evaluation of common cancer symptoms such as fatigue, pain and nausea along as well as physical and emotional functioning).
- **Hemorrhage** – Blood loss.
- **Overall response rate** – Proportion of patients in a clinical trial who have a partial or complete response to a specific treatment within a certain time period.
- **Overall survival** – Time from patient diagnosis or start of treatment until death from any cause.
- **Peripheral neuropathy** – Nerve damage.
- **Progression-free survival** – The length of time during and after cancer treatment that a patient lives with the disease, without it getting worse.
- **Recurrent/metastatic cervical cancer** – Cervical cancer which has returned (recurrent) or has spread to other parts of the body (metastatic).

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. National Cancer Institute. Cervical Cancer Treatment (PDQ®)–Health Professional Version - National Cancer Institute [Internet]. www.cancer.gov. 2020. Available from: <https://www.cancer.gov/types/cervical/hp/cervical-treatment-pdq>
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professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence#heading-Zero

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- recurrent or metastatic cervical cancer: A community oncology-based analysis. *Gynecologic Oncology*. 2021;161(2):422-8.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification Response

October 2025

File name	Version	Contains confidential information	Date
ID3753_Tisotumab Vedotin EAG Clarification Response_FINAL17102025 [CON]	1.0	Yes	17-October-2025

Section A: Clarification on effectiveness data

Clinical pathway

A1. Priority question: Please clarify if the company is positioning tisotumab vedotin as a second-line treatment option, or is positioning it as a second- and third-line therapy option, or as a second-line, third-line and later therapy option in people with recurrent or metastatic cervical cancer that has progressed on or after systemic treatment.

The company is positioning tisotumab vedotin as a second- and third-line therapy option for patients with recurrent or metastatic cervical cancer (r/m CC) that has progressed on or after prior systemic treatment.

This positioning reflects the anticipated full marketing authorisation and is consistent with the InnovaTV 301 trial population—a randomized, open-label, Phase 3 study comparing tisotumab vedotin with investigator's choice chemotherapy in second - and third-line r/m CC. In InnovaTV 301, 61.4% of participants had received one prior line and 38.4% had received two prior lines of systemic therapy before enrolment (1,2).

As outlined in the clinical submission, clinical experts confirmed that immuno-oncology therapies remain the standard of care in first-line r/m CC, supported by widespread PD-L1 testing and high positivity rates (50–70%) (3,4). However, there remains a substantial unmet need for effective and tolerable therapies in the second- and later-line settings for patients who progress following first-line immunochemotherapy.

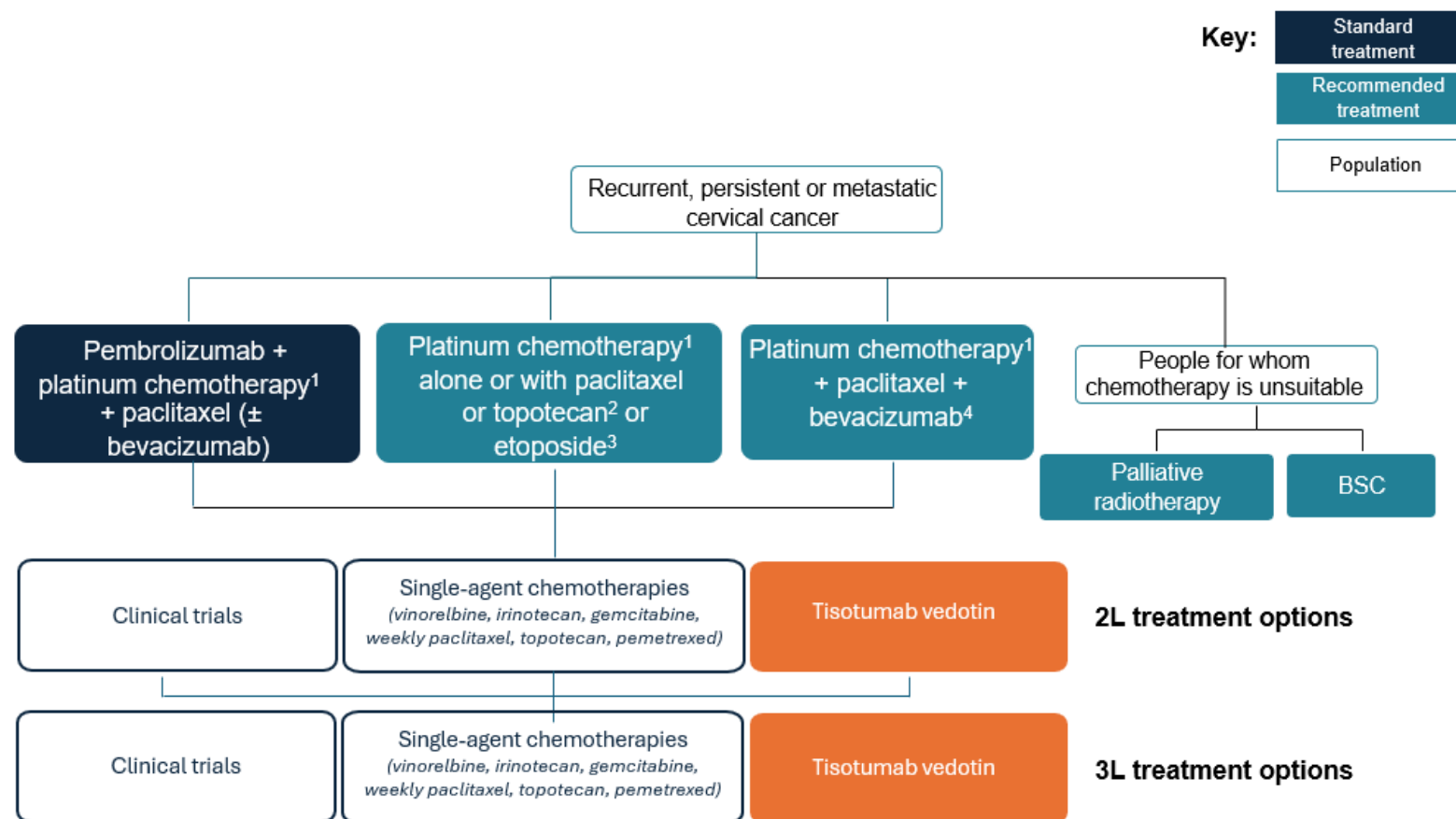
Tisotumab vedotin therefore offers an evidence-based treatment option in the second- and third-line settings, addressing a population with limited therapeutic alternatives and poor outcomes with current therapies.

A2. Priority question: Please replicate company submission (1) Figure 10 here and add a box (or boxes) to show the second-line therapy and later treatment options that are currently used in clinical practice to treat patients with

recurrent or metastatic cervical cancer that has progressed on or after systemic treatment.

An updated version of Figure 10 is outlined below in Figure 1. The BGCS guidelines for r/m CC (2021) do not make any specific recommendations for second-line therapy and later line options for patients with r/m CC that has progressed on or after systemic treatment (2). Treatment options for these patients may include single-agent chemotherapies such as vinorelbine, irinotecan, gemcitabine, paclitaxel, topotecan or pemetrexed, and clinical trials if available (Figure 1).

Figure 1: Proposed positioning of tisotumab vedotin as a 2L or 3L option for treating r/m CC in patients with disease progression on or after systemic therapy (Figure 10 in CS document)



Abbreviations: BSC: best supportive care.

Notes: ¹Cisplatin or carboplatin. ²NICE recommends topotecan with cisplatin as an option for treating recurrent or stage 4B cervical cancer in people who have not previously received cisplatin (TA183). ³Source: Cancer Research UK and NHS chemotherapy protocol (indicated for small cell gynaecological cancers including those affecting the cervix, endometrium and ovaries). ⁴Bevacizumab with paclitaxel and platinum chemotherapy available in routine commissioning for untreated recurrent or metastatic cervical cancer

Source: Adapted from NICE Public Committee Slides ACM1 - TA885 (Committee Slide 4) and BGCS guidelines (2021) (2, 3).

A3. Priority question: Thank you for providing the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) with the CS. Is a draft version of the Medicines and Healthcare products Regulatory Agency (MHRA) SmPC available? If so, please provide a copy.

The draft UK SmPC submitted with the initial Marketing Authorisation Application and currently under MHRA review is provided in PDF format alongside the company's clarification response. MHRA approval of tisotumab vedotin is anticipated in [REDACTED].

Company's systematic literature review and approach to evidence synthesis

A4. CS Appendix B 1.1 Table 1: What was the rationale for limiting the inclusion of studies to those published since 2003 and for excluding studies with fewer than 10 patients with the eligible cervical cancer histologies?

The cut-off date of 2003 was selected to reflect the establishment of cisplatin-based doublet regimens as the first-line standard of care for recurrent or metastatic cervical cancer from 2004 onwards, as well as improvements in supportive care and treatment practices (4). Studies published before 2003 were therefore considered less relevant to current clinical practice.

The exclusion of studies with fewer than 10 eligible patients aimed to maintain the robustness and generalisability of the evidence base. Given the broad inclusion criteria regarding study design, this threshold helped to minimise the influence of case reports or very small studies, which provide limited insight into the effectiveness and safety of the interventions assessed.

A5. How was data extraction and critical appraisal carried out for the clinical effectiveness review described in Appendix B (i.e. were these tasks conducted by two or more reviewers independently?).

The company would like to clarify that data extraction and critical appraisal described in CS Appendix B were conducted by one reviewer, with all data independently checked by a second reviewer to ensure accuracy and consistency.

A6. Priority question: CS section 2.5 and CS Appendix B, section 1.3: Please clarify which tools were used to carry out the critical appraisals of the InnovaTV 301 and InnovaTV 204 trials. Please also provide references for the tools used.

The company would like to clarify that, as described in the CS and Appendix B, the Cochrane Risk of Bias (ROB 1) tool was used to carry out the critical appraisals of the InnovaTV 301 and InnovaTV 204 randomised controlled trials (5). For non-randomised studies, the appropriate CRD checklist was applied according to study design, which in this case included case series for the other Innova trials identified (6).

A7. Priority question: CS Table 1 states that clinicians indicated that “there are no data supporting a difference in efficacy between the trial comparators and Q1W paclitaxel” (CS Table 1). Please clarify if this means that a) studies have been conducted and have not found a difference, or if this means that b) no or limited studies have been conducted.

This statement refers to b) - a limited number of studies have been conducted which do not provide any evidence of differentiated efficacy among the single-agent chemotherapies used in InnovaTV 301 and/ or Q1W paclitaxel. Please refer to Question A8 below for further information.

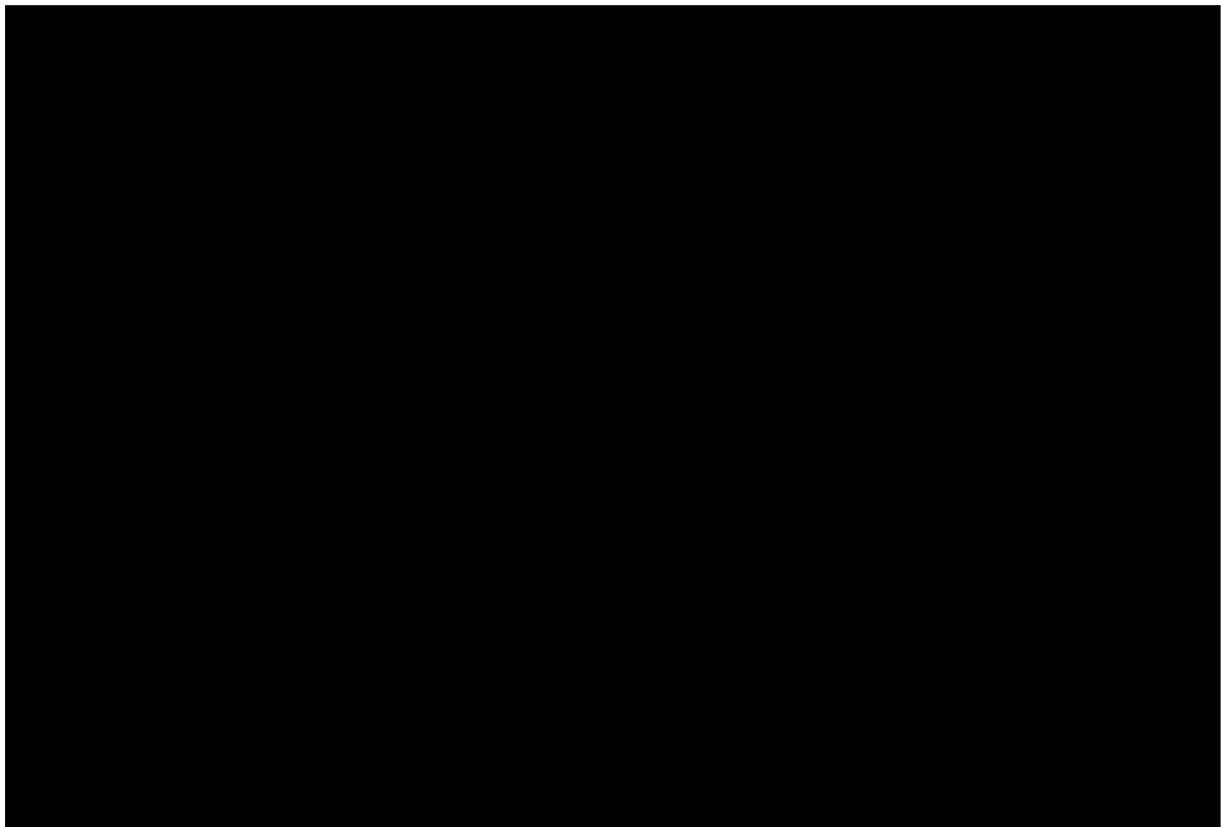
A8. Priority question: CS section 1.3.4.1: Thank you for highlighting reference 20 in the company submission, which the CS states shows that paclitaxel has similar efficacy to the chemotherapies used in the comparator arm of the InnovaTV 301 trial. Is there any additional evidence available to support an assumption that a) the single-agent therapies used in the investigator’s choice of chemotherapy arm in the InnovaTV 301 trial (pemetrexed, gemcitabine, topotecan, irinotecan and vinorelbine) have similar efficacy, and that b) paclitaxel has similar efficacy to these therapies (e.g. from systematic reviews, indirect treatment comparisons or network meta-analyses in the population of people with recurrent or metastatic cervical cancer that has progressed on or after systematic treatment)? If evidence is available, please briefly summarise it and provide copies of any references you cite to support your summary.

The company would like to clarify that there is no published meta-analysis or pooled analysis directly comparing the efficacy of the single-agent chemotherapies (pemetrexed, gemcitabine, topotecan, irinotecan, and vinorelbine) used in the investigator's choice chemotherapy arm of InnovaTV 301.

However, evidence from InnovaTV 301 demonstrates that the 95% confidence intervals for both progression-free survival (PFS) and overall survival (OS) for these agents overlapped, indicating no meaningful differences in efficacy among them (

Figure 2) (7).

Figure 2: Subgroup analyses of PFS (follow-up analysis, Jan 2024)



Consistent findings are observed in the published literature, as summarised in Table 5 of the company submission (replicated as Table 1 below), which further supports that the efficacy of these agents is broadly comparable in patients with recurrent or metastatic cervical cancer previously treated with systemic therapy.

Table 1: Efficacy of single-agent chemotherapies in 2L treatment (Table 5 of CS)

Study and Treatment Regimen (All Comer Populations)			Survival Outcomes Median (months)	
Treatment	Study	N	PFS	OS
Investigator's choice ^a	Tewari 2022 (8)	304	2.9	8.5
Docetaxel	Garcia 2007 (9)	23	3.8	7.0
Erlotinib	Schilder 2009 (10)	25	1.87	4.96
Gemcitabine	Schilder 2005 (11)	22	2.1	6.5
Irinotecan	Verschraegen 1997 (12)	42	6.4	NR
Liposomal doxorubicin	Rose 2006 (13)	27	3.2	8.9
Nab-paclitaxel	Alberts 2012 (14)	35	5.0	9.4
Pemetrexed	Miller 2008 (15)	27	3.1	7.4
Topotecan	Coronel 2009 (16)	18	3.5	7.0
Vinorelbine	Muggia 2004 (17)	44	NR[^]	NR[^]

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response.

Notes: ^aIncludes investigator's choice of single-agent chemotherapy (pemetrexed [37%], topotecan [7%], irinotecan [6%], gemcitabine [40%] or vinorelbine [11%]). [^]PFS and OS were not reported for vinorelbine in Muggia (2004); the study follow-up time is also not reported.

Sources: Detailed in table above.

In addition, data from McLachlan et al. (2017) (Table 2) and Homesley et al. (2008) indicate that weekly (Q1W) paclitaxel demonstrates similar efficacy to these single-agent chemotherapies in this population, supporting the assumption of comparable clinical effectiveness (18, 19).

Table 2: Second-line systemic treatments

	Patients (n=53) n (%)	Partial response (%)	Stable disease (%)
Weekly paclitaxel	15 (28.3)	1 (6.7)	8 (53.3)
Carboplatin-based chemotherapy (carboplatin+paclitaxel)	12 (22.6)	3 (25)	8 (61.5)
Targeted agents monotherapy within clinical trials	12 (22.6)	1 (8.3)	3 (25)
Docetaxel-based regimens (with targeted agent, or gemcitabine, or capecitabine)	8 (15.1)	2 (25)	3 (37.5)
Topotecan	5 (9.4)	0	0
Gemcitabine	1 (1.9)	0	0

Source: McLachlan et al. (2016) (18).

A9. Priority question: We note that the document entitled ‘Data on File. YHEC Updated Clinical SLR Report (2025)’ that was provided with the CS

Please supply a copy of the full systematic review report for the wider review.

Please find the full systematic literature review (SLR) report provided in a separate document (1).

The company notes that minor clarifications and corrections have been made to the SLR report since submission, resulting in small updates to the PRISMA flow diagram. These updates account for the discrepancy between the PRISMA diagrams presented across versions.

- Two recent literature updates were conducted in rapid succession. During consolidation, one study identified in the latest update was incorrectly attributed to the previous update. As a result, the number of studies in the earlier version has been updated from 56 to 55, and the number of new studies from 3 to 4. The total number of new reports remains unchanged, as this was correctly reflected in the study list but not in the count.
- A typographical correction was also made in the right-hand column of the PRISMA diagram, where the non-database total was updated from 97 to 96 to align with the corresponding table.

A10. CS section 2.10 briefly states why an indirect treatment comparison was not conducted. Did the company consider and explore whether there might be other trials or real-world evidence studies available that might be representative of standard care received in the NHS that could have been compared to the InnovaTV 301 trial tisotumab vedotin arm using population matching techniques? Please provide details of any available studies that could potentially have been used for this purpose. Please also summarise

your view on the appropriateness of this as a potential evidence synthesis approach for this appraisal.

As outlined in the CS, YHEC have reported the systematic literature review (SLR) which investigated the clinical effects, safety, and patient-reported outcomes of treatment for previously treated, recurrent or metastatic cervical cancer. This SLR was comprehensive, utilising broad PICO criteria, with inclusion of both randomised controlled and single-arm studies.

The review did not identify any RCTs comparing different single agent chemotherapies. Furthermore, studies identified in the review are heterogenous in their patient baseline characteristics, where reported, and in terms of intervention, with only very small numbers of studies reporting each intervention with small sample sizes. The SLR did identify a single arm study which assessed the treatment of 20 cervical cancer patients with weekly paclitaxel. Baseline characteristics were not reported, hence the inability to assess similarity between the patients in Homesley et al 2008 and patients in InnovaTV 301, which would be required to conduct an unanchored indirect comparison. A copy of this study has been included in the reference pack for this clarification response (19).

The company do not view use of an indirect treatment comparison (ITC) as an appropriate evidence synthesis approach for this appraisal since no studies were identified in the SLR to sufficiently support development of an ITC.

InnovaTV 301 trial

A11. Priority question: Was disease progression only assessed by the investigator? Did an independent review committee (IRC) verify progressive disease? If results for objective response rate (2) and/or progression-free survival (PFS) outcomes are available as assessed by the IRC, please provide these.

Progression was assessed by investigator per RECIST v1.1 only. Verification of progression by the IRC was not performed, therefore results for ORR and PFS as assessed per independent review committee are not available (20, 21).

A12. Priority question: How frequently between baseline and cycle 5 was health-related quality of life measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC-QLQ-C30) and the EQ-5D (descriptive system and visual analogue scale)? Was health-related quality of life measured beyond cycle 5?

EORTC-QLQ-C30 and EQ-5D were performed at baseline (≤ 28 days prior to C1D1), at Day 1 of each cycle, 30 days after last dose, and 60 days after last dose (Table 3 & Table 4) (20).

Health-related quality of life (HRQoL) was measured beyond cycle 5 by the EORTC-QLQ-C30 and EQ-5D questionnaires. Please refer to the InnovaTV 301 CSR Tables, Figures & Listings document provided as data on file in the company submission for this HRQoL data beyond cycle 5 (21):

- Table 14.10.5: Summary of EORTC QLQ-C30 Scores
- Figure 14.10.1: EQ-5D of Anxiety/ Depression
- Figure 14.10.2: EQ-5D-5L of Mobility
- Figure 14.10.3: EQ-5D-5L of Pain/ Discomfort
- Figure 14.10.4: EQ-5D-5L of Usual Activities
- Figure 14.10.5: EQ-5D-5L of Self Care
- Table 14.10.8: Summary of EQ VAS Scores

Table 3: Visit assessment schedule for the tisotumab vedotin arm

	Notes	Screening	Cycle 1-X (1 cycle = 21 days)	End of treatment visit	Survival follow-up	Unscheduled visit
Visit window		≤ 28d Prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Health-related quality of life EQ-5D-5L index EQ-5D VAS EORTC-QLQC30 EORTC-QLQCX24	Strongly recommended to complete prior to other assessments.	<7 days of C1D1	X ^a	X ^b	X ^b	

Notes: ^aEORTC-QLQ-CX24 should be performed on D1 of every cycle for the first 20 cycles only. ^bEQ-5D-5L and EQ-5D VAS only.

Source: Data on File. InnovaTV 301 trial protocol (20).

Table 4: Visit assessment schedule for the chemotherapy arm

	Notes	Screening	Cycle 1-X (1 cycle = 21 days)	End of treatment visit	Survival follow-up	Unscheduled visit
		≤ 28d Prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window			±3d	±5d	±7d	
Health-related quality of life EQ-5D-5L index EQ-5D VAS EORTC-QLQC30 EORTC-QLQCX24	Strongly recommended to complete prior to other assessments.	<7 days of C1D1	X ^a	X ^b	X ^b	

Notes: ^aEORTC-QLQ-CX24 should be performed on D1 of every cycle for the first 20 cycles only. In participants who receive irinotecan, EORTC-QLQ-CX24 should be performed on D1 for the first 10 cycles only. ^bEQ-5D-5L and EQ-5D VAS only.

Source: Data on File. InnovaTV 301 trial protocol (20).

InnovaTV 301 trial statistical analysis

A13. CS Table 17 states that OS, PFS and ORR were hierarchically tested. Please provide details of the hierarchical testing procedure and clarify the statistical significance thresholds that were used to determine the statistical significance of the results for each of these outcomes when analysed at the 24th July 2023 and January 2024 data cut-offs.

The protocol specified testing procedure to control for multiplicity is outlined below. This information is available from the InnovaTV 301 Statistical Analysis Plan which is provided in PDF format alongside the company's clarification response (22).

Hypothesis testing was performed on the primary endpoint OS and two key secondary efficacy endpoints, PFS and ORR, while controlling the overall Type I error rate of 5% (2-sided) using a hierarchical approach with group sequential testing (Maurer 2013).

The endpoints were tested in the hierarchical order as follows: OS first, then PFS, and finally ORR. Hypothesis testing started with OS and only proceeded to the hypothesis testing on the next endpoint, PFS, when the efficacy boundary was crossed for OS at the first time (IA or FA). Similarly, the hypothesis testing on ORR only occurred after the efficacy boundary was crossed for PFS.

For OS, the Lan DeMets (O'Brien-Fleming) spending function was used (Lan 1983). With approximately [REDACTED] and [REDACTED] events estimated to occur at the IA and FA respectively, the OS was tested at a 2-sided nominal [REDACTED] level at the IA/FA corresponding to a HR boundary of [REDACTED].

For PFS, the Lan DeMets (Pocock) spending function was used (Lan 1983). With approximately [REDACTED] and [REDACTED] events estimated to occur at the OS IA and FA respectively, the PFS was tested at a 2-sided nominal [REDACTED] level at the IA/FA corresponding to an HR boundary of [REDACTED].

For ORR, it was estimated that all [REDACTED] participants were fully randomised into the study and have at least two post-baseline scans by the OS IA at 27 months. The ORR was tested at 2-sided 5% level corresponding to an odds ratio boundary of [REDACTED].

For hypothesis testing on all endpoints, the actual nominal significance level applied was adjusted to reflect the actual number of events realised at the time of the IA/FA using the specified spending function for each endpoint. The overall type 1 error for the 3 key endpoints, OS, PFS, and ORR, was controlled at a 2-sided 5% level using the approach of Maurer and Bretz (Maurer 2013).

The actual thresholds for significance and observed p-values at the 24 July 2023 DCO were:

Endpoint	P-value threshold for significance (2-sided 5% level)	Observed p-value
OS	██████████	██████████
PFS	██████████	██████████
ORR	██████████	██████████

Since the efficacy bounds were all crossed at the interim analysis (DCO 24 July 2023), the p-values reported at the Jan 2024 DCO have no strict interpretation.

A14. CS Table 17: Please describe the missing data imputation rules that were used for imputing the missing adverse event dates and missing subsequent cancer-related therapy start dates.

Missing imputation rules used are outlined below for InnovaTV 301. This information is available from the InnovaTV 301 Statistical Analysis Plan which is provided in PDF format alongside the company's clarification response (22).

IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

For an adverse event with a partial start or end date, if it can be determined that the event occurred prior to the date of first dose of study treatment, the partial date will not be imputed; Otherwise, the partial date will be imputed using the rules described below. AE start dates should be imputed before imputation of AE condition end date in all cases.

Incomplete AE Start Date:

AE day only is missing

- If the month/year is the same as the month/year of first dose of any study treatment, then AE start date will be imputed as the first dose date of any study treatment.
- If the month/year is after the month/year of first dose of any study treatment, then AE start date will be imputed as the first day of the month.

AE day and month are missing

- If the year is the same as the year of first dose of any study treatment, then AE start date will be imputed as the first dose date of any study treatment.
- If the year is after the year of first dose of any study treatment, then AE start date will be imputed as January 1st.

AE day, month and year are missing

- AE start date will be imputed as the first dose date of any study treatment.

If AE condition end date is not missing, and the imputed start date is after the end date, the start date will be set to the AE condition end date.

Incomplete AE End Date:

- If AE outcome is “not recovered/resolved”, “unknown”, or blank, then AE condition end date will not be imputed.
- If AE outcome is “recovering/resolving”, “recovered/resolved”, “recovered/resolved with sequelae”, or “fatal”, then apply the following:

AE day only is missing

- AE condition end date will be imputed as the minimum of (death date, DCO date or data extraction date, last day of the end date month/year, end-of-study (EOS) date)

AE day and month are missing

- If the year is equal to the year of the last dose date, then AE condition end date will be imputed as the minimum of (last dose date + 30, death date, DCO date or data extraction date, December 31st of the end date year, EOS date).

- If the year is not equal to the year of the last dose date, then AE condition end date will be imputed as the minimum of (death date, DCO date or data extraction date, December 31st of the end date year, EOS date).

AE day, month and year are missing

- AE condition end date will not be imputed.

Within a single record, if the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

IMPUTATION OF PARTIAL MISSING DATES FOR SUBSEQUENT CANCER-RELATED THERAPY

Subsequent anticancer therapy start date will be imputed:

- If both month and year are present and only day is missing.
- If the year of the subsequent anticancer therapy start date is the same as the year of the EOT date.
- If the month of subsequent anticancer therapy start date is the same as the month of the EOT date, then its start date will be imputed as the EOT date.
- If the month of the subsequent anticancer therapy start date is later than the month of the EOT date, then its start date will be imputed as the first day of the month.
- If the month of the subsequent anticancer therapy start date is earlier than the month of the EOT date, then the subsequent anticancer therapy start date will be imputed as the last day of the month.

If the year of the subsequent anticancer therapy start date is later than the year of the EOT date, then the subsequent anticancer therapy start date will be imputed as the first day of the month.

If the EOT date is missing, then the EOT date will be EOS date or 30 days after the last dose of any study drug, whichever is earlier.

A15. Please clarify the stratification variables included in the primary and ad-hoc analyses (dated July 2023 and January 2024, respectively) of OS and PFS (i.e. from which the results presented in CS section 2.6.1 were generated).

Were these pre-specified and the same as the randomisation stratification factors? If the stratification variables used in the analyses that generated the results presented in CS section 2.6.1 differ to those pre-specified, please explain why.

The primary analyses on efficacy endpoints were analysed using the ITT analysis set, and were stratified by ECOG, prior bevacizumab, and prior anti-PD-[L]1 therapy with values as employed in the randomisation. The stratification factor of region was not included in the stratified primary analyses to avoid problems with sparse strata. The stratification factors and their use in the analyses were all pre-specified (22). Of note, these stratification variables were the same for the primary (July 2023) and follow-up (January 2024) data cut-off analyses.

A16. Were sensitivity analyses carried out for any of the outcomes at either the 24th July 2023 and January 2024 data cut-off analyses, e.g. to test the impact of post-progression cancer therapy on OS, or to test the impact of missing data? If so, please provide details of these analyses and report their results.

Details on any sensitivity analyses carried out during the July 2023 data cut-off analysis are outlined below (21). Sensitivity analyses were not performed for the January 2024 data cut-off analysis.

Sensitivity analyses for OS

A summary of the sensitivity analyses for OS is presented in **Figure 3**. Sensitivity analyses for OS included the following (21):

1. **Unstratified Analysis (Figure 4):** OS analysis by unstratified log-rank test to compare the treatment arms. Additionally, an unstratified Cox regression model was to be used to estimate the hazard ratio and the corresponding 95% CI for the treatment effect. The same censoring method as for the primary analysis of OS was used.
2. **Initiation of Subsequent Cancer-Related Therapy (Figure 5):** Starting subsequent cancer-related therapy was likely to bias the analyses of OS, more specifically, may have underestimated OS comparison when the distribution of subsequent therapies was imbalanced between the 2 arms. To reduce such bias, the following OS sensitivity analysis was planned: Inverse probability of censoring weights method (Robins, 2000). Subjects

who took subsequent therapy were censored at the time of sequent cancer-related therapy, but subjects were weighted according to their probability to have taken subsequent therapy.

Figure 3: Summary of Sensitivity Analyses of OS ITT Analysis Set (July 2023)

	Hazard Ratio ^a (95% CI)
Sensitivity analysis 1	0.71 (0.55, 0.90)
Sensitivity analysis 3 ^b	0.65 (0.48, 0.88)

Notes: a. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model.
b. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation, except for sensitivity analysis 1 (do not use stratified analysis) and sensitivity analysis 2 (use eCRF defined strata).
Sensitivity Analysis 1 (Unstratified Analysis): OS analysis use unstratified log-rank test and unstratified cox regression model.
Sensitivity Analysis 3 (Initiation of subsequent cancer-related Therapy): using Inverse probability of censoring weights (IPCW) method, subjects are weighted according to their probability to take subsequent therapy. Subjects who took subsequent therapy will be censored at the time of subsequent cancer-related therapy.
Only applicable sensitivity analysis are presented.
Source: Data on File. Table 14.3.3.3 InnovaTV 301 CSR (21).

Figure 4: Summary of OS Sensitivity 1 (Unstratified Analysis) ITT Analysis Set (July 2023)



Notes: a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.
Source: Data on File. Table 14.3.3.4 InnovaTV 301 CSR (21).

Figure 5: Summary of OS Sensitivity 3 (Initiation of Subsequent Cancer-Related Therapy) ITT Analysis Set (July 2023)

	Tisotumab Vedotin (N=253)	Chemotherapy ^a (N=249)
Number of deaths, n (%)	62 (24.5)	78 (31.3)
Stratified hazard ratio ^{b,c} (95% C.I.)	0.65 (0.48, 0.88)	
Median OS (months) (95% C.I.) ^d	21.3 (9.5, -)	10.7 (7.2, 11.7)
Q1, Q3	6.8, -	4.6, -
Min, Max ^e	0.1+, 22.8+	0.0+, 20.9+

Notes: a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model using Inverse probability of censoring weights (IPCW).

c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.

d. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

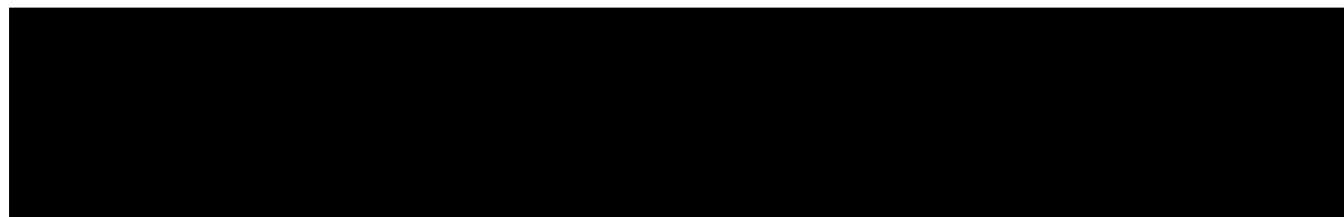
Source: Data on File. Table 14.3.3.6 InnovaTV 301 CSR (21).

Sensitivity analyses for PFS

A summary of the sensitivity analyses for PFS is presented in **Figure 6**. Sensitivity analyses for PFS included the following (21):

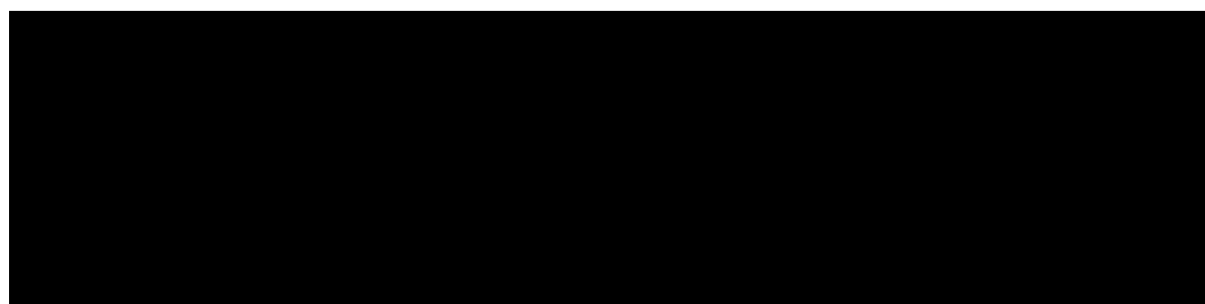
- 1. New Subsequent cancer-related therapy before progressive disease (PD)/death (Figure 7 and Figure 8):** For subjects who received subsequent cancer-related therapy before PD or death, 2 sensitivity analyses were to be performed:
 - Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason.
 - Consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as an event.
- 2. Missing Tumor Assessments (Figure 9):** To explore the potential impact of missing tumor assessments on PFS, subjects who missed 2 or more consecutive scheduled assessments before death or PD were considered to have had an event, with the earlier date of death or progression as event date.

Figure 6: Summary of Sensitivity Analyses of PFS per Investigator ITT Analysis Set (July 2023)



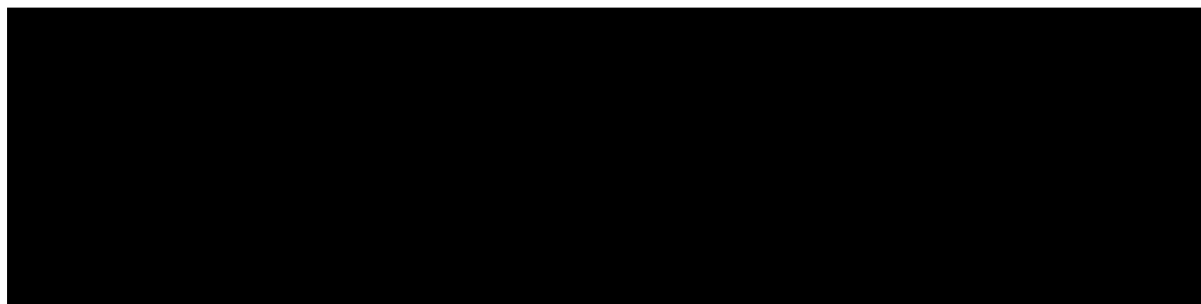
Notes: a. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model.
b. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation, except for sensitivity analysis 4 not shown in the table uses stratification factor from eCRF.
Sensitivity analysis 1a: Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason. A PD or death after a new anti-cancer treatment will still be considered to be a PFS event with the PD date or death date as the PFS date.
Sensitivity Analysis 1b (New Subsequent cancer-related therapy before PD/death): consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as an event at start date of subsequent therapy.
Sensitivity Analysis 2 (Missing Tumor Assessments): consider subjects who missed two or more consecutive scheduled assessments before death or PD as having had an event, with the earlier date of death or progression as event date.
Only applicable sensitivity analysis are presented.
Source: Data on File. Table 14.3.2.4 InnovaTV 301 CSR (21)

Figure 7: Summary of PFS per Investigator, Sensitivity 1a (New Subsequent Cancer-Related Therapy Before PD/Death) ITT Analysis Set (July 2023)



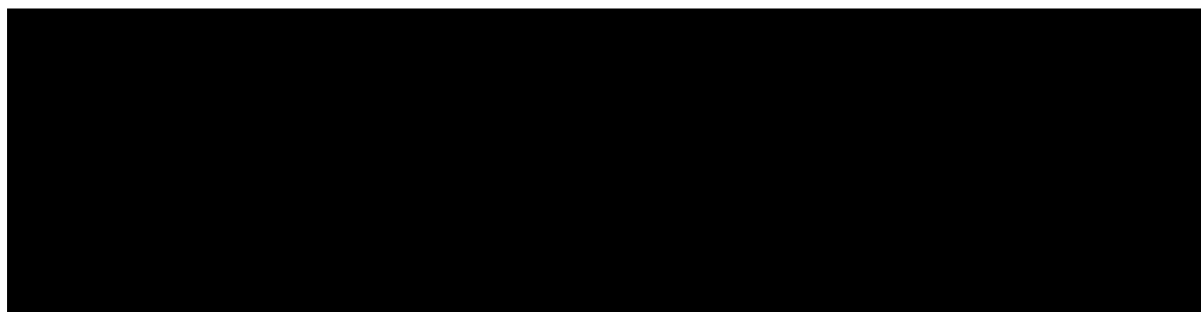
Notes: a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.
c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
d. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).
e. '+' means the observed time is from a censored subject.
Sensitivity analysis 1a: Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason. A PD or death after a new anti-cancer treatment will still be considered to be a PFS event with the PD date or death date as the PFS date.
Source: Data on File. Table 14.3.2.5.1 InnovaTV 301 CSR (21).

Figure 8: Summary of PFS per Investigator, Sensitivity 1b (New Subsequent Cancer-Related Therapy Before PD/Death) ITT Analysis Set (July 2023)



Notes: a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.
c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
d. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).
e. '+' means the observed time is from a censored subject.
Sensitivity Analysis 1b (New Subsequent cancer-related therapy before PD/death): consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as an event at start date of subsequent therapy before PD/death.
Source: Data on File. Table 14.3.2.5.2 InnovaTV 301 CSR (21).

Figure 9: Summary of PFS per Investigator, Sensitivity 2 (Missing Tumour Assessments) ITT Analysis Set (July 2023)



Notes: a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.
c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
d. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).
e. '+' means the observed time is from a censored subject.
Sensitivity Analysis 2 (Missing Tumor Assessments): consider subjects who missed two or more consecutive scheduled assessments before death or PD as having had an event, with the earlier date of death or progression as event date.
Source: Data on File. Table 14.3.2.6 InnovaTV 301 CSR (21).

During European Medicines Agency (EMA) approval of tisotumab vedotin, a new sensitivity analysis was conducted (**Table 5**). This sensitivity analysis used the EMA-preferred approach of PFS censoring rule as follows (EMA 2011):

- Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason.
- Not to consider missing two or more missed scheduled tumour scans as a censoring reason (i.e. subjects who died or experienced progressive disease [PD] on or after the start of any subsequent anti-cancer-related therapies, or on or after two or more missed consecutive scheduled tumour scans, are considered to have had a PFS event, with the earlier date of death or progression as event date. Otherwise, subjects are censored at their last tumour scan prior to the data cutoff date.

Table 5: Summary of Progression-Free Survival per Investigator, Sensitivity 3 SGNTV-003 ITT Analysis Set (July 2023)

	Tisotumab Vedotin (N=253)	Chemotherapy ^a (N=249)
Subjects with progression or death, n (%)	212 (83.8)	208 (83.5)
Stratified hazard ratio ^{b, c} (95% C.I.)	0.69 (0.57, 0.84)	
Median PFS (months) (95% C.I.) ^d	4.3 (4.0, 4.5)	2.9 (2.7, 3.1)
Q1, Q3	2.7, 7.1	1.5, 5.5
Min, Max ^e	0.0+, 21.0+	0.0+, 20.8+

Source: EMA assessment report for tisotumab vedotin (23).

InnovaTV 301 trial results

A17. CS section 2.6.1 confirmed ORR: Please state whether responses were confirmed in the same way as for the InnovaTV 204 trial (i.e. repeat imaging conducted 4 weeks or more after the initial response assessment).

Yes, objective response (according to RECIST v1.1) was confirmed by a repeat imaging assessment at least 4 weeks (28 days) after the initial response was recorded. Participants who obtained a confirmation scan did not need to undergo the

next scheduled tumor imaging if it was <4 weeks later; tumor imaging resumed at the subsequent scheduled imaging time point (21).

If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation was not necessary. In participants who discontinued study treatment without evidence of radiographic disease progression, tumor imaging was performed until evidence of radiographic disease progression or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurred first (21).

A18. CS section 2.6.1 – EORTC-QLQ-C30 and EQ-5D results: are the 10-point threshold used to define a clinically meaningful change in score for the EORTC-QLQ-C30 and the 7-point threshold used to define improved, worsened, or stable scores for the EQ-5D visual analogue scale validated thresholds for these measures? If so, please provide the references for these.

A minimum important difference (MID) of 5 to 10 points is generally recommended for interpreting group differences and changes in the EORTC QLQ-C30 scale scores as clinically meaningful. Several papers specific to the QLQ-C30 have provided rationale supporting the use of MID of 5 to 10 points, including the publication by King et al., (1996) (24). In addition, Osoba et al., (1998) found that a 10-point change on a 0-100 scale represented a moderate but clinically meaningful difference in most domains (25). While some recent guidelines have highlighted that the 5 to 10 points rule is more simplistic, the scale has been validated as a threshold for this measure (26, 27). A recent review of meaningful change thresholds for EORTC QLQ-C30 in oncology found that most clinical trials used for regulatory label submissions between 2016 and 2021 used the 10 point MID demonstrating that it is a widely accepted benchmark for interpreting QOL changes (25, 28).

Previous studies estimating the MID for the EQ-VAS reported a value of between 7 and 10 points on the 0 to 100 scale (29). A change of 0.07 on a 0-1 scale has also been identified as a minimally important difference using both anchor-based and distribution-based approaches across patient populations, including both chronic illness and general population samples (30). However, it was unclear whether the 7 point MID threshold is a recommended validated threshold in this population (29).

A19. CS section 2.6.1 – follow-up analysis (January 2024), OS: Please provide the p-value associated with the reported hazard ratio .

At the time of the 16 January 2024 DCO, █████ OS events (█████ in the tisotumab vedotin arm and █████ in the chemotherapy arm) had been observed. The OS benefit in the tisotumab vedotin arm vs the chemotherapy arm was maintained, with a █████% reduction in the risk of death (stratified hazard ratio [HR] = █████ [95% CI: █████]; descriptive nominal 2-sided p-value from stratified log-rank test = █████) (Table 6) (7). It is important to note that the p-value associated with the reported hazard ratio has no formal statistical interpretation given that the efficacy bound was crossed at the primary analysis (data cutoff: 24 July 2023).

Table 6: Summary of Overall Survival (16Jan2024 DCO) – InnovaTV301 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy^a (N=249)
Number of deaths, n (%)	176 (69.6)	174 (69.9)
Stratified hazard ratio ^{b,c} (95% CI)	0.79 (0.63, 0.97)	
Stratified log-rank p-value ^{c,d}	0.0280	

Abbreviations: CI=confidence interval.

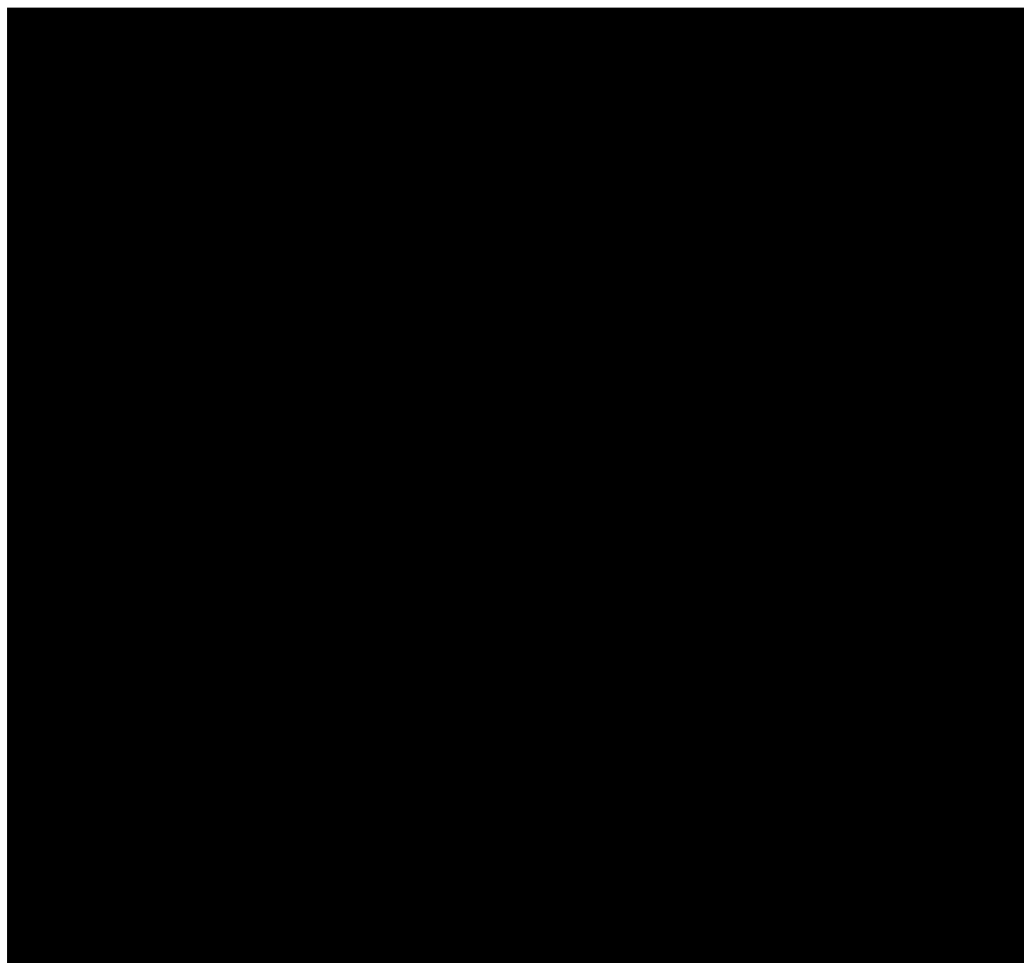
Notes: a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed. b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties. c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no] at randomisation. d. Two-sided p-value calculated from stratified log-rank test. Provided as a descriptive nominal p-value.

Source: Data on File. Summary of OS Data (Jan 2024 DCO) (7).

A20. CS section 2.6.1 – follow-up analysis (January 2024), PFS: Please provide the confidence intervals associated with the median PFS months reported for each trial arm and the p-value associated with the reported HR. Please also provide the number of events (Event/Total) as this information is missing from CS Figure 15.

Please see Figure 10 below for requested information. It is important to note that the p-value associated with the reported hazard ratio has no strict interpretation given that the efficacy bound was crossed at the primary analysis (data cutoff: 24 July 2023).

Figure 10: PFS Kaplan-Meier for tisotumab vedotin and chemotherapy arms for InnovaTV 301 (follow-up analysis, January 2024)



A21. CS section 2.7: Please comment on how representative the subsequent treatments received by participants in each arm of the Innova 301 trial are of those used in NHS clinical practice.

The subsequent treatments received by participants in each arm of InnovaTV 301 are a reasonable representation of the treatments used in NHS clinical practice. This is supported by clinician input from seven UK oncologists specialising in gynaecological cancers who were surveyed ahead of the UK cervical cancer advisory board, and additional input solicited from four further oncologists in preparation of a response to question A21 above.

In the survey of seven UK oncologists, the use of chemotherapies was unanimously recognised as standard treatment option amongst r/mCC patients opting for further treatment after receiving two or more prior systemic therapies. Notably, this initial

survey did not probe specifically on the use of best supportive care (or palliative care) (31).

In preparation of a response to question A21 above, four additional UK oncologists specialising in gynaecological cancers were approached and asked to advise on treatment options in r/mCC patients progressing after two or more prior systemic therapies. These clinicians reported either chemotherapy, a clinical trial, or palliative management with best supportive care as the subsequent options for r/mCC patients progressing after two or more prior therapies. The survey questions and responses are provided as data on file (32).

It is important to note that there is no recognised standard of care for 2L 3L or 4L r/mCC in NHS practice as highlighted through guidance presented in the CS section 1.3.4. Furthermore, the BGCS and ESGO guidance upon which NICE guidelines are based are both outdated. As also highlighted in this section clinicians at the UK Cervical Cancer advisory board in 2025 emphasised that clinical decisions for these patients primarily driven by treatment availability and access to clinical trials due to the limited benefit from available therapies (33, 34). A wide range of agents are therefore used as subsequent treatments in practice, which is also reflected in the InnovaTV 301 trial.

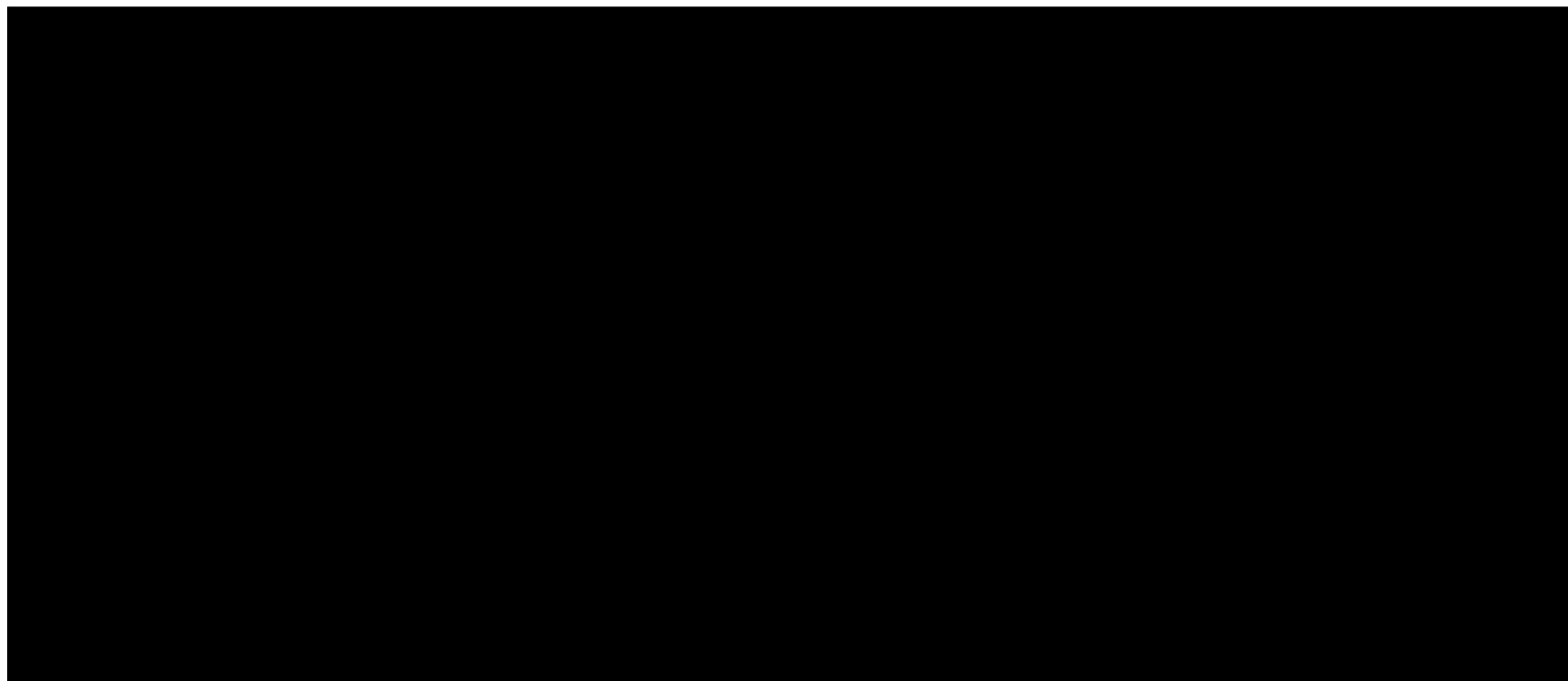
A22. Please provide the subgroup analysis results from the Innova 301 trial for the prespecified subgroups of histology (SCC and adenosquamous carcinoma, adenocarcinoma) and number of prior r/m CC systemic regimens (1, 2) for the outcome of PFS as these are not reported in CS Appendix C Figure 5.

In InnovaTV 301, subgroup analyses for progression-free survival (PFS) were pre-specified and conducted as exploratory analyses.

A PFS advantage was observed for patients with squamous cell carcinoma ([REDACTED] [REDACTED]) and adenocarcinoma and adenosquamous carcinoma ([REDACTED] [REDACTED]). This was also the case for patients with one prior line ([REDACTED] [REDACTED]) and two prior lines ([REDACTED]) of systemic regimens (21).

The forest plot of the exploratory analyses of the investigator assessed PFS for prespecified subgroups is outlined below in Figure 11.

Figure 11: Hazard ratio and 95% CI for PFS per investigator by subgroups (InnovaTV 301, ITT analysis set)



Abbreviations: TV= Tisotumab Vedotin; CT= Chemotherapy.

Notes: HR is computed from the Cox proportional hazards model using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.

Chemotherapy subgroups are based on the investigator's pre-specified chemotherapy choice before randomisation for each subject if randomised to the chemotherapy arm.

Subgroup except Chemotherapy is defined based on eCRF records. Chemotherapy subgroup is based on RTSM records. If the subgroup is defined by a randomisation stratification factor, Cox model is stratified for the randomisation stratification factors other than the one that defines the subgroup.

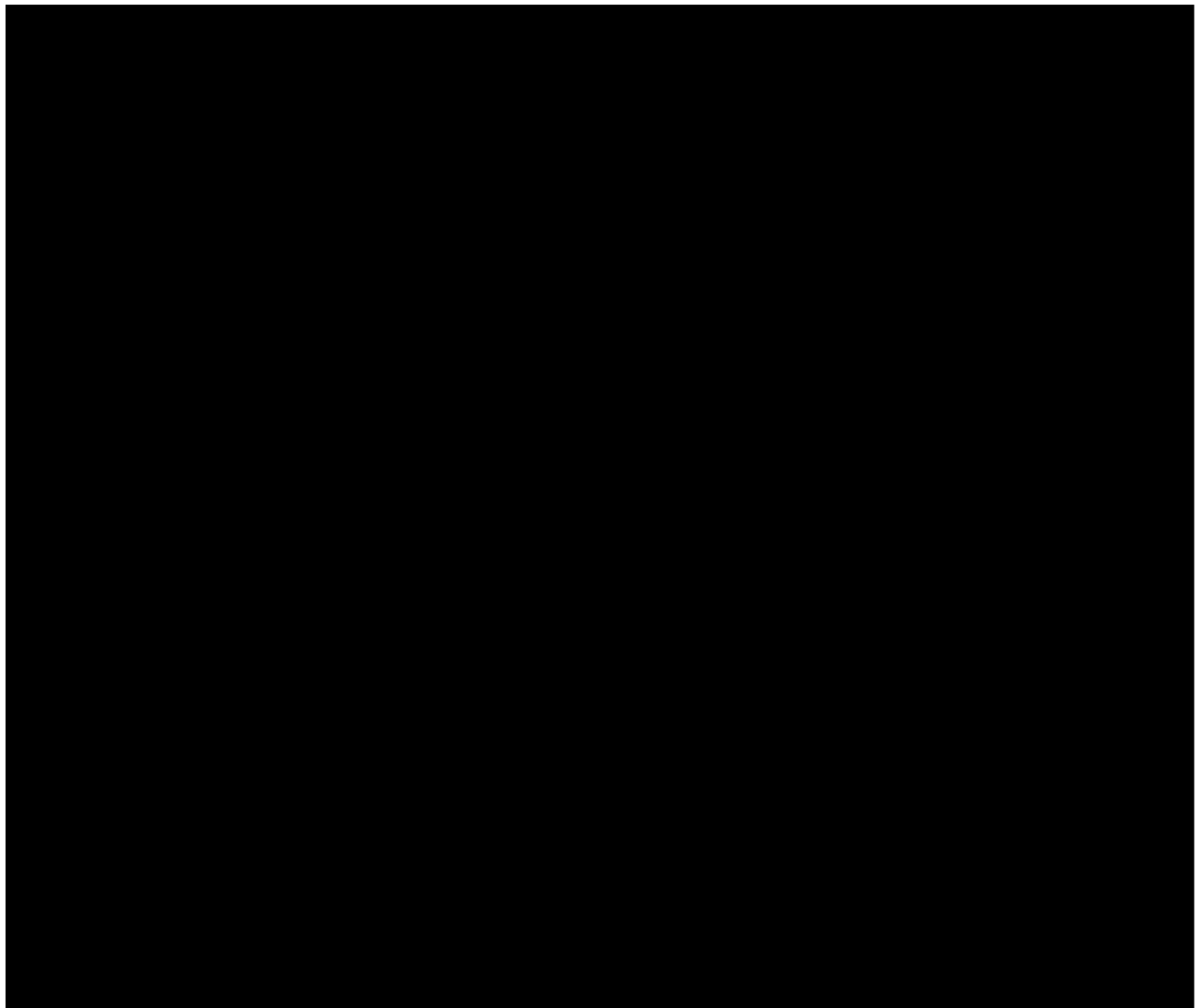
* Indicates subgroup with HR<1.

Source: Data on File. Figure 14.3.2.2 InnovaTV 301 CSR (21).

A23. CS section 2.8.1 and CS Appendix C, section 1.1: Please clarify if any subgroup analyses of PFS were conducted at the follow-up analysis (January 2024), and, if they were, please provide the results for all subgroups examined.

Subgroup analyses of PFS were also explored in the later follow up of the InnovaTV 301 follow-up analysis (January 2024). Results from these subgroup exploratory analyses are outlined below in Figure 12.

Figure 12: Subgroup analyses of PFS (InnovaTV 301, data cutoff: January 2024)

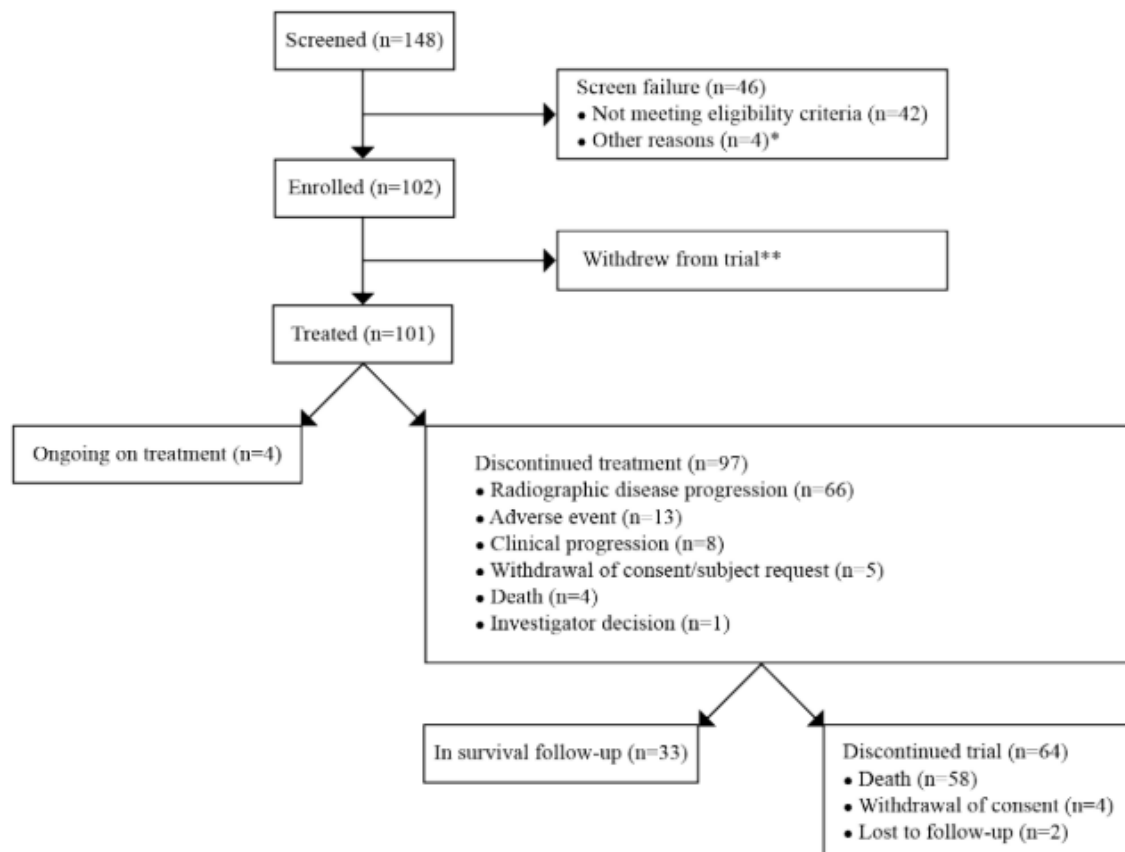


InnovaTV 204

A24. Please provide a participant flow chart for the InnovaTV 204 trial.

A participant flow diagram is provided from the InnovaTV 204 CSR below (Figure 13) (35).

Figure 13: Participant flow diagram for the InnovaTV 204 trial



Notes: *Other reasons for screening failure included death (n=2), withdrawal of consent (n=1), and lost to follow-up (n=1).

** Subject did not receive planned first dose due to SAE of spinal cord injury cauda equina.

Source: Data on File. Figure 2 InnovaTV 204 CSR (35).

Section B: Clarification on cost-effectiveness data

Model structure

B1. The rationale given for use of a semi-Markov model structure is that the tails of the OS KM curves from the InnovaTV 301 trial converge at a time when very few patients remain at risk or on randomised treatment (CS 3.2.2). This is true, but a standard partitioned survival model with appropriate fitted PFS and OS curves should still be able to provide plausible extrapolations. The model includes parameters for a range of survival distributions, including flexible spline models. Please provide scenario results using a partitioned survival model with appropriate PFS and OS extrapolations. Alternatively, please explain more clearly why this is not possible.

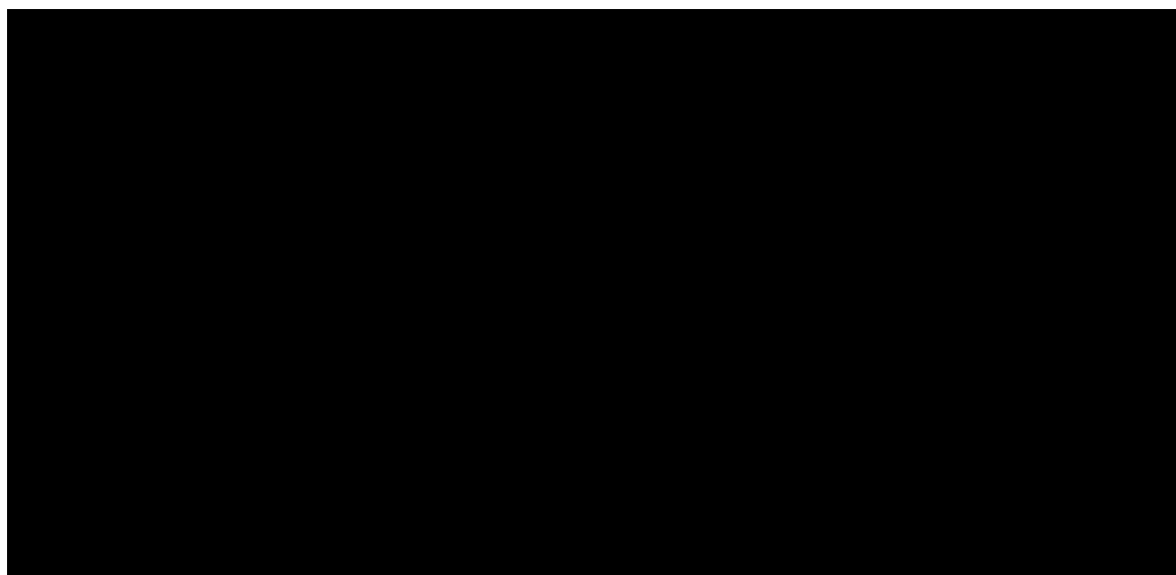
The company initially explored a partitioned survival model (PSM) using both standard parametric and flexible spline approaches but ultimately did not adopt the PSM approach due to lack of clinical and external validity, particularly for the chemotherapy arm, and the need to adequately implement a key assumption of comparable post-progression mortality from the time of progression.

First, the PSM produced clinically implausible long-term OS projections for the chemotherapy arm, with a 2-year overall survival estimate of approximately 16–20%, notably higher than external benchmarks. For example, McLachlan et al. (2017) reported a 2-year OS rate of 13% for patients receiving second-line chemotherapy at the Royal Marsden Hospital—a population expected to have better outcomes than the mixed second- and third-line cohort in InnovaTV 301 (18).

In addition, clinician input from the UK advisory board indicated that a 2-year OS rate of around 10% would be expected for available chemotherapy agents, consistent with evidence from the EMPOWER-Cervical 1 trial (11%) (8). This further supported the view that the OS tail observed in the chemotherapy arm of InnovaTV 301 likely reflected statistical variability arising from a small number of patients at risk (N = 7 at 24 months) rather than a true survival benefit. Figure 14 below shows the overlay of the predicted OS curve for chemotherapy, generated by fitting a standard partitioned survival model to the observed OS data from the TV301 trial, along with the

observed OS from TV301 and the OS data from the EMPOWER trial. The best-fitting standard parametric model for chemotherapy OS was the log-logistic model.

Figure 14. Overlay of predicted and observed OS from TV301, and external data (EMPOWER trial) for chemotherapy



Second, the PSM structure could not adequately operationalise the clinical assumption of a comparable post-progression mortality rate, from the time a patient experiences a progression event, within both treatment arms. Implementing this approach within a semi-Markov model was considered more appropriate than using PSM and selecting an arbitrary time point to apply a common OS curve and extrapolating that for the two trial arms. Input from the clinical oncologists at the UK clinical advisory board advised that it is clinically more appropriate to implement the assumption from the time each patient progresses, using a semi-Markov approach (33, 34).

Taken together, these considerations demonstrate that a semi-Markov model provides a more clinically plausible and methodologically appropriate framework, to model comparable post-progression mortality and avoid over-extrapolation of chemotherapy survival.

Transition probabilities

B2. Priority question: Please provide copies of the Kaplan Meier (KM) curves in CS Figures 18 to 23 including the numbers of patients at risk by 3-monthly

timepoints (as for OS and PFS in CS Figures 12 and 13). It is difficult to judge the importance of visual fit at the tails of these curves without this information.

Please find Figures 14-17 below (i.e., corresponding to Figures 18–23 in the original submission document), with the number of patients at risk at 3-month intervals displayed along the bottom of each figure.

For Figure 17 and Figure 18 below, (i.e., corresponding to Figures 20 and 21 in the original submission document), please find plots comparing the model-predicted progression-free survival (PFS) from the semi-Markov model with the corresponding Kaplan–Meier (KM) curves, also annotated with the number of patients at risk.

Because PFS was not directly used for parametric function estimation in the semi-Markov model, the original Figures 20 and 21 are not relevant in that case. The new figures provide a more relevant visual assessment of the model fit and its alignment with the observed data.

Figure 15: Overlay of observed Kaplan-Meier and predicted curves of TTP for tisotumab vedotin (Figure 18 in CS document)

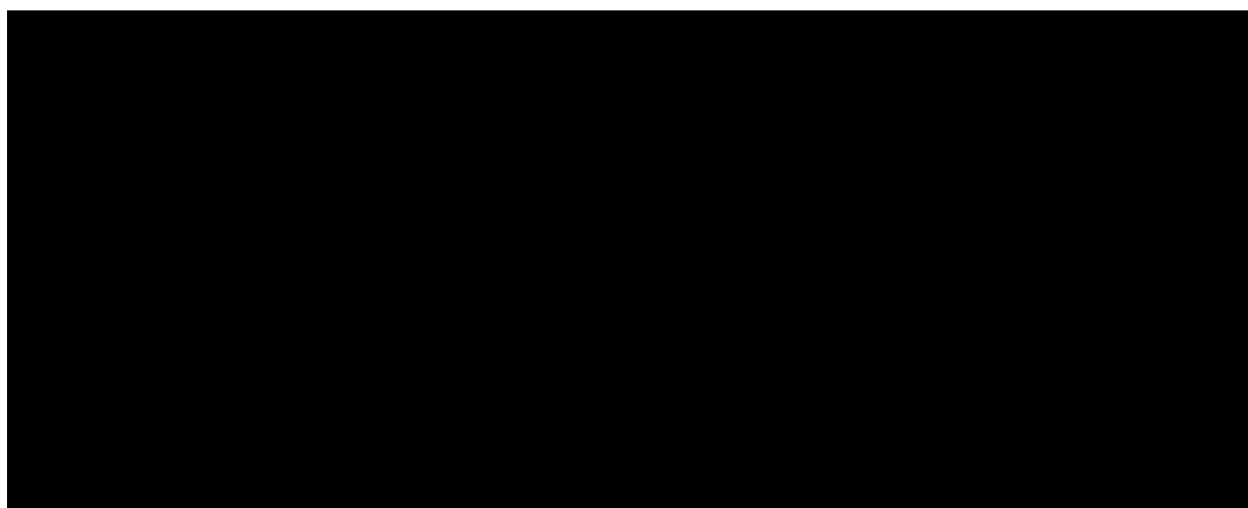


Figure 16: Overlay of observed Kaplan-Meier and predicted curves of TTP for chemotherapy (Figure 19 in CS document)

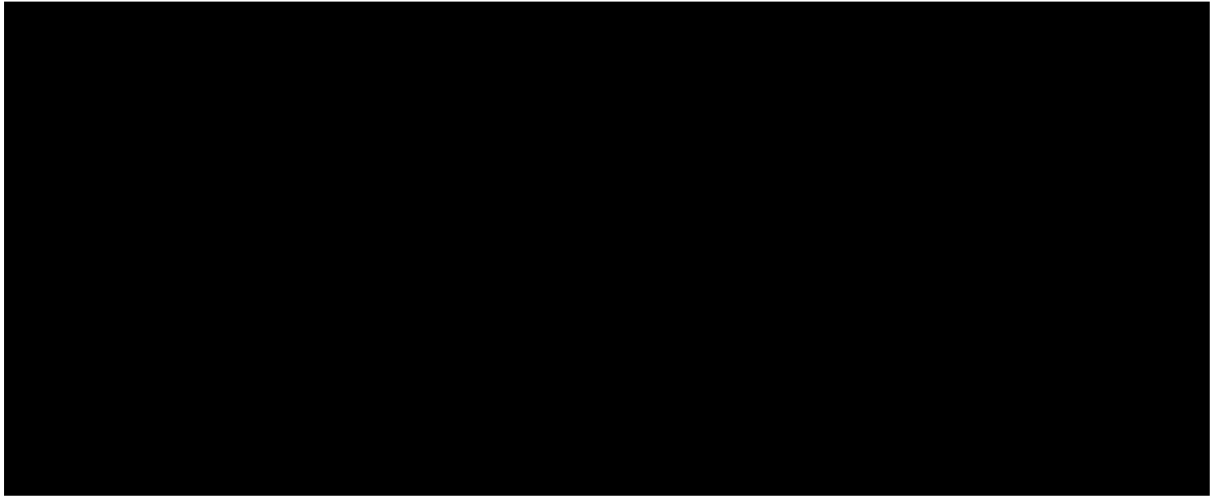


Figure 17: Overlay of observed Kaplan-Meier and predicted curves of time from PF to death for tisotumab vedotin (Figure 20 in CS document)

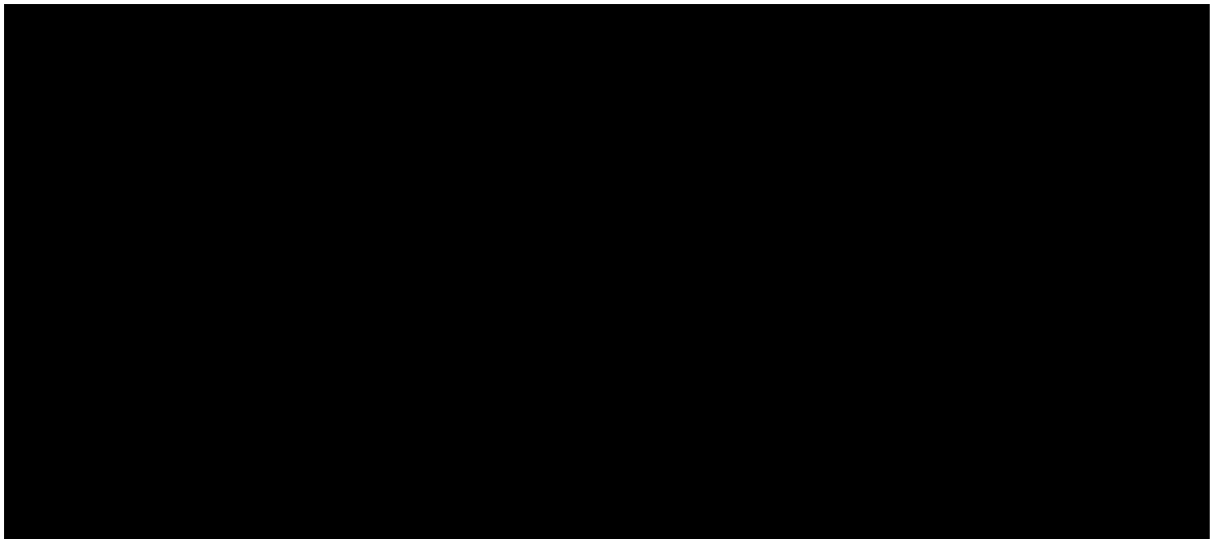


Figure 18: Overlay of observed Kaplan-Meier and predicted curves of time from PF to death for chemotherapy (Figure 21 in CS document)

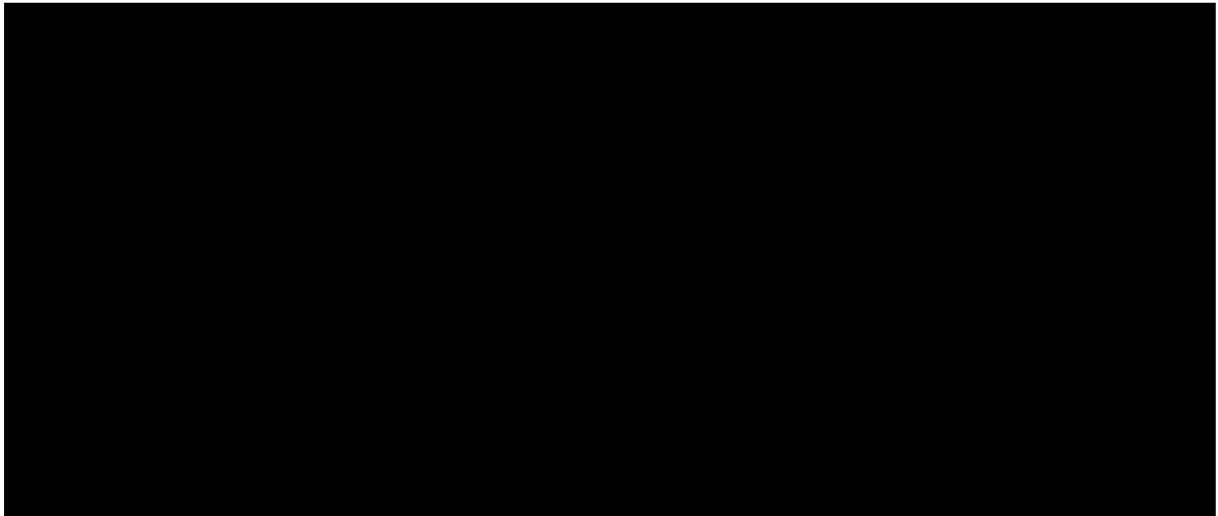


Figure 19: Overlay of observed KM and predicted curves of PF survival (tisotumab vedotin) (Figure 22 in CS document)

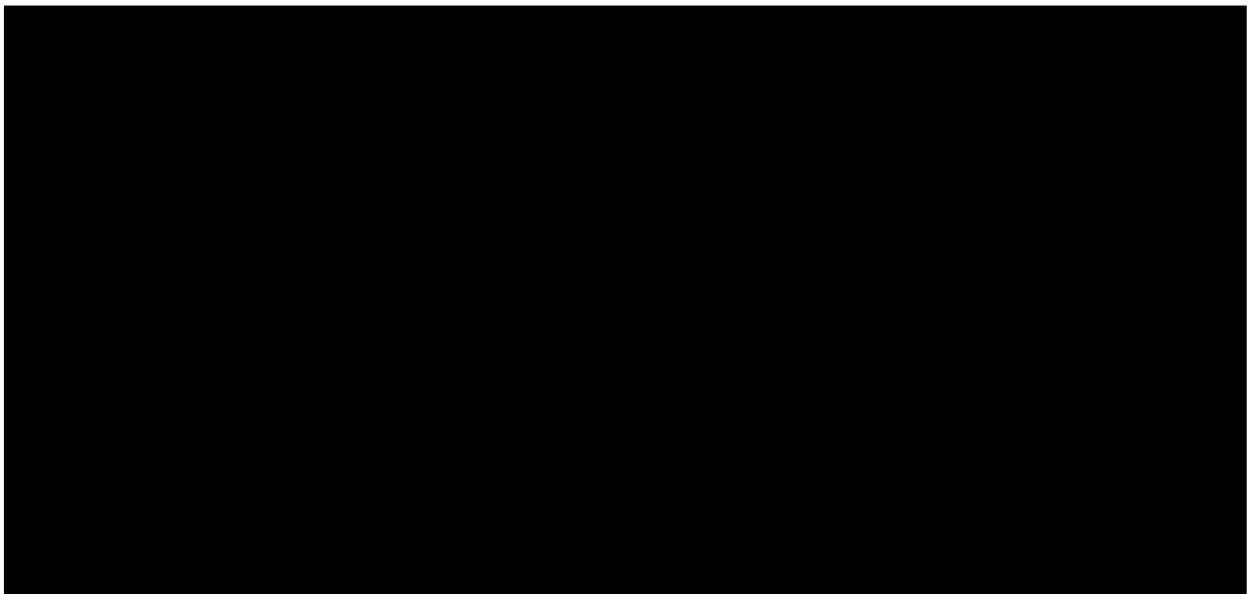
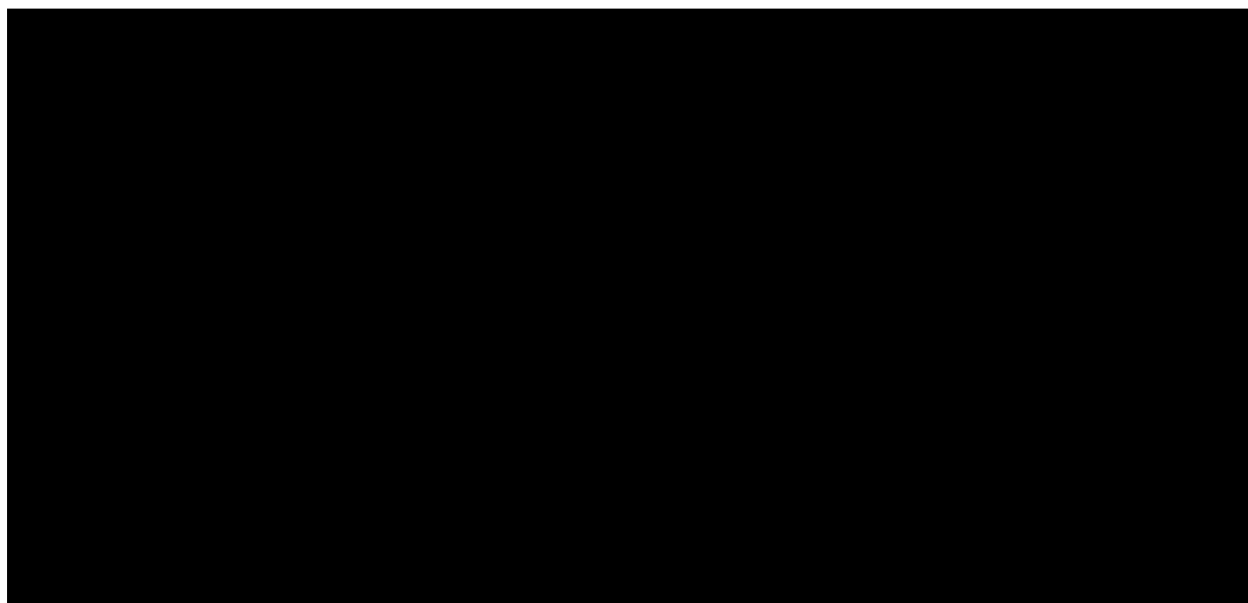


Figure 20: Overlay of observed KM and predicted curves of PF survival (chemotherapy) (Figure 23 in CS document)



B3. Priority question: Please provide a more complete explanation of the rationale for selection of the base case parametric curves for time to progression (TTP), and progression-free (PF) to death. CS section 3.3.2 lists the key criteria cited in Decision Support Unit (DSU) Technical Support Document (TSD) 14, but it is not clear how these have been applied. In particular, further explanation of how the hazard functions reported in CS Appendix Figures 22-26 informed the choice of distributions would be helpful.

Below are clarifications on the application and rationale for selection of the base case curves for TTP and PF to death.

1. Time to progression (TTP) curves were fitted separately for TV and chemotherapy with generalised gamma models selected for both. The model selection process is summarised below:
 - For TTP curves, the log-cumulative hazard plots for TV and chemotherapy were not parallel (CS Appendix K, Section 1.2: Figure 23), suggesting that separate model fitting by treatment arm was appropriate.
 - The hazard plots (CS Appendix K, Section 1.2: Figure 22) showed no monotonic decreasing or increasing trend for either arm, suggesting that generalised gamma, log-normal or log-logistic should be considered.

- Based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) results (CS Tables 43 and 44), the generalised gamma models were deemed as best fit for both tisotumab vedotin and chemotherapy arms.
 - The visual inspection of the fitted curves further supported this choice (Figure 14 and Figure 15 of this document), as the generalised gamma models captured the observed data patterns well in both treatment arms.
2. PF to death curves were fitted separately for TV and chemotherapy, with Gompertz model selected for TV and log normal model selected for chemotherapy. The model selection process is summarised below:
- For PF to death, the log-cumulative hazard plots for TV and chemotherapy (CS Appendix K, Section 1.2: Figure 25) were not parallel, suggesting that separate model fitting by treatment arm was appropriate.
 - The hazard plots (CS Appendix K, Section 1.2: Figure 24) showed a near monotonically decreasing hazard for TV, whereas the chemotherapy arm exhibited a non-monotonic hazard pattern.
 - Based on AIC and BIC results (CS Tables 45 and 46), Gompertz model provided the best statistical fit for TV, consistent with the observed decreasing hazard trend. Log-normal was deemed as the best statistical fit for chemotherapy, consistent with its non-monotonic hazard pattern.
 - The visual inspection of the fitted curves supports these choices (Figure 16 and Figure 17 of this document), with both models appropriately reflecting the flattened tail observed in the observed data.
3. Post-progression to death was modelled using an exponential distribution, fitted to the pooled post-progression survival data from both treatment arms. Clinical input obtained during the advisory board meeting indicated post-progression survival is not expected to differ between the two arms (refer to the response to Question B1). Accordingly, data from both arms were pooled for model fitting. Without tunnel states or alternative functionality to track time

in state, survival functions with a time-changing hazard rate cannot be implemented within the post-progression state of a Markov cohort structure and only an exponential model - which assumes a constant hazard over time is suitable. Given the very short post-progression survival time, a time-varying hazard function was deemed unnecessary, and the exponential distribution was considered appropriate. Furthermore, as shown in CS Figure 24, the exponential model provided a good visual fit to the observed data, and the Cox–Snell residual plots (CS Appendix K, Figure 26) further confirmed the adequacy of the exponential assumption.

After the model fitting, internal, external and clinical validation is done for PFS and OS. Details are described in CS Section 3.13 Validation and CS Appendix H. These are not repeated here.

B4. Priority question: Please explain the rationale for using raw KM data to model OS up to 12 months, rather than the modelled estimates based on fitted curves for PF to death and the fixed post-progression hazard (as in sheet TP_tx1&2 of the economic model). We suggest that the raw KM data is subject to uncertainty from trial-specific factors or random variation, and that there is a risk of bias due to the choice of timepoint to switch from KM to fitted curves. For example, it is apparent from CS Figure 12, that the extrapolated tails for the treatment arms would differ substantially if use of KM data were to be stopped at 9 months.

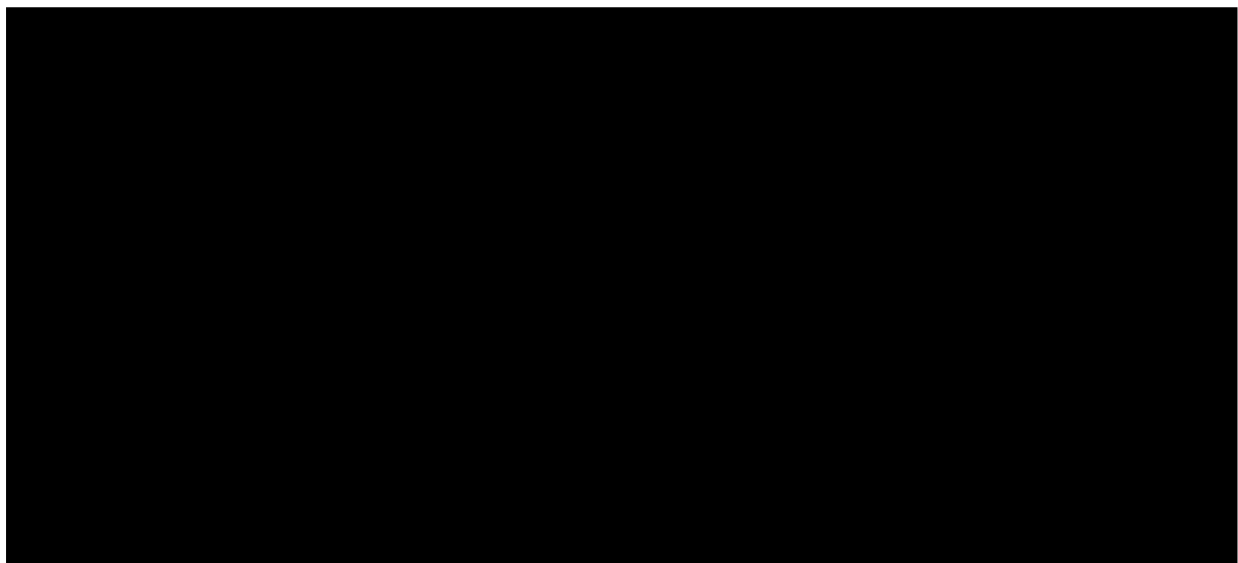
The 12-month cutoff for transitioning from observed (raw) OS data to model-fitted curves was selected to optimise the use of robust empirical data while ensuring reliable model validation. This decision was informed by empirical inspection, clinical expert input, and validation of predicted OS from fitted curves against observed data for both the TV and chemotherapy arms.

Clinical input from the advisory board supported adopting a semi-Markov model to appropriately implement the assumption of comparable post-progression mortality across treatment arms. Within this modeling framework, predicted OS was generated for each arm and compared with the observed OS from the InnovaTV 301 trial. Empirical inspection and clinical validation showed that fitted curves overestimate OS for chemotherapy and underestimate OS for TV (**Figure 21**).

To mitigate these biases, the model relied on observed data up to the point where a substantial proportion of patients remained at risk, maximising the use of robust data before applying fitted curves. Treatment exposure data indicated that by month 12, fewer than 5% of patients remained on randomised therapy (4.8% TV; 3.8% chemotherapy), yet the number at risk was still meaningful (TV = 119; chemotherapy = 83 per DCO2). Beyond this point, the number at risk changes substantially, while the incremental impact on ICER was minimal. Conversely, using an earlier cutoff would have reduced the amount of robust observed data used and amplified OS estimation biases.

Therefore, 12 months was determined to be the optimal cutoff, balancing the optimal use of robust observed data with model stability and clinical plausibility (Section 3.13.1).

Figure 21. OS curves: observed vs. predicted OSs with fitted data from time 0



To further explore the impact of the cutoff selection, we tested earlier (9 months) and later (15 months) cutoff points while keeping all other model assumptions identical to the CS submission. The resulting ICER per QALY gained ranged from £[REDACTED] (9-month cutoff) to £[REDACTED] (15-month cutoff), showing only minor variation from the base-case estimate (£[REDACTED]). This demonstrates that the model results are not highly sensitive to the choice of cutoff. Notably, when the 9-month cutoff was applied, greater deviations between predicted and observed OS were evident for

both the TV and chemotherapy arms, compared to the 12 months cutoff (Figure 22 and Figure 23).

Figure 22. OS curves: observed vs. predicted OSs with fitted data starting from 9 months

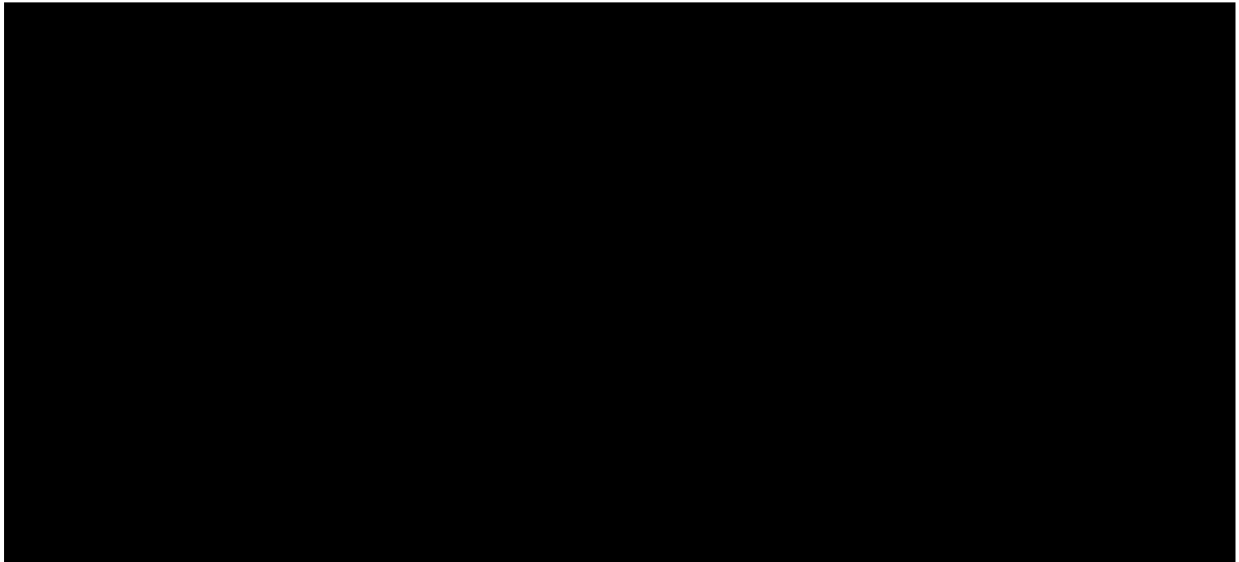
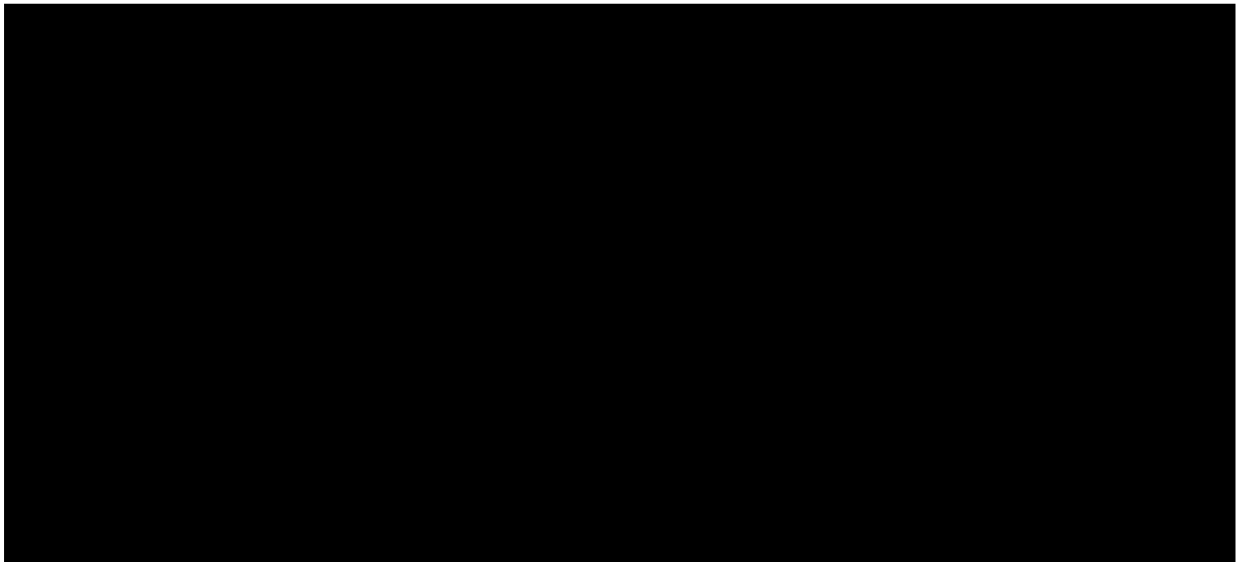


Figure 23. OS curves: observed vs. predicted OSs with fitted data starting from 9 months



B5. Priority question: Please provide a hazard plot and log cumulative hazard plot for progressive disease (PD) to death by treatment arm (as in Figures 22 and 23 for PF to death).

Figure 24 and Figure 25 show the hazard and log cumulative hazard plots by treatment arm in InnovaTV 301, while Figure 26 and

Figure 27 present the corresponding plots for pooled arms. These plots indicate that the hazard of death remained consistently lower for patients initially randomised to the TV arm compared with those in the chemotherapy arm, considerable long after disease progression.

Over time, as patients cycled through various subsequent therapies, the hazard plots began to converge among patients initially randomised across treatment arms. As the number of patients at risk continued to reduce, notable variability and uncertainty are observed in converged plots.

As discussed in Section B1, the long-term OS data for chemotherapy deviated from both clinical expectations and external evidence, suggesting that the later divergence in hazard patterns likely reflects statistical uncertainty in those estimates.

Furthermore, the similarity in subsequent treatment patterns between the TV and chemotherapy arms (CS Table 27) supports this interpretation. We present hazard the plot and log cumulative hazard plot by treatment arms. We also provided these plots for pooled arms (Figure 26 and

Figure 27).

Figure 24. Hazard plot for PD to death by treatment arm

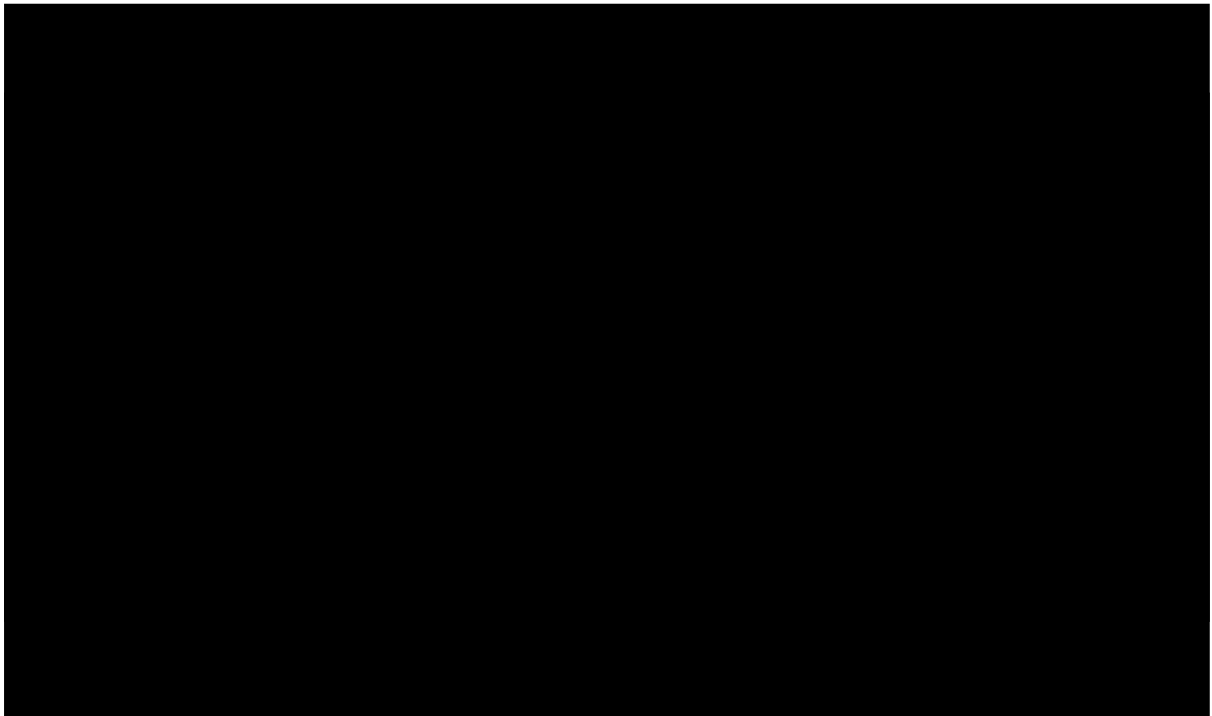


Figure 25. Log cumulative hazard plot for PD to death by treatment arm

Figure 26: Hazard plot for PD to death using pooled arms

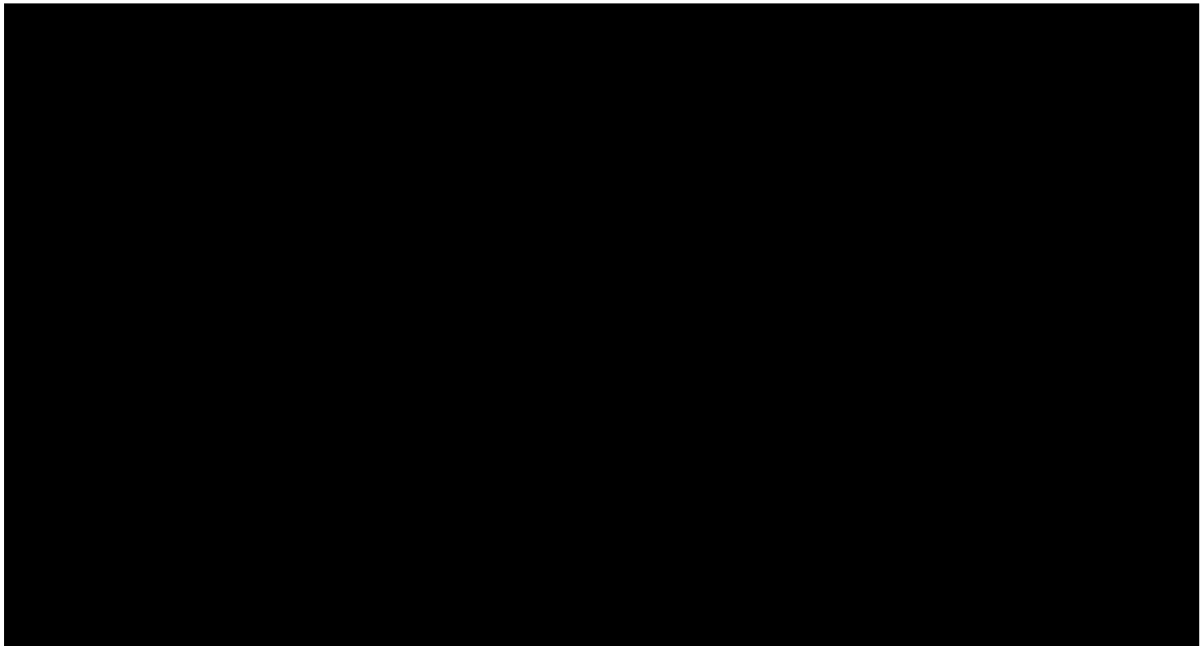
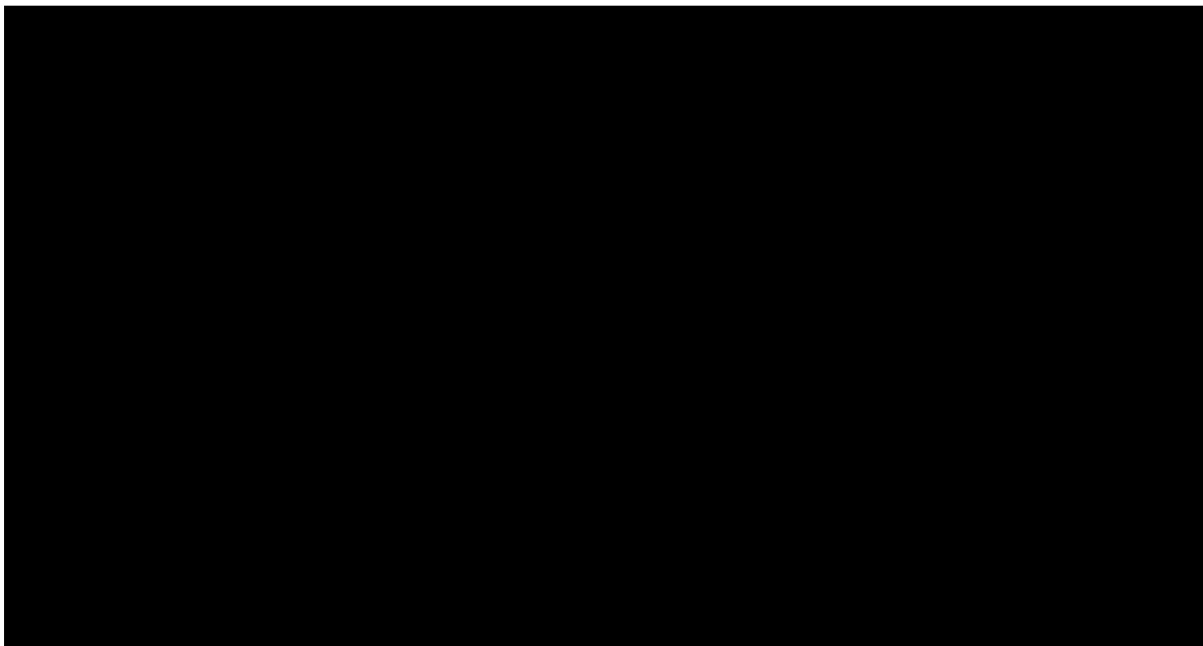


Figure 27: Log cumulative hazard plot for PD to death using pooled arms



Adverse events

B6. The adverse event rate of 4% for ocular event in the tisotumab group used in the model differs from the rate reported in CS Table 47 (52.8%). Please clarify which value should be considered in the company's base case.

The 52.8% reported in CS Table 47 reflects all-grade ocular adverse events. This rate should be used for AE costs as even mild events may trigger the requirement for some eye checkup prior to an infusion. However, the QALY disutility (-0.04) should be applied only to patients with grade ≥ 3 ocular adverse events (i.e., 4%) as those with milder events are typically managed without meaningful quality-of-life impact.

In a conservative scenario where all patients with ocular events (52.8%) incurred the QALY decrement and required eye exams, the ICER per QALY gained increased modestly to £[REDACTED], compared with £[REDACTED] in the base case.

Section C: Textual clarification and additional points

C1. CS Appendix A states that a UK public assessment report is not available, yet CS Table 2 refers the reader to the UK public assessment report. Please clarify whether a report is available. If one is available, please supply a copy.

Thank you for highlighting this. The MHRA approval of tisotumab vedotin is anticipated in [REDACTED] therefore a UK public assessment report is currently not available.

Table 2 in the CS is referring to Appendix A which is titled: 'Summary of product characteristics (SmPC) and UK public assessment report'. As indicated in response to question A3, the draft UK SmPC submitted with the initial MAA and currently under MHRA review is provided in PDF format alongside the company's clarification response.

C2. Please provide the following documents: i) the statistical analysis plan for the InnovaTV 301 trial, and ii) the protocol and statistical analysis plan for the Innova 204 trial.

The following documents have been provided in PDF format alongside the company's clarification response:

- i. Statistical analysis plan (SAP) for the InnovaTV 301 trial (22)
- ii. Protocol for the Innova 204 trial (36)
- iii. SAP for the Innova 204 trial (37)

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Single Technology Appraisal

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

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating recurrent or metastatic cervical cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Gemma Eminowicz
2. Name of organisation	University College London Hospital
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with cervical cancer? ☐ A specialist in the clinical evidence base for cervical cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
8. What is the main aim of treatment for recurrent or metastatic cervical cancer that has progressed on or after systemic therapy?	The main aim is symptomatic benefit and improvement in quality of life with addition of survival if possible. Often patients with metastatic or recurrent cervical cancer are young with young families and quality of life to be able to spend with family is a priority.

Clinical expert statement

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in survival amount depends upon burden of the treatment as only a few months survival does make a big difference providing it is accompanied by good quality of life. Symptomatic improvement with increase in quality of life on treatment more important.
10. In your view, is there an unmet need for patients and healthcare professionals in recurrent or metastatic cervical cancer that has progressed on or after systemic therapy?	Treatment options very limited in this cohort and often young patient population (with young families) with high symptom burden. In patients with PDL1-ve disease they are usually excluded from trials due to not being exposed to immunotherapy so this is huge unmet need. Standard of care is weekly paclitaxel which has poor response rates.
11. How is recurrent or metastatic cervical cancer that has progressed on or after systemic therapy treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	The standard treatment used in the UK is single agent chemotherapy, most commonly weekly paclitaxel with other options including topotecan, vinorelbine, gemcitabine etc. Due to the poor outcomes in general with these treatments, any fit patients are often referred for trials where possible including phase 1 or 2 trials. TV could be used as an alternative to weekly paclitaxel or as an option after weekly paclitaxel.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? How does healthcare resource use differ between the technology and current care?	The treatment is given on chemotherapy day unit in specialist centres only. Compared to paclitaxel it's a 3 weekly infusion instead of weekly. The administration does not involve anything additional to standard of care but the ophthalmology baseline review and need for cooling eyepads is something that would need to be set up specifically for this protocol.

Clinical expert statement

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	This treatment provides a progression free survival advantage ((4.2 vs 2.9 months (HR 0.67)) compared with single agent chemotherapy but paclitaxel was not included in the investigator choice chemotherapy standard arm. Overall survival was improved by 2 months (OS 11.5 vs 9.5 HR 0.70). Through control of the disease we expect there to be some improvement in QoL.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This treatment will be similar to deliver except for the ophthalmology reviews – this is an additional step from our standard carepaths and does need some work to ensure this is a clear pathway (different in each trust I suspect) and the use of cooling eyepads may be difficult as these are not routinely supplied and there is unlikely to be space to keep them therefore patients may need to bring themselves. Otherwise pathways and infrastructure similar to other treatments in this setting.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Usual stopping rules ie progression on imaging or symptomatic progression or unmanageable toxicity No additional imaging compared with standard of care

Clinical expert statement

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes, This would add an additional treatment option for this population of significant need and does improve their survival in addition. This is especially a significant step change for PDL1 negative patients who have limited systemic treatment options.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Toxicity is similar to chemotherapy (a little lower in the trial) other than the ocular aspects (discussed above). 98.4% had at least 1 AE vs 99.2% on chemo G3 or greater AEs 52% vs 62.3% with chemo 14.8% stopped TV due to toxicity NB biggest difference with chemo is ophthalmic toxicity and this means patients need to use topical steroid drops and lubricating drops but in addition use cooling eyepads during infusion and need ophthalmology review at baseline
20. Do the clinical trials on the technology reflect current UK clinical practice? If not, how could the results be extrapolated to the UK setting?	The trial did not include paclitaxel in the investigators choice standard of care arm. It is unlikely that there is a significant survival difference between the standards used in the trial compared with paclitaxel but there is no good data comparing these.

Clinical expert statement

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Otherwise the trial outcomes and recording of AEs etc was all in line with UK practice and no AEs have come to light that are in addition to those published. Within the gynae community we are also becoming more confident in managing patients with ADCs and therefore should feel confident managing most of the toxicities here.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	No large volume real world data available
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	Nil to consider

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- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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.

Tisotumab Vedotin has been proven to provide a survival advantage compared to single agent chemotherapy with a slightly lower toxicity profile

The only increase in burden is the risk of ophthalmic toxicity and therefore the need for ophthalmology baseline review and input if toxicities occur as well as the use of cooling pads during treatment delivery and eye drops.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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Clinical expert statement

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

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Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating recurrent or metastatic cervical cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Lisa Barraclough
2. Name of organisation	The Christie NHS Foundation Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with cervical cancer? ☐ A specialist in the clinical evidence base for cervical cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for recurrent or metastatic cervical cancer that has progressed on or after systemic therapy?	To improve survival with improved symptom control and quality of life enabling the patient to enjoy their well-being.

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(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in symptom control. Reduction in tumour burden, measured as at least 30% reduction in size of the tumour on radiological assessment.
10. In your view, is there an unmet need for patients and healthcare professionals in recurrent or metastatic cervical cancer that has progressed on or after systemic therapy?	Absolutely. There is no standard of care for anticancer treatment in this setting in the UK. This leaves patients with no clear option for improving their symptoms or their survival. This is in stark difference to most other cancer types where there are often 2 or 3 further treatment options, with some offering 7 or more further treatment options.
11. How is recurrent or metastatic cervical cancer that has progressed on or after systemic therapy treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	- British Gynaecological Cancer Society guidelines 2021. These recommend re-challenge with platinum/paclitaxel if more than 6 months from previous exposure, or vinorelbine, mitomycin C/5 Fluorouracil, gemcitabine, weekly paclitaxel. - Most consultants in the NHS use carboplatin and paclitaxel every 3 weeks or weekly paclitaxel, depending on bone marrow reserve or renal function. Many do not offer any further chemotherapy especially if there is progression within 6 months of initial treatment after systemic therapy. - The technology would offer a treatment option associated with improved overall survival, reduced toxicity – in particular bone marrow toxicity – with improved symptom control, physical, cognitive and social functioning.

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12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• Current care involves intravenous chemotherapy delivery every 1-3 weeks. The technology would be delivered intravenously every 3 weeks, reducing the burden on chemotherapy suites. • The technology would be delivered in specialist cancer care centres. This is standard for current practice with chemotherapy in this setting. • Ocular toxicity management is required with eye pads during the delivery of the technology and eyed drops given throughout the course of treatment – steroid eye drops for 3 days and vasoconstrictor eye drops pre infusion then continuous lubricating eye drops. These were delivered on the chemotherapy suite during the trial delivery with no difficulty. Ophthalmological review pretreatment is required. This is a new service that is in the process of being set for the use of Antibody Drug Conjugates (ADC) which are a growing group of drugs under development for many cancer types. Ocular toxicity is more commonly seen with this group of drugs. For the trial we had an arrangement with the local eye hospital for review with an ophthalmologist and an agreement that further ocular toxicity concerns would be managed by the emergency eye hospital.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• Yes. Tisotumab Vedotin for second or third line therapy for recurrent cervical cancer trial (Vergote et al, NEJM 2024;391:44) is associated with a median overall survival improvement of 2 months, with a median survival of 11.5 months in comparison to 9.5 months with investigator's choice of chemotherapy, hazard ratio 0.7. The median progression free survival was 4.2 months in comparison to 2.9 months, hazard ratio 0.67. A retrospective study from the Royal Marsden Hospital (McLachlan et al, Clin Oncol (R Coll Radiol) 2017;29:153) reviewed the impact of systemic therapy beyond first line treatment for advanced cervical cancer and demonstrated a median overall survival of 9.3 months and a median progression free survival

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	of 3.2 months. These results are comparable to the outcomes in the investigator's choice of therapy in the phase 3 Vergote trial. • Yes. Patient reported outcomes demonstrate an improvement in quality of life and symptom improvement favouring tisotumab vedotin on Forest plot comparison. The median time to a clinically meaningful deterioration (≥ 10-point change) was longer with tisotumab vedotin compared with chemotherapy across most of the key domains for EORTC QLQ-C30 and QLQ-CX24, specifically for the Global Health status, physical, cognitive and social functioning. Improvements in symptom control were also seen with tisotumab vedotin in nausea and vomiting, pain, breathlessness, insomnia and appetite in comparison to investigator's choice on therapy (Jordan et al, Patient-reported outcomes from the phase 3 ENGOT-cx12/GOG-3057/innovaTV 301 trial of tisotumab vedotin as second-/third-line treatment for recurrent or metastatic cervical cancer poster, IGCS, 2025).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not that I am aware of.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It will be easier that weekly treatments with reduced burden on clinics, health care professional time and chemotherapy suite capacity. Increased ocular toxicity management is an extra part of the supportive management. The development of ocular toxicity pathways for antibody drug conjugates are currently being developed in response their increase in use.

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16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	- Yes, this new technology is associated with improved survival and quality of life for a patient group who are often not offered any treatment. This is therefore a 'step-change' in the care of patients in this setting. - There is a lack of clear evidence of benefit with chemotherapy in this second line setting. Treatment is given on a patient suitability basis. The only other systemic therapy of proven benefit in a randomised trial is cemiplimab, a PD-1 inhibitor, associated with improved overall survival in comparison to investigator's choice of chemotherapy irrespective of PDL1 status. The median overall survival with cemiplimab was 11.7 months in comparison to 8.5 months with investigator's choice of therapy, hazard ratio 0.67. The 2 year overall survival was 11.9% for investigator's choice of therapy (Oaknin et al, European Journal of Cancer 2025;216:115146). Second line cemiplimab is approved in Europe, Canada, Japan and Brazil.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side effect is ocular toxicity for which regular use of eye drops is recommended. The risk of ocular toxicity is 53%, occurring at about 5 weeks after first treatment and completely resolves on 70% of cases within about 2-3

Clinical expert statement

	weeks. This is mostly manageable with only 6% of the patients in the trial stopping early due to ocular toxicity. There is reduced anaemia with tisotumab vedotin at 23% in comparison to investigator's choice at 52%. There is reduced neutropenia with tisotumab vedotin at 7% in comparison to 23%. Other toxicities are very similar to the other systemic therapies for which there are well established management pathways.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• Yes, the trial compares the technology with a range of systemic treatments available in the UK. A consideration for the trial is the lack of carboplatin or paclitaxel in the options specified for investigator's choice of systemic therapy. This could be explained by first line treatment for metastatic or recurrent cervical cancer always being carboplatin and paclitaxel. Weekly paclitaxel is a favoured option by many in this second line setting, though would only be considered with a disease free interval of at least 6 months. This is a readily available drug which is mostly well tolerated and with less bone marrow toxicity than some alternatives eg topotecan. Of note, the median progression free survival after first-line systemic therapy in the McLachan study was 6.6 months with a narrow 95% confidence interval of 5.5-7.6 months. As stated above, the median overall survival noted in this retrospective study was 9.3 months, similar to the median overall survival with investigator's choice of therapy in the Vergote trial investigating this technology. The current standard of care for first line metastatic or recurrent cervical cancer is carboplatin and paclitaxel +/- bevacizumab +/- pembrolizumab. Previous PDL1 targeted treatment was given in 27% of the Vergote study. Increased access to pembrolizumab means that more of the population will have received it prior to the setting of this technology use. I am not aware of this having any effect on the effectiveness of the technology.

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	• In my view, the most important outcomes are overall survival and improvement in symptom control and well-being. Yes, these were measured. • Surrogate outcome measures were not used. • I am not aware of any subsequently noted adverse events.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There is not yet any specified real world data published recently. A good surrogate for this is the McLachlan study, which presented a retrospective review of patient in this clinical setting treated at the Royal Marsden Hospital from 2004 – 2014.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	The use of this technology will not be affected by equality issues other than a potential for improved access as it is delivered every 3 weeks rather than every week (if using weekly paclitaxel) which could be limiting for people with transport difficulties.

Clinical expert statement

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Tisotumab vedotin presents an exciting opportunity to have an evidence based standard of care for metastatic or recurrent cervical cancer in the second line setting.

Tisotumab vedotin is associated with improved overall survival in comparison to standard chemotherapy options.

Tisotumab vedotin is associated with improved quality of life and symptom control.

Tisotumab vedotin is well tolerated with reduced toxicities in comparison to standard chemotherapy options.

Tisotumab vedotin has increased ocular toxicities that were manageable within the trial setting with supportive measures and ophthalmological input that is also required for some other antibody drug conjugates.

Thank you for your time.

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Clinical expert statement

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

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with cervical cancer or caring for a patient with cervical cancer. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

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Your response should not be longer than 15 pages.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with cervical cancer

Table 1 About you, cervical cancer, current treatments and equality

1. Your name	Joan Campbell
2. Are you (please tick all that apply)	☒ A patient with cervical cancer? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with cervical cancer? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference

Patient expert statement

	☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with cervical cancer? If you are a carer (for someone with cervical cancer) please share your experience of caring for them	Living with cervical cancer has meant learning to survive day by day. I live with the physical toll of treatment, constant fatigue, pain, and changes to my body that I didn't choose. There are days when fear of recurrence and uncertainty about the future feel overwhelming. I've had to navigate hospital visits, side effects, and the emotional weight of losing my sense of normal life. At the same time, this experience has forced me to become stronger, to advocate for myself, and to find meaning in simply being here. Cervical cancer has changed my life, but it hasn't taken my will to keep going.
7a. What do you think of the current treatments and care available for recurrent or metastatic cervical cancer after systemic therapy on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Overall, I think the NHS has made important progress in treating recurrent or metastatic cervical cancer, especially with the introduction of immunotherapy alongside chemotherapy. For many patients, this has brought renewed hope and, in some cases, better quality of life compared to chemotherapy alone. Care teams are generally compassionate and multidisciplinary, and there is a real effort to manage symptoms and support patients emotionally as well as physically. These advances matter, particularly in a space where options were very limited for many years. That said, from a patient's perspective, the options after first-line systemic therapy still feel frustratingly few. Once chemotherapy and immunotherapy stop working, choices can become limited to less effective treatments or supportive care, which can feel like hitting a wall. Promising newer treatments are emerging, but access on the NHS can be slow or inconsistent. While the care itself is often excellent, there's still a strong sense that more needs to be done, especially in expanding later-line treatment options and giving patients more time, hope, and choice. 7b. My views are very similar to those of many other people I've come across, there's a shared mix of gratitude and disappointment. Most of us appreciate that treatments like immunotherapy are now available and recognise how hard NHS

Patient expert statement

	teams work to provide good care. At the same time, there's a common feeling of frustration and vulnerability when those treatments stop working and options quickly run out. Many people feel hopeful about progress, but also anxious and let down by how limited later-line choices still are, leaving a strong sense that patients with advanced cervical cancer deserve more effective and accessible treatments.
8. If there are disadvantages for patients of current NHS treatments for recurrent or metastatic cervical cancer after systemic therapy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	From a patient point of view, the main disadvantages of current NHS treatments are how demanding they are on both the body and daily life. Most treatments involve regular hospital infusions, which can be exhausting and disruptive, especially when you're already unwell. Side effects often build up over time ongoing fatigue, nausea, nerve pain, lowered immunity, and emotional strain are common and immunotherapy or drugs like bevacizumab can bring their own serious risks. For many people, it can feel like trading one struggle for another, particularly when treatment is about control rather than cure, leaving patients managing long-term side effects while still living with uncertainty about how long the benefits will last.
9a. If there are advantages of tisotumab vedotin over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does tisotumab vedotin help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9a. 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. When the treatment works, my symptoms ease, and I have more energy to take care of myself and my family, and even handle some daily tasks or work. It gives me a sense of hope that my cancer is being targeted more precisely, and for the first time in a while, I feel like I have a treatment that can help me keep some normalcy in my life despite living with advanced cervical cancer.
10. If there are disadvantages of tisotumab vedotin over current treatments on the NHS please describe these.	As a patient receiving tisotumab vedotin, I can say that while it offers hope, it also comes with real challenges. The eye problems, dryness, irritation, and the need for constant monitoring are exhausting, and the nerve tingling in my hands and feet makes everyday tasks harder. I've also had nosebleeds and other side effects that can be alarming, and every infusion means another round of check-ups and careful

Patient expert statement

For example, are there any risks with tisotumab vedotin? If you are concerned about any potential side effects you have heard about, please describe them and explain why	watching for complications. Living with these side effects while trying to manage my cancer can be draining, and it's a constant balancing act between the hope the treatment brings and the practical and emotional toll it takes on my life.
11. Are there any groups of patients who might benefit more from tisotumab vedotin or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	From my experience as a patient, I feel that tisotumab vedotin seems most helpful for people whose cervical cancer has already come back or spread after other treatments, especially if their tumours carry the protein it targets. Being physically able to manage regular hospital visits and the extra monitoring, particularly for eye health, makes a big difference in how well someone can benefit. On the other hand, patients who already have serious eye problems, nerve damage, or who are very frail may struggle more with the side effects, and for them the treatment can feel harder than the potential benefit. For me, it's about balancing hope with the practical realities of living with the treatment day to day.
12. Are there any potential equality issues that should be taken into account when considering cervical cancer and tisotumab vedotin? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	From my perspective as a patient, I can see that not everyone has the same chance to benefit from treatments like tisotumab vedotin. People who live far from specialist hospitals, who can't easily get time off work, or who face financial or transport challenges may struggle to attend the frequent appointments and monitoring the treatment requires. Older patients, those with other health conditions, or people from certain ethnic or cultural backgrounds might also be less likely to be offered or able to manage this treatment. For many of us, it feels like access to the newest therapies depends as much on circumstances and support as it does on the cancer itself, and that can be really frustrating and unfair.
13. Are there any other issues that you would like the committee to consider?	No

Patient expert statement

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Living with cervical cancer is physically and emotionally exhausting, and treatments take a heavy toll on daily life and independence.
- The NHS has made important progress with chemotherapy and immunotherapy, providing hope and improved care, but options after first-line therapy remain limited, leaving many patients frustrated.
- Current treatments are demanding, with cumulative side effects such as fatigue, nausea, and nerve pain that affect quality of life.
- Tisotumab vedotin offers a more targeted option that can ease symptoms, improve energy, and help maintain some normalcy, but it also brings challenges like eye toxicity, nerve symptoms, and the need for frequent monitoring.
- Access to new treatments can be unequal, with geographic, financial, age, and cultural factors affecting who can benefit fully.

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Patient expert statement

External Assessment Group (EAG) Report

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

Produced by Southampton Health Technology Assessments Centre
(SHTAC)

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Karen Pickett critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor; Mary Onoja critically appraised the economic evaluation, and drafted the report; Jo Picot critically appraised the clinical effectiveness systematic review, and drafted the report; Marcia Takahashi critically appraised the economic evaluation, and drafted the report; Joanne Lord critically appraised the health economic systematic review and the economic evaluation, and drafted the report.

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List of Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
BIC	Bayesian information criterion
BSC	Best supportive care
CI(s)	Confidence interval(s)
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
DoR	Duration of response
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency

eMIT	Drugs and pharmaceutical electronic market information tool
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC-QLQ-CX24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cervical cancer module
EU	European Union
GEE	Generalised estimating equation
HR	Hazard ratio
HRQoL	Health-related quality of life
HPV	Human Papillomavirus
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
IQR	Interquartile range
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
ml	millilitres
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
ORR	Objective response rate

OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease or progressed disease
PD-L1	Programmed cell death-ligand 1
PF	Progression free
PFS	Progression-free survival
PICOD	Population-Intervention-Comparator-Outcome-Design
PK	Pharmacokinetics
PRO FAS	Patient-reported outcome final analysis set
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
Q1W	Once weekly
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
r/m CC	Recurrent or metastatic cervical cancer
RMST	Restricted mean time survival
RTSM	Randomisation and Trial Supply Management
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TTP	Time to progression
TV	Tisotumab vedotin
UK	United Kingdom
US	United States

VAS	Visual analogue scale

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues is in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of EAG's key issues

Table 1 Summary of key issues

ID3753	Summary of issue	Impact on results	Report sections
1	Implementation of eye care management plan for tisotumab vedotin	Unknown	2.2.3, 3.3.6.3.1, 3.7, 4.2.8.1.1.2
2	Appropriateness of the company's semi-Markov model structure and assumptions	High	4.2.2, Error! Reference source not found.
3	Uncertainty over OS predictions: impact of direct use of KM data and selection of OS distributions for the partitioned survival model	High	4.2.6.5.1, 4.2.6.5.2.2

ID3753	Summary of issue	Impact on results	Report sections
4	Uncertainty over extrapolations of time to progression and pre-progression survival in the semi-Markov model	Moderate	4.2.6.2, 4.2.6.3
5	Administration cost for paclitaxel – does it differ from other single-agent chemotherapies?	Moderate	4.2.8.1.1.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company use a semi-Markov model structure, with assumptions that the risk of death after disease progression is constant, and the same in both treatment arms. The EAG prefers partitioned survival approach, based on PFS and OS extrapolations with an assumption that the risk of death is the same in both arms when the OS curves converge.
- The company use KM data from the InnovaTV 301 trial to override model estimates of during the first 12 months. The EAG prefers not to use KM data in this way.
- The company assume that administration of paclitaxel is more expensive than for other chemotherapy agents in the comparator arm. The EAG assumes the same cost of treatment administration for all chemotherapy agents.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing time to progression (TTP)
- Increasing overall survival (OS)

Overall, the technology is modelled to affect costs by:

- Increasing drug acquisition costs
- Reducing drug administration cost (higher cost for paclitaxel in the company's base case analysis, but not in the EAG's analysis)

The modelling assumptions that have the greatest effect on the ICER are:

- OS extrapolations in a partitioned survival model (PSM)
- TTP extrapolations in the semi-Markov model
- Pre-progression survival extrapolations in the semi-Markov model
- Direct use of Kaplan-Meier (KM) data for overall survival
- The administration cost for paclitaxel

1.3 EAG's key issues

Issue 1 Implementation of the company's eye care management plan for patients receiving tisotumab vedotin in clinical practice

Report section	2.2.3, 3.3.6.3.1, 3.7, 4.2.8.1.1.2
Description of issue and why the EAG has identified it as important	Tisotumab vedotin is associated with ocular adverse reactions. In the company submission (CS), the company outlines an eye care management plan developed to be used in the United Kingdom (UK), [REDACTED] [REDACTED] [REDACTED].¹⁵ The EAG's advising clinical experts expressed concern about implementation of the plan in clinical practice, including: • Questioning whether adequate resource is available in treating centres' eye departments for an eye care professional to perform ophthalmic examination of patients before their first infusion of tisotumab vedotin and then as clinically indicated. • Anticipating it might be challenging for treating clinicians, who are not eye specialists, to assess patients' eyes during treatment to judge when referral to an eye care professional might be needed. • Availability of access to emergency eye referrals, when needed. This issue has limited impact on clinical and cost effectiveness estimates presented in the CS, but is a practical implementation issue.
What alternative approach has the EAG suggested?	None.

Report section	2.2.3, 3.3.6.3.1, 3.7, 4.2.8.1.1.2
What is the expected effect on the cost-effectiveness estimates?	The economic model includes costs for an ocular assessment by an eye care professional and preventive treatments prior to first use of tisotumab vedotin, and eye checks by the treating physician at subsequent infusions. We have applied a correction to the company's base case analysis to include costs for eye checks for ocular adverse events of any grade (52.8%), rather than just for grade 3+ events (4%), reflecting the company's response to clarification question B6. This increases the company's base case ICER by £3,383 per QALY. We have not conducted further EAG scenario analysis on this issue, as there is uncertainty over how the eye care management will be applied in practice, and how this will vary between centres.
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG does not suggest that any additional evidence or analyses are needed, as we consider that this is largely an implementation issue. Further discussion of the practicality of implementing the company's eye care management plan in clinical practice may be beneficial.

Issue 2 Appropriateness of the company's semi-Markov model structure, and assumptions over the risk of death after disease progression

Report section	4.2.2, Error! Reference source not found.
Description of issue and why the EAG has identified it as important	The EAG has concerns over potential bias in the company's base case semi-Markov model, due to the assumptions that the risk of death after progression is constant and the same in the tisotumab vedotin and chemotherapy arms. We do not consider that these assumptions are supported by the hazard plots for post-progression survival (clarification response B5), or by AIC/BIC statistics (reported in the model). It is not possible to change the assumption of constant (exponential) hazards for post-progression survival because the semi-Markov model does not retain information about time of progression. The company's model includes options that can be used to run a partitioned survival model (PSM): with PFS and OS extrapolations from InnovaTV 301 data, and options to prevent unrealistic crossover of OS. The company report that they explored the PSM approach, but rejected it due to poor clinical plausibility and external validity (clarification response B1). They report a PSM scenario assuming dependent models for PFS (generalised gamma) and OS (lognormal). We note that evidence to support the failure time ratios for this scenario has not been provided.
What alternative approach has the EAG suggested?	PSM model with PFS and OS extrapolations, with no override of OS with KM data, and an assumption that the risk of mortality is the same in both treatment arms from the point where the OS curves converge. We report three PSM scenarios (8-10 in Table 27):

Report section	4.2.2, Error! Reference source not found.
	• Log-logistic for both arms (EAG preferred) • Generalised gamma for both arms • Weibull for tisotumab vedotin and log-logistic for chemotherapy
What is the expected effect on the cost-effectiveness estimates?	The ICER for the company's base case analysis, including EAG corrections is £83,360 (£49,035 with x1.7 QALY multiplier) ICERs for EAG PSM scenarios (8-10 in Table 28): • £111,826 (£93,188 with x1.2 QALY multiplier) • £135,322 (£79,601 with x1.7 QALY multiplier) • £129,136 (£75,962 with x1.7 QALY multiplier) We note that the QALY multiplier differs between these scenarios (x1.7 for the company's base case and EAG scenarios 2 and 3, x1.2 for EAG scenario 1).
Could any additional evidence or analyses be provided to resolve this key issue?	Further evidence on hazard trends for post-progression mortality, and whether this differs for patients randomised to tisotumab vedotin or chemotherapy (log-cumulative hazard plots and hazard plots by treatment arm from the InnovaTV 301 trial). Additional OS data from the InnovaTV 301 trial, with longer follow up.

Issue 3 Uncertainty over survival predictions: impact of direct use of KM data and selection of survival distributions

Report section	4.2.6.5.1, 4.2.6.5.2.2
Description of issue and why the EAG has identified it as important	The company state that empirical inspection and clinical validation shows that the OS predictions from the semi-Markov model overestimate survival for chemotherapy and underestimate survival for tisotumab vedotin, which they attribute to random variation caused by the diminishing sample size (clarification response B4). To produce what they consider to be more plausible extrapolations, the company use KM data from InnovaTV 301 to override modelled OS for the first 12 months. They argue that the 12 month cutoff is appropriate as it maximises the use of robust empirical data before applying the fitted curves. The EAG agrees that overlap of the KM plots for OS is likely to be related to the diminishing number of patients at risk. However, this uncertainty applies in both arms, and an alternative interpretation of the OS KM plots is that the survival advantage of tisotumab vedotin does not persist beyond the point where the KM curves converge. We also suggest that there is a risk of bias from the post-hoc decision to use KM data to override the model predictions, and the choice of timepoint to switch from KM to the fitted curves.
What alternative approach has the EAG suggested?	For EAG analysis, we prefer not to use KM data to override model predictions of OS, and we report company scenarios with 9 or 15 months of KM data (scenarios 5 to 7 in Table 29) As described Issue 2 above, we also use EAG PSM model to test the impact of alternative OS extrapolations on the ICER.

Report section	4.2.6.5.1, 4.2.6.5.2.2
What is the expected effect on the cost-effectiveness estimates?	The ICER for the company's base case analysis, including EAG corrections is £83,360 (£49,035 with x1.7 QALY multiplier) Removing use of KM data for OS was • No KM: £100,691 (£59,230 with x1.7 QALY) • 9 months KM: £87,419 (£51,423 with x1.7 QALY) • 15 months KM: £81,713 (£48,067 with x1.7 QALY)
Could any additional evidence or analyses be provided to resolve this key issue?	Additional clinical opinion on the plausibility of the extrapolations with, and without use of KM data.

Issue 4 Uncertainty over extrapolations of time to progression and pre-progression survival in the semi-Markov model

Report section	4.2.6.2, 4.2.6.3
Description of issue and why the EAG has identified it as important	The company use a generalised gamma distribution for time to progression (TTP) in their base case and lognormal in a scenario, each fitted independently to both treatment arms. The EAG notes uncertainty over the TTP extrapolations due to the periodic timing of assessments and diminishing sample size (see Figure 3 and Figure 4). The AIC/ BIC statistics and the visual fit of the generalised gamma, lognormal and log-logistic distributions are similar. However, given the structural dependency between TTP and OS in the semi-Markov model structure, one might expect ICERs would be sensitive to the choice of TTP extrapolation. For pre-progression survival, the company use a Gompertz distribution for tisotumab vedotin, and lognormal for chemotherapy. We note the high degree of uncertainty over pre-progression survival, due to the low numbers of observed events in the InnovaTV 301 trial (see Figure 5 and Figure 6). For EAG analysis, we prefer to use the same distribution in both arms, and we also consider the exponential distribution.
What alternative approach has the EAG suggested?	We report EAG scenario analysis using lognormal and log-logistic extrapolations for TTP in both arms (Table 28, scenarios 1 and 2).and exponential and lognormal for pre-progression survival arms (Table 28, scenarios 3 and 4).

Report section	4.2.6.2, 4.2.6.3
What is the expected effect on the cost-effectiveness estimates?	All four scenarios increase the ICER • Company base case: £83,360 (£49,035) • Lognormal TTP: £103,920 (£61,129) • Log-logistic TTP: £96,566 (£56,804) • Exponential PF to death: £97,573 (£57,396) • Exponential PF to death: £91,452 (£53,795) All scenarios reported without (with) adjustment for severity, with a QALY multiplier of x1.7.
Could any additional evidence or analyses be provided to resolve this issue?	No. We have included this issue to highlight the sensitivity of the ICER to TTP and pre-progression survival extrapolations in the semi-Markov model.

Issue 5 Administration cost for paclitaxel – does it differ from other single-agent chemotherapies?

Report section	4.2.8.1.1.1
Description of issue and why the EAG has identified it as important	Although paclitaxel was not included in the comparator arm of the InnovaTV 301 trial, the company included it for costing single-agent chemotherapy in the health economic model. They applied a higher cost for administration of paclitaxel (£352 for complex chemotherapy including prolonged infusion, SB14Z), than for other single- chemotherapy agents pemetrexed, gemcitabine, topotecan, irinotecan, vinorelbine (£152, SB12Z). Clinical experts advising the EAG questioned this assumption, and noted that, while issues of allergies related to paclitaxel could introduce complexities in drug administration, single-agent paclitaxel is typically administered as a relatively short infusion around one hour and should not differ from other chemotherapies. As the proportion of patients assumed to be on paclitaxel in clinical practice is high (64.3% in the company's analysis and 66.7% in EAG analysis; Table 14), the higher administration cost increases the overall cost of chemotherapy.
What alternative approach has the EAG suggested?	We assume the same administration cost for paclitaxel as for the other chemotherapies (£152 per infusion, for simple parenteral chemotherapy).

Report section	4.2.8.1.1.1
What is the expected effect on the cost-effectiveness estimates?	When applied to the company's base case, the reduced administration cost for paclitaxel increases the ICER from £83,360 (£49,035 with x1.7 QALY multiplier) to £99,434 (£58,490 with x1.7 QALY multiplier) (scenario 13 in Table 28)
Could any additional evidence or analyses be provided to resolve this issue?	Further advice on the appropriate costing code for administration of single-agent paclitaxel in clinical practice.

1.4 Secondary issues identified by the EAG

Issue 6 Use of the comparator arm of the InnovaTV 301 RCT to represent the efficacy of single-agent chemotherapy

Report section	2.2.2, 2.3, 3.2.1.1.1, 3.4, 3.7
Description of issue and why the EAG has identified it as important	In the company's decision problem and economic model, the comparator for tisotumab vedotin is specified to be single-agent chemotherapy. This is represented by an investigator's choice of chemotherapy comparator arm from the InnovaTV 301 pivotal RCT of tisotumab vedotin, in which investigators could choose to use topotecan, gemcitabine, irinotecan, vinorelbine or pemetrexed as the comparator therapy. Paclitaxel, which the EAG's clinical experts advised is the most commonly used second-line or later therapy in clinical practice, was not included as a comparator in the trial nor the company's decision problem. It was, however, included in the company's economic model for costing. The proportions of participants receiving each chemotherapy in the InnovaTV 301 RCT also do not reflect use in National Health Service (NHS) clinical practice. The EAG has determined that, despite these limitations, it is likely that the comparator arm of the InnovaTV 301 RCT reasonably represents the efficacy of the therapies used in practice, including weekly paclitaxel, and we believe the company's approach is acceptable. However, this may represent an area of uncertainty.
What alternative approach has the EAG suggested?	None.

Report section	2.2.2, 2.3, 3.2.1.1.1, 3.4, 3.7
What is the expected effect on the cost-effectiveness estimates?	Unknown.
Could any additional evidence or analyses be provided to resolve this issue?	Further discussion with clinical experts about whether the single agent chemotherapies included in the comparator arm of the InnovaTV 301 RCT, and weekly paclitaxel, can be considered to all have similar efficacy in people with recurrent or metastatic cervical cancer that has progressed on or after systemic treatment.

Issue 7 Is platinum doublet re-challenge at second-line therapy widely used?

Report section	2.2.2, 2.3, 3.2.1.1.1, 3.7
Description of issue and why the EAG has identified it as important	Clinical experts advised the EAG that re-challenge with platinum doublet is a commonly used second-line therapy and the company collected data that also indicates this. However, platinum doublet was not included in the NICE scope nor the company's decision problem, so it is not included in company's clinical or cost-effectiveness evidence in the CS. Clinical experts told us that it is uncertain if platinum doublet has similar efficacy to the single-agent chemotherapies included in the comparator arm of the InnovaTV 301 RCT, due to a lack of clinical trial evidence. Therefore, the clinical effectiveness and cost-effectiveness estimates in the CS cannot be assumed to capture how platinum doublet compares to tisotumab vedotin.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
Could any additional evidence or analyses be provided to resolve this issue?	Discussion on whether platinum doublet is in widespread use in clinical practice at second-line or later therapy and thus if it might be a relevant comparator for tisotumab vedotin (or subsequent treatment).

1.5 Company's modelling errors identified by the EAG

The EAG have identified four errors in the company's economic model. We describe these errors in section 5.2.3.

1. **Selection of the methods and source for progression-free survival (PFS) and overall survival (OS) curves:** The controls to select the method of extrapolation and data sources had broken references. This does not affect the company's base-case results, but correcting this has allowed the EAG to explore additional scenarios.
2. **PFS should be capped by the OS:** when the model includes direct Kaplan-Meier (KM) data for OS in the initial months, as in the company's base case, PFS estimates could exceed OS estimates. Correcting this has a marginal impact (less than £1) on the ICER.
3. **Resource use per week estimates for colposcopy:** There is a typing mistake in the formula, with 365.27 days used instead of 365.25 days. This does not affect the results.
4. **Rate for ocular adverse event:** The rate of ocular adverse events applied in the company's model for costing is corrected to include ocular assessments prior to administration of tisotumab vedotin infusions for all patients who had presented with an ocular event, not only patients with grade 3+ adverse events. This increases the company's base case ICER by £3,383.

The corrections above increase the company's base case ICER from £79,978 (£47,046) to £83,360 (£49,035) per QALY gained, with and without the 1.7 QALY severity weighting.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 Summary of EAG's preferred assumptions and ICER (deterministic)

Scenario	Incremental cost	Incremental QALYs (x1.2 or 1.7 weight)	ICER (x1.2 or 1.7 weight)
Company's base case (deterministic)			£79,978 (£47,046) ^b
EAG's corrected company base case			£83,360 (£49,035) ^b

Scenario	Incremental cost	Incremental QALYs (x1.2 or 1.7 weight)	ICER (x1.2 or 1.7 weight)
Key issue 3: Use only the fitted OS curve (no OS KM data)	██████████	██████████	£100,691 (£59,230) ^b
Key issue 2: Partitioned Survival Model with Log-logistic extrapolation of PFS and OS in both arms	██████████	██████████	£111,826 (£93,188) ^a
Key issue 5: Administration cost for paclitaxel based on simple parenteral chemotherapy	██████████	██████████	£133,918 (£111,598) ^a
Single-agent chemotherapy distribution based on the EAG experts' estimates	██████████	██████████	£131,243 (£109,369) ^a
Subsequent treatment distribution based on the EAG experts' estimates	██████████	██████████	£131,256 (£109,380) ^a
Healthcare disease management cost based on the EAG experts' estimates	██████████	██████████	£129,803 (108,169) ^a
EAG's preferred base case deterministic	██████████	██████████	£129,803 (108,169) ^a
EAG's preferred base case probabilistic	██████████	██████████	£110,120 (£91,767) ^c

^a QALY weight of 1.2^b QALY weight of 1.7^c QALY weights: 1.2 for 68.5% of PSA iterations; 1.7 for 31.5% of PSA iterations

1.7 Outline of confidential comparator or subsequent treatment prices

A confidential addendum to this report includes confidential prices for comparator and subsequent treatments (see 5.4).

2 Background

This report critiques the company submission (CS) for tisotumab vedotin monotherapy for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE in October 2025. A response from the company via NICE was received by the EAG 17th October 2025 and this can be seen in the NICE committee papers for this appraisal.

2.1 Critique of the company's description of underlying health problem

The company provide a clear overview of cervical cancer in CS section 1.3.1 and provide information on the epidemiology of cervical cancer (CS section 1.3.2), and the burden of the disease (CS section 1.3.3), covering symptoms (CS section 1.3.3.1), mortality (CS section 1.3.3.2), impact on patients' health-related quality of life (HRQoL) (CS section 1.3.3.3), and the societal and economic (CS section 1.3.3.4) burdens of this disease. The CS also sets out the unmet need for therapies in the second- and later-lines of therapy for recurrent or metastatic cervical cancer (CS section 1.3.6).

Most cases of cervical cancer are caused by a persistent Human Papillomavirus (HPV) infection with one of the high-risk HPV types. A persistent HPV infection eventually leads to the development of precancerous lesions which, if not identified by regular cervical screening, eventually lead to cervical cancer. The main histological subtypes of cervical cancer are squamous cell carcinoma (accounting for up to 80-90% of cases¹), adenocarcinoma (accounting for 10-20% of cervical cancers¹) and adenosquamous (sometimes called mixed) carcinoma and small cell cancer accounting for the remaining small proportion of cases (approximately 3-10% and less than 5% respectively¹). There is a commonly used, standardised classification system for staging cervical cancer: the International Federation of Gynecology and Obstetrics (FIGO) staging system. The current (2018) version is shown in CS Figure 1.² The population relevant for this appraisal is patients with

recurrent or metastatic cervical cancer with disease progression on or after systemic therapy. These patients have either previously been diagnosed and treated for cervical cancer but have a recurrence of disease with one or more distant metastases, or they have received an initial diagnosis of metastatic cervical cancer (i.e. FIGO stage IVB). They have already received systemic therapy for their recurrent or metastatic disease but have either continued to experience disease progression during systemic therapy or have experienced disease progression after completing systemic therapy.

2.2 Critique of the company's overview of current service provision

The company outlines the clinical pathway of care for cervical cancer in CS section 1.3.4, drawing on British Gynaecological Cancer Society,³ European Society of Gynaecological Oncology,⁴ European Society for Radiotherapy and Oncology,⁴ European Society of Pathology⁴ and NICE guidelines.^{5, 6} The EAG notes that there appears to be no general NICE guideline on the management of cervical cancer but a NICE clinical knowledge summary for cervical cancer and HPV is available⁷ and this informed the company's depiction of NICE's first-line treatment recommendations for confirmed cervical cancer in CS Figure 8, which depend on the stage of the disease.⁷ For disease that has spread to the distant organs (stage IVB disease) the NICE clinical knowledge summary suggests that systemic chemotherapy is typically offered as a first-line intervention (as shown in CS Figure 8).⁷ NICE technology appraisal (TA) guidance is available on the use of pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer (TA939; an update of and replacement of TA885)⁶ and use of topotecan for the treatment of recurrent and stage IVB cervical cancer (TA183).⁵ We outline the NICE recommendations in these guidelines below (section 2.2.1).

2.2.1 First-line therapy for recurrent or metastatic cervical cancer

As stated in CS section 1.3.4.2, NICE's clinical knowledge summary⁷ outlines that the treatment options for recurrent or metastatic disease depend on several factors, including a patient's preferences, prior treatment(s) received, site of disease, the disease-free interval, symptoms, co-existing conditions and a patient's performance

status.⁷ Options may include salvage surgery if relapse occurs only in the central pelvis and if chemoradiotherapy has been unsuccessful, or chemotherapy and/or radiotherapy if the disease has not been controlled by initial surgery.⁷ CS Figure 9 shows the first-line systemic and other treatment options available for recurrent or metastatic cervical cancer. The company's depiction of first-line treatment in this figure is also replicated in CS Figure 10 in which the proposed positioning of tisotumab vedotin is additionally shown. In clarification question A2, we asked the company to adapt CS Figure 10 to show the second line and later treatment options available in clinical practice (which were not included in the original version of the figure). The company supplied an amended figure (clarification response Figure 1). We have reproduced this as Figure 1 below. CS Figures 9 and 10 were adapted from one used in the NICE Public Committee Slides for Appraisal Committee Meeting 1 for TA885.⁸

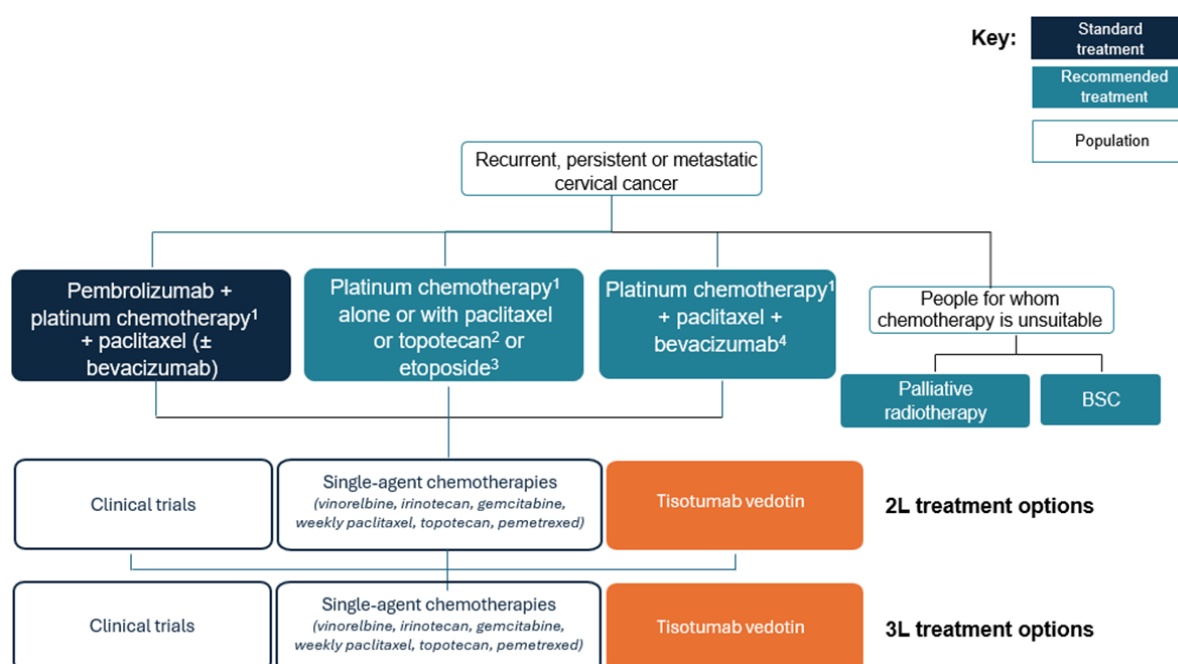


Figure 1 Company's depiction of NICE's first-line treatment recommendations for recurrent or metastatic cervical cancer, the second- and third-line therapies used in clinical practice, and the company's proposed positioning of tisotumab vedotin in the treatment pathway.

Source: Reproduced from clarification response Figure 1, which was adapted from NICE Public Committee Slides ACM1 – TA885 (Committee Slide 4)⁸ and BGCS guidelines (2021)⁹

Notes: ¹Cisplatin or carboplatin. ²NICE recommends topotecan with cisplatin as an option for treating recurrent or stage 4B cervical cancer in people who have not previously received cisplatin (TA183), ³Source: Cancer Research UK and NHS chemotherapy protocol (indicated for small cell gynaecological cancers including those affecting the cervix, endometrium and ovaries). ⁴Bevacizumab with paclitaxel and platinum chemotherapy available in routine commissioning for untreated recurrent or metastatic cervical cancer.

BSC, best supportive care.

The EAG notes that TA939⁶ recommends pembrolizumab and chemotherapy with or without bevacizumab as a treatment option for persistent, recurrent or metastatic cervical cancer in adults who have tumours that express programmed cell death-ligand 1 (PD-L1) with a combined positive score of one or more. One of our clinical experts advised us that pembrolizumab can be continued as a maintenance treatment. The NICE guidance states that it should be stopped after two years of continuous treatment.¹⁰ In TA183,⁵ topotecan in combination with cisplatin is recommended as a treatment option for recurrent or stage IVB cervical cancer only in people who have not previously received cisplatin.

One of the EAG's clinical experts advised us that the backbone of first-line treatment is carboplatin and paclitaxel. If patients have tumours that are PD-L1 positive, they receive pembrolizumab. Clinicians consider adding in bevacizumab if there is no risk of fistula formation. This expert advised us that before the NICE approval of pembrolizumab, standard first-line treatment was carboplatin, paclitaxel and bevacizumab. The company's clarification response A1 indicates that 50-70% of patients have tumours that are PD-L1 positive. This expert also advised that in the rare situation it is not possible to treat a patient with pembrolizumab or bevacizumab, but the patient is fit enough for chemotherapy, carboplatin and paclitaxel would be used. The other expert advising us generally concurred: they stated that first-line treatment is platinum and paclitaxel combination, with or without bevacizumab, and plus or minus pembrolizumab if PD-L1 positive. This expert noted that bevacizumab is rarely used and in their centre use of bevacizumab is avoided in patients who have received previous radical pelvic radiotherapy because it can cause fistulae. The

expert acknowledged, however, that practice may vary between centres and clinicians. We note that the clinical experts advising the EAG in TA885 indicated that over 50% patients who are suitable for systemic chemotherapy receive concomitant bevacizumab.¹¹ Our second advising expert cited here did not comment on the management of small cell cervix cancer with carboplatin and etoposide (as depicted in Figure 1), but noted that this is a different disease. This expert also stated that in their practice, they would not use topotecan in the first-line treatment for metastatic disease setting.

In summary, the CS depiction of the first-line treatments patients with recurrent or metastatic cervical cancer may receive in clinical practice is broadly accurate, but the CS does not mention that pembrolizumab plus chemotherapy with or without bevacizumab is recommended in TA939 as a treatment option specifically for patients who have PD-L1 positive tumours.⁶

2.2.2 Second-line and later therapy for recurrent or metastatic cervical cancer

In Figure 1 (the revised version of CS Figure 10 provided in response to clarification question A2), the company outlines the second- and third-line treatment options used in practice for treating recurrent or metastatic cervical cancer and some information about this is also provided in the text of the CS. The company points out that there is no standard of care second-line or later therapy for recurrent or metastatic cervical cancer and that patients may receive a range of single-agent chemotherapies, which offer similarly poor outcomes. Single agents listed in the CS and Figure 1 include topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed or weekly paclitaxel, but the CS notes that this is not an exhaustive list. Figure 1 also shows that clinical trial treatments may also be offered, if available. CS section 1.3.4.2 reports that the 2020 version of the British Gynaecological Cancer Society Guidelines suggests that re-challenge with platinum chemotherapy doublet can be considered if a patient has had a sufficient platinum-free interval. The company notes this option was not mentioned by clinicians at a UK Cervical Cancer advisory board (which, from confidential data-on-file information supplied by the company with the CS, [REDACTED]¹²). However, the company acknowledges that a survey they conducted of eight responding clinicians

in the UK found that five “*would consider platinum rechallenge for some cases*” (CS section 1.3.4.2) at second-line treatment.

The EAG’s advising clinical experts both agreed with the company’s statement that there is no absolute standard of care second-line therapy for recurrent or metastatic cervical cancer. It was also noted that the treatment landscape for cervical cancer is changing currently due to the introduction of pembrolizumab, which can be continued as a maintenance treatment and thus can lead to a longer treatment-free interval between first- and second-line therapy.

One of our advising experts noted that of patients treated at their centre who experience disease progression, at least half move onto best supportive care. If patients have been off treatment for a short time before disease progression and are fit enough, then at their centre they would offer the patient participation in a clinical trial. This expert estimated that between 30-40% of the patients at their centre may move onto a trial.

Both clinical experts advising us indicated that if a patient has had a treatment-free interval of at least six months, has experienced disease progression and they are fit enough, re-challenge with platinum doublet (e.g. paclitaxel and carboplatin) will be considered. Our experts estimated that between 10-20% of patients receive re-challenge with platinum doublet. Both experts also noted that single-agent weekly paclitaxel is a commonly used second-line or later therapy, with one expert estimating that 60% of patients receive this, while the other expert stated that it is not used in their centre but is often used in others. Both experts advised that single-agent gemcitabine and topotecan are also used in practice, but less often than paclitaxel.

The common use of platinum doublet treatment at second-line therapy in clinical practice is also indicated by findings from the company’s survey of eight clinicians in the UK, as mentioned above. [REDACTED]

[REDACTED]¹³ One of our advising clinical experts indicated that it is uncertain if re-challenge with platinum doublet would have a similar efficacy to single-agent chemotherapies such as

topotecan, gemcitabine, irinotecan, vinorelbine and pemetrexed. The other expert also suggested that this is uncertain but was of the opinion that it can be assumed to likely have a similar efficacy. Both experts indicated that there is a lack of trial evidence available to inform this.

We received clinical expert advice that current second-line treatment options are limited, not particularly effective and have toxicities. Paclitaxel, for example, is associated with a risk of peripheral neuropathy and so is used with caution, especially in patients with existing peripheral neuropathy. We also received advice that best supportive care is not a relevant comparator for tisotumab vedotin; systemic therapy is the relevant comparator. This is because a patient who is not fit enough to receive systemic treatment would also not be fit enough to receive tisotumab vedotin.

We asked the clinical experts advising us if there were any variations in practice within the National Health Service (NHS). One indicated that they did not believe there was for standard therapies, while the other stated that there is regional variation. Both experts pointed out that there is variable patient access to clinical trial treatments. Larger centres, for example, are more likely to run trials. We were also told that it is difficult for patients being treated in the palliative care setting to travel out-of-area to access a clinical trial treatment. In summary, single-agent weekly paclitaxel appears to be the most commonly used second-line or later therapy for recurrent or metastatic cervical cancer in clinical practice in patients who can receive systemic therapy. To a lesser extent, platinum doublet, gemcitabine and topotecan are also used. However, the EAG acknowledges that there are likely to be variations in practice across centres.

2.2.3 Background information on tisotumab vedotin

Tisotumab vedotin is an antibody-drug conjugate (CS Table 2) and the UK marketing authorisation is expected in [REDACTED]. The company outline the anticipated marketing authorisation indication in CS Table 2. A link to the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC)¹⁴ was provided in CS Appendix A section 1.1, but the CS did not contain a copy of the draft Medicines and Healthcare products Regulatory Agency (MHRA) SmPC. The company supplied the

draft MHRA SmPC¹⁵ in response to clarification question A3. As CS Table 2 states, tisotumab vedotin is expected to be indicated “*as a monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy*”. The CS states that the recommended dose is 2 milligrams per kilogramme (mg/kg) (up to a maximum of 200 mg), administered intravenously over 30 minutes every three weeks. The EAG notes that the [REDACTED] [REDACTED] the draft MHRA SmPC. One of the clinical experts advising us agreed that they expected that the infusion would take 30 minutes, while the other commented that they did not have experience using tisotumab vedotin yet. The MHRA SmPC states that tisotumab vedotin is to be given until disease progression or unacceptable toxicity.

Of note, tisotumab vedotin is associated with a risk of ocular adverse reactions (see section 3.3.6.3.1) and in CS section 2.11.1 and CS Figure 16 the company outline an eye care management plan developed to be used in the UK. This plan and the draft MHRA SmPC stipulates that before the first infusion, and then as clinically needed, an eye care professional should carry out an ophthalmic examination (including a visual acuity test and a slit lamp examination). The plan and draft SmPC also states that the treating clinician should inspect the patient’s eyes before each infusion and identify if a patient has any ocular signs and symptoms that require referral to an eye specialist. A schedule for administration of three different types of eyes drops during the treatment period is also outlined (preservative-free corticosteroid eye drops before and after the infusion, topical preservative-free vasoconstrictor eye drops immediately before each infusion and topical preservative-free lubricating eye drops throughout treatment and for 30 days after the last dose), as well as the need to apply cooling eye pads prior to the infusion (after the administration of the eye drops), during the infusion and for 30 minutes after the infusion. The plan and draft SmPC state that use of contact lenses should be avoided during treatment, unless an eye care professional advises otherwise. A more detailed eye care management plan for tisotumab vedotin was also supplied with the CS,¹⁶ providing information on the clinical presentation of conjunctival disorder, corneal disorder and periorbital disorder adverse events, as well as tisotumab vedotin dose modification guidelines for ocular adverse events.

Both the EAG's clinical experts pointed out that there are no facilities in oncology to carry out eye examinations, and this is not normally done before chemotherapy. We were advised that an ophthalmology doctor would need to carry out this task at least prior to treatment, because it requires specific expertise. One expert commented that they were uncertain whether a mechanism could be put into place for the checks to be done by opticians (and indicated that they did not know if that could be funded). We were also told that it is difficult for non-eye doctors to assess ocular toxicity during treatment, that oncologists might feel uncomfortable with performing eye examinations and that they may not be familiar enough with the signs and symptoms that should prompt referral for specialist assessment. Both experts believed that, if tisotumab vedotin were approved, eye departments would not have available resources to manage referrals for eye assessments both before and during treatment (note that 52.8% of participants in the pivotal tisotumab vedotin trial had an ocular event, with 4% of these being a grade 3 ocular event; see section 3.3.6.3.1). One expert said that the need to carry out eye assessments would require centres to set-up agreements with local eye specialists. It was also noted that emergency access to treatment would be challenging. Furthermore, one expert commented that attending an eye examination might cause patients inconvenience. We were advised that the eye care requirements associated with delivering tisotumab vedotin could present a barrier to introducing the treatment into a centre.

2.2.4 The position of tisotumab vedotin in the treatment pathway

The company outlines their proposed positioning of tisotumab vedotin in the clinical pathway for recurrent or metastatic cervical cancer in CS section 1.3.5. They argue that there is an unmet need for more effective second-line or later therapies which avoid repeated chemotherapy exposures. The company is positioning tisotumab vedotin as a second- and third-line monotherapy treatment option for adults with recurrent or metastatic disease progression on or after systemic therapy, as shown in Figure 1 and as confirmed in clarification response A1. Both the EAG's clinical experts expect that tisotumab vedotin will be used as a second-line or subsequent therapy.

EAG comment

The company provides a clear overview of cervical cancer and a generally accurate summary of the first-line, second-line and later therapies available for treating recurrent or metastatic cervical cancer. Clinical expert advice to the EAG is that single-agent weekly paclitaxel and re-challenge with platinum doublet chemotherapy are commonly used second-line or later treatments in practice. The company's positioning of tisotumab vedotin as a second- or third-line therapy is appropriate. The EAG's advising clinical experts expressed concern about the anticipated need for treating clinicians to assess patients for potential ocular toxicity during treatment with tisotumab vedotin and about a lack of available resources in treating centres to carry out eye examinations by eye care professionals before and during tisotumab vedotin treatment.

2.3 Critique of the company's definition of decision problem

Table 3 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. Overall, the company's decision problem adheres to the NICE scope, but notably the single-agent chemotherapy comparator specified by the company does not include paclitaxel, which were advised by clinical experts is the most commonly used second-line or later single-agent therapy in NHS practice (see section 2.2.2). Additionally, neither the NICE scope nor the company's decision problem include re-challenge with platinum doublet as a comparator, yet we understand from clinical expert advice that this is a commonly used second-line therapy in practice (see section 2.2.2).

In the company's decision problem and their economic analysis, the single-agent chemotherapy comparator is represented by an investigator's choice of chemotherapy comparator arm from the InnovaTV 301 pivotal randomised controlled trial (RCT) of tisotumab vedotin, in which investigators could choose to use topotecan, gemcitabine, irinotecan, vinorelbine or pemetrexed. Paclitaxel was not included in the trial comparator. The CS states that clinicians consulted at the UK Cervical Cancer advisory board did not consider the absence of paclitaxel from the InnovaTV 301 RCT a concern *"as there are no data supporting a difference in*

efficacy between the trial comparators and Q1W [once weekly] paclitaxel” (CS Table 1). In clarification question A7, we queried the meaning of “*no data*”. The company responded that this means that a limited number of studies have been conducted and that those carried out did not show that there is a difference in efficacy (clarification response A7).

The company provided some evidence in the CS and their clarification response to support an assumption of clinical efficacy equivalence between the single-agent chemotherapies included in the InnovaTV 301 RCT comparator with each other, as well as with paclitaxel. The EAG considers and comments on this evidence in detail, along with relevant findings from the CS clinical systematic literature review (SLR)¹⁷ and other evidence identified by the EAG, in Appendix 1. Overall, we conclude – from the information available to us (the EAG has not conducted its own systematic searches) – that the evidence base is subject to uncertainty due to sparse data.

The EAG received clinical expert advice that the agents included in the InnovaTV 301 RCT comparator arm can be assumed to have similar efficacy to each other. One clinical expert advising the EAG also believed paclitaxel has similar efficacy to the trial comparator agents (noting that even if a patient responds to paclitaxel, the response and duration of response are relatively limited). The other expert advising us considered that the response rate with paclitaxel would likely be greater than that achieved with the other agents, but they agreed its non-inclusion was not a concern.

Overall, in the absence of more convincing data and based on our experts’ advice, it seems reasonable to assume that the agents included in the InnovaTV 301 comparator arm have similar efficacy and that the efficacy of paclitaxel may also be reasonably represented by the InnovaTV 301 comparator arm. The EAG therefore agrees with the company’s approach of representing single-agent chemotherapy as the basket of single agents used in the comparator arm of the InnovaTV 301 RCT, even though the agents used and the percentage of participants who received each of them in the trial is not representative of NHS clinical practice (see section 2.2.2, which outlines the therapies used in practice, and see Table 5 in section 3.2.1.1.1, which shows the proportion of patients who received each therapy in the trial,

alongside the company's estimates of rates of use in clinical practice used for costings in the company's economic model, which were informed by a survey).

We note that, based on clinical expert advice to us (as outlined in Table 3), it is uncertain if the efficacy of re-challenge with platinum doublet might be adequately represented by the InnovaTV 301 RCT comparator arm. However, we acknowledge that platinum doublet was not a comparator specified in the NICE scope.

Table 3 Summary of the decision problem

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Population	People with recurrent or metastatic cervical cancer that has progressed on or after systemic treatment	Adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy	Population wording updated to align with expected MHRA marketing authorisation	The population is appropriate and aligns with the stated expected marketing authorisation indication set out in CS Table 2. In the CS, the company focuses on a second- and third-line therapy population.
Intervention	Tisotumab vedotin monotherapy	Tisotumab vedotin (Tivdak) as a monotherapy	Not applicable	In line with scope.

Comparators	Single-agent chemotherapy (including but not limited to paclitaxel, doxorubicin, gemcitabine and topotecan) Best supportive care	Single-agent chemotherapy (including topotecan, gemcitabine, irinotecan, vinorelbine, pemetrexed)	There is currently no standard of care in second line r/m CC. The chemotherapies included in the comparator list (i.e., topotecan, gemcitabine, irinotecan, vinorelbine, pemetrexed) reflect chemotherapies from InnovaTV 301 and represent single-agent chemotherapy as a comparator in the economic model. Since tisotumab vedotin is an antibody-targeted chemotherapy the majority of patients unsuitable for chemotherapy would likely also be unsuitable for treatment with tisotumab vedotin. BSC would therefore not comprise a suitable comparator to tisotumab vedotin	The EAG agrees with the company's approach of representing single-agent chemotherapy as the basket of single agents used in the comparator arm of the InnovaTV 301 RCT, even though the agents used and the percentage of participants who received them in the trial is not representative of NHS clinical practice (see sections 2.2.2, 3.2.1.1.1 and text above in this section). We received clinical expert advice that these agents can be assumed to have similar efficacy. The EAG notes that paclitaxel has not been included in the company's decision problem as a comparator, yet this is the most commonly used single agent at second-line or later therapy in clinical practice (see section 2.2.2). However, the EAG believes that the efficacy of paclitaxel may also be reasonably represented by the InnovaTV 301 comparator arm (please see the text above in this

			since BSC is generally reserved for patients who are unsuitable for chemotherapy. During clinician engagement at the UK Cervical Cancer advisory board and an additional survey of 8 UK based oncologists with expertise in gynaecological cancers, Q1W paclitaxel was identified as a frequently used chemotherapy monotherapy in this population. Clinicians also agreed at the UK Cervical Cancer advisory board that the absence of paclitaxel from the clinical trial is not a concern as there are no data supporting a difference in efficacy between the trial comparators and Q1W paclitaxel. Q1W	report section for a discussion of the EAG's reasons). We note that re-challenge with platinum doublet is also used in clinical practice at second-line therapy, and thus is a relevant comparator for tisotumab vedotin (see section 2.2.2) but this was not included in either the NICE scope nor the company's decision problem. We were advised by clinical experts that it is uncertain if platinum doublet has a similar efficacy to the single-agent chemotherapies used in the InnovaTV 301 comparator arm (due to lack of trial evidence) (see section 2.2.2), but one believed it is likely it would. Therefore, there is some uncertainty about whether the efficacy of re-challenge with platinum doublet may also be adequately represented by the comparator arm of the Innova 301 trial. Our clinical experts agreed with the company that best

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
			paclitaxel is included in the base-case modelling scenario as a cost comparator to reflect this element of UK clinical practice.	supportive care is not a relevant comparator for tisotumab vedotin (see section 2.2.2).
Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • response rates • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • PFS • OS • Response rates • Adverse effects of treatment • HRQoL	Not applicable	In line with scope.

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Economic analysis	Reference case requirements (NICE scope wording abridged by EAG here for brevity): Costs to be assessed as incremental cost per quality-adjusted life year (QALY), adequate time horizon, NHS and Personal Social Services perspective, commercial arrangements and managed access taken into account, and availability and cost of biosimilar and generic products taken into account.	Cost-effectiveness expressed as incremental cost per quality-adjusted life year as per the reference case.	Not applicable	The company's economic analysis aligns with the requirements set out in the NICE reference case (see section 4.2.1). The CS provides details about a patient access scheme discount for tisotumab vedotin (CS section 3.5.1.1), which is applied in the company's cost-effectiveness analyses (see Table 19 of this report).

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Subgroups	None specified.	-	-	No subgroups were specified in the NICE scope, but the company have provided results of subgroup analyses of OS, PFS and confirmed ORR by various patient characteristics for the key phase 3 RCT included in the CS (InnovaTV 301) and of confirmed ORR for the included supportive phase 2 single-arm trial (InnovaTV 204) (CS Appendix C).
Special considerations including issues related to equity or equality	None specified.	Cervical cancer affects females, often in their younger child-bearing years and while they are actively raising families. The disease burden of cervical cancer is greater among those with lower socioeconomic status and non-white ethnic populations in the UK.	Not applicable	No special considerations were outlined in the scope, but the company comments on equity and equality issues in their decision problem. Neither the EAG, nor our advising clinical experts, have identified any additional equity or equality issues.

Source: Partly reproduced from CS Table 1.

A dash (-) indicates that the associated table element was not included in CS Table 1.

BSC, best supportive care; CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q1W, once weekly; QALY, quality adjusted life year; r/m CC, recurrent or metastatic cervical cancer; UK, United Kingdom

3 Clinical effectiveness

This section presents a summary and critique of the clinical effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Sections 3.4 to 3.5 critique any indirect comparisons presented by the company. Section 3.6 covers additional work done by the EAG.

3.1 Critique of the methods of review

The systematic literature review of clinical effectiveness evidence in the CS was underpinned by a broad search to identify evidence for the efficacy of second-line or later treatments for previously treated, persistent/recurrent or metastatic cervical cancer. This search and the inclusion and exclusion criteria for the SLR encompassed a wider range of comparators than specified in the NICE scope and company decision problem (further details are provided in Appendix 2, Table 41). The review was generally well conducted, and it is unlikely that the searches missed any relevant studies. However, the inclusion and exclusion criteria limited eligibility to studies published since 2003 and studies with fewer than 10 patients with the eligible histologies were excluded. The company explained in their response to clarification question A4, that the 2003 cut-off date reflected cisplatin-based doublet regimens becoming the first-line standard of care from 2004 onwards for patients with recurrent or metastatic cervical cancer. Limiting studies to those from 2003 onwards also meant that older studies, with treatment practices less relevant to current clinical practice were not included. We view this as appropriate. Studies with fewer than 10 eligible patients were excluded to help minimise the influence of case reports and very small studies with the aim of achieving a robust and generalisable evidence base. We feel this is acceptable in this case.

3.2 Critique of the methods of the trials of the technology of interest

3.2.1 Included studies

The CS clinical effectiveness systematic literature review identified five studies of tisotumab vedotin for inclusion in the review (InnovaTV 301,¹⁸ InnovaTV 201,¹⁹ InnovaTV 204,²⁰ InnovaTV 206²¹ and Innova TV 205;²² see Table 42 in Appendix 3). Of these, the company included data from InnovaTV 301 (a phase 3 randomised RCT) and InnovaTV 204 (a phase 2 single arm trial) in the CS. The EAG considers this appropriate. We note that of the remaining studies, one evaluated tisotumab vedotin plus pembrolizumab (InnovaTV 205) and thus does not match the intervention specified in the NICE scope nor in the company's decision problem. The other two studies were phase 1/2 dose escalation and expansion studies (InnovaTV 201 and InnovaTV 206) that provided limited clinical efficacy data. Please see Table 42 in Appendix 3 for our more detailed comments.

The following outcome data from the InnovaTV 301 RCT informed the company's economic analyses: overall survival (OS), progression-free survival (PFS), adverse effects and health-related quality of life.

The company does not directly use the InnovaTV 204 single-arm trial in their cost-effectiveness analyses in either their base case or scenario analyses. Instead, the only way that data from this trial are utilised is to externally validate the modelled OS and PFS extrapolations from InnovaTV 301 (through a visual comparison with of the modelled curves with the curves from the InnovaTV 204 single-arm trial; CS section 3.13.1.2 and CS Appendix H Figures 15 and 16). Therefore, in this chapter, we mainly focus on describing and critiquing the pivotal InnovaTV 301 RCT and we briefly summarise the InnovaTV 204 single-arm trial.

InnovaTV 301 was funded by Genmab and Seagen.¹⁸ InnovaTV 204 was funded by Genmab, Seagen, the Gynaecologic Oncology Group and the European Network of Gynaecological Oncological Trial Groups.²⁰

3.2.1.1 Study characteristics

3.2.1.1.1 *InnovaTV 301*

The characteristics of the InnovaTV 301 RCT (also known as SGNTV-003; NCT04697628) are summarised in Table 4. InnovaTV 301 is an ongoing, phase 3, global, multicentre, open-label trial that compares tisotumab vedotin to investigator's choice of single-agent chemotherapy in 502 randomised participants with recurrent or metastatic cervical cancer who had disease progression on or after prior systemic therapy. The trial evaluates the dose of tisotumab vedotin which CS Table 2 states is the recommended dose [REDACTED] ¹⁵ (provided in response to clarification question A3). The trial's participant eligibility criteria are shown in Table 4. The criteria limited inclusion to participants with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. One of the EAG's advising clinical experts commented that the criteria are representative of the patient population with recurrent or metastatic cervical cancer that has progressed on or after systemic treatment who are expected to be treated with tisotumab vedotin in clinical practice. One expert commented that some patients have an ECOG performance status of 2 or more. Both experts expect that tisotumab vedotin will only be used to treat people with an ECOG performance status of 0 or 1 (as per the trial).

In the investigator's choice of chemotherapy arm, participants could receive either topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed, all given as single-agent chemotherapies and administered as per the dose regimens outlined in Table 4. The proportion of participants who received each chemotherapy in the trial is shown in Table 5. This table also shows the EAG's clinical experts' estimations of the proportions of patients in NHS practice with recurrent or metastatic cervical cancer who have had disease progression on or after systemic therapy who receive each of the trial single-agent chemotherapies and other treatments, alongside the proportions assumed for costing in the company's economic model which were informed by the company's survey of eight responding clinicians in the UK (see section 4.2.8.1.1 for a further discussion of the single-agent chemotherapy costing assumptions used in the model). As discussed in section 2.3 and as suggested by the estimated use in clinical practice shown in Table 5 (which we acknowledge is

limited to information from two clinicians), the proportions of participants receiving each chemotherapy in the InnovaTV 301 RCT are not representative of clinical practice, especially because weekly paclitaxel (a commonly used chemotherapy in NHS practice) was not a comparator treatment option in the trial. Note, though, that weekly paclitaxel is included in and costed in the company's economic model. In the model, the distribution of patients assumed to receive each included single-agent chemotherapy is adjusted based on a survey of eight UK clinicians for the purpose of costing to try to better reflect use in clinical practice (see section 4.2.8.1.1). As argued in section 2.3, the EAG considers that the InnovaTV 301 investigators' choice of chemotherapy arm adequately represents the likely efficacy of the single-agent chemotherapy treatments used in practice, including weekly paclitaxel. Platinum doublet was also not comparator treatment option in the trial, but is commonly used in NHS practice (see section 2.2.2 and Table 5). However, re-challenge with platinum doublet falls outside the NICE scope for this appraisal and was not included in the company's economic model as a comparator.

The EAG notes that none of the single-agent chemotherapies used in the InnovaTV 301 RCT comparator arm appears to have an MHRA marketing authorisation for use as a monotherapy in the cervical cancer indication.²³⁻²⁶ Topotecan in combination with cisplatin has a marketing authorisation for use in cervical cancer that has recurred after radiotherapy or for stage IVB disease²⁷ (and, as mentioned in section 2.2.1, is approved by NICE as a treatment option for recurrent or stage IVB cervical cancer, if cisplatin has not previously been received⁵). Therefore, the doses of these agents used in the InnovaTV 301 RCT could not be checked against SmPCs. Our clinical experts were unable to fully comment on whether the dose regimens of all the agents used in the comparator arms reflect those used in clinical practice because they did not have experience of using all the chemotherapies, but where known, they generally indicated that they did. However, we were informed by one expert that topotecan is given weekly in practice rather than on Days 1 to 5 of a 21-day cycle as used in the trial because it is not feasible in a palliative care setting for patients to attend clinic that frequently. Thus, there is some uncertainty about the extent to which the dose regimens of the comparator agents used in the trial reflect those used in clinical practice.

As noted in section 2.3, tisotumab vedotin is associated with a risk of ocular adverse reactions. The trial paper¹⁸ outlines that in InnovaTV 301 all patients had a baseline ophthalmic examination and that patients in receipt of tisotumab vedotin received referral to an eye specialist if they had declining ocular symptoms or if new ocular symptoms occurred. At each study visit, except the survival follow-up visit, the investigator performed an eye examination and the treating clinician or a delegate carried out an ocular examination as needed (trial paper supplementary appendix, page 20¹⁸). This reflects the company's anticipated eye care management plan (CS Figure 16) and the procedure set out in the EMA SmPC.¹⁴

The primary outcome of the InnovaTV 301 RCT was OS and the key secondary outcome was PFS. The other outcomes assessed are listed in Table 4. Disease progression was assessed by the investigator only; there was no verification by an independent review committee (IRC) (clarification response A11). The clinicaltrials.gov record for InnovaTV 301 states that it is estimated that the trial will complete in May 2026.²⁸ The CS presents results from a primary analysis data cut of InnovaTV 301 dated 24th July 2023 and from an ad-hoc follow-up analysis dated January 2024 (OS and PFS only), which the CS states was conducted in response to regulatory queries. The median follow-up times for OS at each data cut are shown in Table 4. Study visits appear to have taken place on [REDACTED] (company data on file, 'InnovaTV 301 Clinical Study Report [CSR] Tables, Listings, Figures [July-2023], Table 14.5.3.5²⁹).

Table 4 Summary of the characteristics of the InnovaTV 301 RCT

Characteristic	InnovaTV 301 RCT (also known as SGNTV-003; NCT04697628)
Role in this evaluation	Pivotal trial of tisotumab vedotin; the key source of the clinical effectiveness data that informs the economic model (OS, PFS, AEs) and the source of the health state utilities used in the company's economic model base case (which were estimated from the EQ-5D-5L data collected during the trial; CS section 3.4.1).
Study type	Ongoing phase 3, randomised, active-comparator, open-label study.
Patient group	People with recurrent or metastatic cervical cancer who have received 1 or 2 prior lines of systemic therapy.

Characteristic	InnovaTV 301 RCT (also known as SGNTV-003; NCT04697628)
Summary of key inclusion criteria	• Age ≥18 years, or considered an adult by local regulations at trial consent. • Recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology. • Experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible), defined as either: • paclitaxel+cisplatin+bevacizumab+ anti-PD-(L)1 agent, or • paclitaxel+carboplatin+bevacizumab+ anti-PD-(L)1 agent, or • paclitaxel+topotecan/nogitecan+bevacizumab+ anti-PD-(L)1 agent (EAG note: trial paper¹⁸ states that the requirement for patients to have received bevacizumab or anti-PD-L1 agent such as pembrolizumab was dependent on availability and patient eligibility.) • Received 1 or 2 prior systemic therapy regimens for recurrent or metastatic cervical cancer. This could include single agent therapy with an anti-PD(L)1 agent, but not chemotherapy, administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy. • Measurable disease according to RECIST v1.1 (investigator assessed). • ECOG PS of 0 or 1. • Life expectancy ≥3 months.
Intervention	Tisotumab vedotin 2.0 mg/kg IV every 3 weeks, administered on Day 1 of each 21-day treatment cycle until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, study termination by the sponsor, pregnancy, or death, whichever occurred first.
Comparator	Investigator's choice of single-agent chemotherapy: • Topotecan 1 or 1.25 mg/m² IV on Days 1 to 5, every 21 days • Vinorelbine 30 mg/m² IV on Days 1 and 8, every 21 days • Gemcitabine 1000 mg/m² IV on Days 1 and 8, every 21 days • Irinotecan 100 or 125 mg/m² IV weekly for 28 days, every 42 days • Pemetrexed 500mg/m² IV on Day 1 every 21 days

Characteristic	InnovaTV 301 RCT (also known as SGNTV-003; NCT04697628)
Number of randomised participants	502 (tisotumab vedotin n = 253, and investigator's choice of chemotherapy n = 249)
Randomisation stratification factors	• ECOG PS (0 vs. 1) • prior bevacizumab administration (yes vs. no) • region (US, EU or other) • prior anti-programmed cell death protein 1 or PD-(L)1 therapy administration (yes vs. no)
Duration	OS median follow-up times: • 10.8 months (95% CI: 10.3, 11.6)¹⁸ (primary analysis dated 24th July 2023) • [REDACTED] (ad-hoc follow-up analysis dated 16th January 2024; company data on file,³⁰ page 1)
Location	27 countries (168 sites) across North America, Asia, Europe and Latin America. [REDACTED] participants from the UK were enrolled ([REDACTED] in each arm).
Endpoints	• Primary efficacy endpoint: OS • Key secondary efficacy endpoint: PFS • Other secondary endpoints: time to response, duration of response, safety, side-effect profile, and patient-reported outcomes.

Source: Partly reproduced from CS Tables 6, and 7, CS sections 2.3.1.1, 2.3.2.1 and 3.4.1, and CS Appendix Figure 3.

AEs, adverse events; CS, company submission; CSR, clinical study report; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; EU, European Union; IV, intravenous; OS, overall survival; PD-(L)1, Programmed cell death-ligand 1; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours; US, United States

Table 5 Proportion of participants in the InnovaTV 301 RCT who received each chemotherapy in the comparator arm, the EAG's clinical experts' estimations of treatment use in clinical practice and the chemotherapy distributions used in the company's economic model for costing

Single-agent chemotherapy / treatment	Investigator's choice of chemotherapy in the InnovaTV 301 trial, number of participants (%)	Chemotherapy distribution used for costing in company's economic model, % of patients	EAG's Expert 1's estimation of distribution in clinical practice, %	EAG's Expert 2's estimation of distribution in clinical practice, %
Used in comparator arm in InnovaTV 301 trial:				
Pemetrexed	80 (33.5)	0.3	0	0
Gemcitabine	109 (45.6)	28.4	20	0
Topotecan	19 (7.9)	4.7	10	Used rarely
Irinotecan	14 (5.9)	0.3	0	0
Vinorelbine	17 (7.1)	2.0	0	0
Not used in comparator arm in InnovaTV 301 trial, but used in NHS practice:				
Paclitaxel	0	64.3	60	0 ^a
Platinum doublet	0	0	10	20 to 40
Clinical trial	Not applicable	Not applicable	No comment	60 to 80

Source: Partly reproduced from CS Tables 10 and 14.

Note. Expert 2 commented that in their centre, of the patients who experience disease progression, at least 50% move onto best supportive care. Of the remaining patients, they estimated that between 30-40% enter a clinical trial, 10-20% receive re-challenge with platinum doublet and very occasionally topotecan is used as a single agent. Therefore, to arrive at the percentages presented

in the table, the EAG has doubled the expert's estimates to present the percentage of participants who do not receive best supportive care who are estimated to receive each intervention.

RCT, randomised controlled trial.

^a Not used in this expert's centre, but the expert stated that it is commonly used in other treating centres.

No cross-over was permitted between the treatment arms in InnovaTV 301.¹⁸ Subsequent treatments were used (CS section 2.7) and these are shown in CS Tables 27 (primary analysis data cut; July 2023) and 28 (ad-hoc follow-up analysis for OS; January 2024). We note that 50.2% and 43.4% of participants in the tisotumab vedotin and chemotherapy arms received subsequent anti-cancer therapies, respectively,¹⁸ [REDACTED] (InnovaTV 301 RCT CSR,³¹ Table 14.2.6). In clarification response A21, the company argue that the subsequent treatments received in the trial are a reasonable representation of those used in NHS practice, based on responses from seven UK oncologists to their survey and feedback from a further four oncologists consulted to inform their clarification response. The company also reiterated that there is no standard of care for second-line or later therapy and that a range of agents are used as subsequent treatments.

We received advice from one of our clinical experts that most of the patients at their centre would move onto best supportive care or a clinical trial. This expert advised that, of the subsequent treatments used in the trial as third- to fifth-line therapies, [REDACTED] is not available in England and Wales to treat cervix cancer, [REDACTED] is used as a first-line therapy only, [REDACTED] is not licensed in the UK and [REDACTED] is rarely used (see CS Tables 27 and 28 for the numbers and proportions of participants receiving each of these treatments). Therefore, the subsequent therapies received by a small proportion of the participants in the trial by the ad hoc, follow-up analysis are not fully representative of those used in clinical practice. The company explores potential bias from initiation of subsequent therapy receipt in a sensitivity analysis of OS (see sections 3.2.4 and 3.3.1 and Table 43 in Appendix 4).

3.2.1.1.2 *InnovaTV 204*

InnovaTV 204 (also known as GCT1015-04; NCT03438396) was a single-arm, phase 2, multicentre trial of tisotumab vedotin which enrolled 102 participants from the United States and Europe who had previously treated recurrent or metastatic cervical cancer with disease progression during or after doublet chemotherapy (paclitaxel plus either platinum or topotecan) with bevacizumab (if eligible by local standards) (CS Table 8 and Coleman et al., 2021²⁰). Participants were included if

they had received two or fewer prior systemic therapy regimens (excluding adjuvant or neoadjuvant chemotherapy with or without radiotherapy) and had an ECOG performance status of 0 or 1. More information about the trial inclusion and exclusion criteria is reported in CS Table 8. No participants from the UK were enrolled (CS Table 11). Participants received tisotumab vedotin 2.0 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity (i.e. the stated recommended dose in CS Table 2 and the draft MHRA SmPC¹⁵). Progressive disease was verified by an independent review committee. The primary outcome was objective response rate, as assessed by the independent review committee, with PFS and investigator assessed confirmed objective response rate as key secondary outcomes. Median follow-up at the time of the primary analysis was 10.0 months (interquartile range [IQR] 6.1-13.0) (CS section 2.4.2).

3.2.1.2 Patients' baseline characteristics

3.2.1.2.1 *InnovaTV 301*

The company presents participants' demographic and clinical baseline characteristics from the InnovaTV 301 RCT in CS section 2.3.2.1. The company comments that these were balanced between the trial arms, and the EAG agrees.

We received feedback from our experts that the following baseline characteristics of the participants in the InnovaTV 301 RCT are representative of the characteristics of the patients seen in clinical practice:

- histological type of cervical cancer (in the trial, 63.1% overall had SCC, 31.9% overall had adenocarcinoma and 5% overall had adenosquamous carcinoma),
- the proportion with recurrent or persistent disease (in the trial, 10.2% overall; the remaining proportion had metastatic disease [stage IVB] at baseline), and,
- the number of prior lines of therapy participants had had (in the trial, one prior line: 61.4% overall; two prior lines: 38.4% overall).

Most of the participants (>98% in each arm) had received a platinum agent at first-line treatment. In their assessment report for tisotumab vedotin, the EMA commented that prior platinum therapy is not considered to be a treatment effect modifier.³²

Regarding the median age of the participants at baseline in the trial (50 years overall, range 26-80), one of the EAG's clinical experts commented that the median age in practice is 60, while the other expert commented that median age is slightly lower in practice than it was in the trial. The EAG's experts thought that the proportion of White participants at baseline (48.6% overall) was lower than in clinical practice in the UK, but it was acknowledged that this is often the case in trials and that there is geographical variation in the UK.

At baseline, 54.4% of the participants overall had an ECOG performance status of 0, while 45.6% had a performance status of 1. One expert thought this split was reflective of clinical practice, while the other suggested that the ratio of patients with a performance status of 1 to those with a status of 0 is about 2:1 in clinical practice.

In the trial, 63.9% of the participants overall had received prior bevacizumab. One expert informed us that bevacizumab is rarely used in practice and that in their centre around 10-20% of patients are likely to receive bevacizumab (we were told that patients who have had radiotherapy and develop metastatic disease would not be treated with bevacizumab). The other expert advising us estimated that around 60-70% of the patients in their practice will have received prior bevacizumab. As stated in section 2.2.1, we note that in TA885 the clinical experts advising the EAG suggested that over 50% of the patients who are suitable for systemic chemotherapy receive concomitant bevacizumab.¹¹

Overall, the baseline characteristics of the participants in the InnovaTV 301 RCT appear relatively representative of the patients treated in NHS clinical practice, except there may be some uncertainty about whether the performance status distribution and extent of prior use of bevacizumab is reflective of practice. We were informed by one of the clinical experts advising us that performance status is the most important predictor of outcomes such as OS and PFS, with burden and site of disease also being important.

3.2.1.2.2 *InnovaTV 204*

The baseline characteristics of the participants included in the InnovaTV 204 single-arm trial are presented in CS Table 12 and we briefly summarise them here. Median age was 50 years (range: 43-58) and most of the participants were White (95%). The

majority (58%) had an ECOG performance status of 0 and 42% had a performance status of 1. CS Table 13 shows that most (94%) were living with extrapelvic metastatic disease at baseline, and 27% had a tumour with an adenocarcinoma histology. The majority (70%) had received one prior line of therapy for recurrent or metastatic disease, with 30% having received two prior lines. Most (69%) had also received prior bevacizumab.

EAG comment on included studies

The single-agent chemotherapies included in the investigator's choice of chemotherapy arm of the InnovaTV 301 RCT and the proportions of participants receiving these are not fully representative of the therapies used in NHS clinical practice, particularly because weekly paclitaxel and platinum doublet were not options in the trial. However, despite this, the EAG considers that the comparator arm will likely adequately capture the expected efficacy of second- and third-line treatment in practice, for the reasons set out in section 2.3. Thus, we suggest that the results of the trial can be considered generalisable to NHS practice. The baseline characteristics of the participants in the InnovaTV301 RCT are reasonably representative of the patients treated in clinical practice.

3.2.2 Risk of bias assessment

3.2.2.1 InnovaTV 301 RCT

The company summarise their risk of bias assessment of the InnovaTV 301 RCT in CS section 2.5 with further detail provided in CS Appendix B 1.3 Table 5. In response to clarification question A6 the company stated that they had used the Cochrane Risk of Bias (ROB 1) tool.³³ We have used the same tool to independently assess the InnovaTV 301 RCT and present our findings alongside those of the company in Appendix 5 Table 44. Our main concern is that, as an open-label trial, InnovaTV 301 is considered to be more susceptible to bias than would have been the case if blinding had been possible. Although the primary outcome, OS, is considered to be an objective outcome, there is at least the theoretical possibility that knowledge of treatment received during the trial could affect decisions made by investigators about which post-progression therapies or other aspects of care to offer

and trial participants' decisions about which options to take up. For the key secondary outcome of PFS, disease progression was documented by the investigator and there was no central review of this outcome (clarification response A11). This aligns with clinical practice (where a clinician will judge whether disease progression has occurred or not) but we would have preferred to see PFS by blinded independent central review in addition to increase our confidence in the results for this outcome (in the InnovaTV 204 single-arm trial PFS was assessed both by investigators and by blinded central review and the estimates of median PFS were similar). We therefore have some concerns about the potential for bias in the PFS outcome, and to a lesser degree the OS outcome.

Although not all trial outcomes were reported in the published paper, we had access to the trial CSR and found that all outcomes are reported there so, in the context of this appraisal, we have no concerns about selective outcome reporting.

3.2.2.2 InnovaTV 204 single-arm trial

The summary of the company's risk of bias assessment of the InnovaTV 204 single-arm trial is provided in CS section 2.5 with further detail provided in CS Appendix B 1.3 Table 6. In response to clarification question A6 the company states they used the Cochrane Risk of bias tool for the critical appraisal of the InnovaTV204 single-arm trial, but describe this as a randomised controlled trial (when it is single-arm study). The company's response to clarification A6 further states that the case series Centre for Reviews and Dissemination (CRD) checklist was applied to the other Innova trials, so our assumption is that the company used the CRD checklist for case series to assess the InnovaTV 204 single-arm trial. As results from this trial are only used to validate the modelled OS and PFS extrapolations from the InnovaTV 301 RCT we have not conducted an independent assessment of the risk of bias for this study. However, we note that the absence of a control arm and the lack of blinding put the trial at significant risks of bias and the results of this trial are therefore subject to uncertainty.

EAG conclusion on risk of bias

For the InnovaTV 301 RCT the EAG has concerns that the risks of bias inherent in an unblinded trial could lead to biases in the trial results, particularly for PFS

because there was no blinded independent central review for this key secondary outcome. The InnovaTV 204 study was an unblinded single-arm trial and therefore at significant risk of bias.

3.2.3 Outcomes assessment

The outcomes measured in the InnovaTV 301 RCT that are specified in the decision problem are listed in CS Table 6 (OS, PFS, response rates, adverse effects of treatment and health-related quality of life), with CS Table 7 also listing the primary outcome and other outcomes used in the model or specified in the NICE scope. OS, PFS, adverse effects of treatment and health-related quality of life outcomes were used in the company's economic model and we focus on discussing those here. The InnovaTV 301 RCT also included exploratory outcomes (e.g. tumour tissue factor expression, anti-drug antibodies)³⁴ which are not included in the CS, do not contribute to the economic model and are not included here.

In the InnovaTV 204 single-arm trial the primary outcome was confirmed objective response rate assessed by an independent review committee. Other response-based outcomes, PFS (assessed by independent review committee and by the investigator) and OS were secondary outcomes.²⁰ As previously noted, results from this study are not used directly in the company's cost-effectiveness analyses so we only include a brief summary here.

3.2.3.1 Efficacy outcome(s)

The primary outcome of the InnovaTV 301 RCT was OS (CS section 2.3.1.1 Table 7) and PFS is described in the CS as a key secondary outcome. Other secondary efficacy outcomes included in the CS were confirmed objective response rate, time-to-response and duration of response. The company definitions of these outcomes are shown in Table 6 below.

The outcomes in Table 6 are standard oncology trial outcomes. During the trial, imaging to assess disease progression was conducted every 6 weeks for the first 30 weeks and thereafter every 12 weeks until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death or the end of the study (which ever

occurred first). Clinical expert advice to the EAG indicated that imaging to assess disease progression during treatment would usually occur every 3 months in NHS practice, therefore more frequent imaging occurred during the first 30 weeks of the trial than would be expected in practice. The investigators assessed disease progression and response outcomes; there was no blinded independent central review of disease progression (confirmed by company response to clarification question A11).

Table 6 Definitions for the efficacy outcomes reported in the company submission for the InnovaTV 301 RCT

Outcome	Definition
Overall survival (primary outcome)	The time from randomisation to the date of death from any cause (CS section 2.3.1.1)
Progression-free survival (key secondary outcome)	The time from randomisation to the first documentation by the investigator of disease progression according to RECIST v1.1, or to the date of death from any cause, whichever occurred first (CS section 2.3.1.1).
Confirmed objective response rate	Complete response + partial response based on RECIST v1.1 as assessed by the investigator (CS Table 24).
Time-to-response	The time from randomisation to the first confirmed objective response (complete response or partial response that is subsequently confirmed) assessed by the investigator (CS section 2.6.1).
Duration of response	The time from the date of the first confirmed objective response (complete response or partial response that is subsequently confirmed) to the date of the first documented progressive disease per RECIST v1.1 or death from any cause, whichever occurs first (CS section 2.6.1).

Source: EAG table created from information presented in CS Table 6, CS Table 7, CS Table 24 and CS sections 2.3.1.1 and 2.6.1

CS, company submission; RECIST, Response Evaluation Criteria in Solid Tumours

The efficacy outcomes from the InnovaTV 204 single-arm trial were defined similarly to those of the InnovaTV 301 RCT except that there was an independent review committee that assessed response and progression (for response outcomes and PFS) as well as an investigator assessment and the starting time for PFS and OS was the time from the first dose of study drug²⁰ (whereas in the InnovaTV 301 RCT these outcomes were measured from randomisation).

3.2.3.2 HRQoL outcomes

The patient-reported outcome measures used in the InnovaTV 301 RCT were the European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) (index score³⁴ and visual analog scale), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cervical cancer module³⁵ (EORTC-QLQ-CX24) which is the cervical cancer-specific module that supplements the core EORTC-QLQ-C30 questionnaire. All were secondary outcomes of the trial.³⁴ The CS reports rates of participant compliance with and completion of these patient-reported outcome measures. The compliance rate is defined in the CS as the percentage of participants who completed the questionnaire among those who were alive and receiving treatment. The completion rate is not defined in the CS but the CSR states that this is [REDACTED]. The HRQoL measures are briefly described in Appendix 6 Table 45.

The InnovaTV 204 single-arm trial assessed quality of life using the EORTC-QLQ-C30 and the EORTC-QLQ-CX24 questionnaires as exploratory endpoints.³⁶ The results are not reported in the CS.

3.2.3.3 Safety outcomes

The protocol for the InnovaTV 301 RCT states that the Medical Dictionary for Regulatory Activities (MedDRA, [REDACTED]) would be used to list and summarise the following types of adverse events: treatment-emergent adverse events (TEAEs), treatment-related TEAEs, grade 3 and higher TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related treatment-emergent SAEs, deaths, TEAEs

leading to dose modification, and TEAEs leading to study treatment discontinuation.³⁴ TEAEs were defined as “*events that are new or worsened on or after the first dose of study treatment (tisotumab vedotin or chemotherapy) and with onset date on or before 30 days after the last dose of study treatment*” (definition provided in footnote to CS Table 30). Adverse events of special interest (ocular events, bleeding events and peripheral neuropathy) are also reported in CS section 2.11.1

The adverse events assessed and reported in CS section 2.11.2 from the InnovaTV 204 single-arm trial are treatment-related adverse events, serious adverse events and adverse events of special interest.

EAG comment on outcomes assessment

The outcomes assessed during the InnovaTV 301 RCT and the InnovaTV 204 single-arm trial are appropriate for an oncology trial and we do not have any concerns about outcome assessment.

3.2.4 Statistical methods of the included studies

We summarise and critique the statistical methods used in the InnovaTV 301 RCT trial in Table 7, and more briefly comment on the methods used in the InnovaTV 204 single-arm trial after the table.

Table 7 Statistical methods of the InnovaTV 301 RCT

Analysis populations
Brief description The CS describes four analysis sets for the InnovaTV 301 RCT in CS Table 16 indicating how many participants are included and for which analyses they are used. The CS includes results based on analyses of the intention-to-treat (ITT), safety and patient-reported outcome full analysis (PRO FAS) sets but no results from the fourth set, pharmacokinetics (PK), are reported in the CS (these are available in the CSR).
EAG comment: The CS has clearly defined the analysis populations used for different analyses and we do not have any concerns about these.

Sample size calculations
Brief description The CS summarises the sample size calculation in CS Table 17 (the footnotes include the assumptions needed for the calculation). The study was powered for the RCT's primary hypothesis that tisotumab vedotin would prolong OS when compared with the investigator's choice of chemotherapy. As 502 participants were randomised to the study, this [REDACTED] the estimated [REDACTED] randomised participants needed to give 90% overall power. The CSR provides additional details indicating that [REDACTED] [REDACTED] [REDACTED] [REDACTED] (there were 392 events) [REDACTED] [REDACTED] [REDACTED]
EAG comment: The EAG has no concerns about the sample size calculations.
Methods to account for multiplicity
Brief description The outcomes of OS, PFS and objective response rate were tested hierarchically in that order (CS Table 17). The CSR provides additional detail [REDACTED] [REDACTED] [REDACTED] [REDACTED]
EAG comment: The described hierarchical multiple testing procedures appear appropriate and EAG has no concerns.
Analysis of outcomes
Brief description CS Table 17 describes the statistical analyses used for OS, PFS and confirmed ORR. DoR was summarised descriptively. CS Table 17 does not state how the HRQoL outcomes were analysed. The CSR states that [REDACTED] [REDACTED] [REDACTED] [REDACTED]
EAG comment: Appropriate statistical methods were used.

Handling of missing data
Brief description CS Table 17 describes the circumstances that would lead to a participant being withdrawn from the study. Missing data were not imputed, aside from the following missing items which were handled as described in CS Table 17: adverse event dates, disease diagnosis date, subsequent cancer-related therapy start date, and prior therapy start date and end date (providing month and year information were available for these, otherwise there was no imputation). Censoring rules for time-to-event outcomes are not described in the CS but are available from the publicly available statistical analysis plan.³⁸
EAG comment: For the most part missing data were not imputed and censoring rules appear to follow censoring rules seen in other cancer treatment trials.
Sensitivity & post-hoc analyses
Brief description No sensitivity or post-hoc analyses are described in the CS. In response to clarification question A16 the company provide information for two sensitivity analyses conducted for OS and three sensitivity analysis conducted for PFS from the July 2023 data-cut. The two OS analyses were an unstratified analysis and an analysis in which participants were censored at the time they took subsequent cancer-related therapy with participants weighted according to the probability of them taking subsequent therapy. The three PFS analyses include two analyses for participants who received subsequent cancer-related therapy (either not considering a subsequent cancer-related therapy as a censoring reason or considering any subsequent-related therapy as an event) and one exploring the potential impact of missing tumour assessments by considering participants who had missed two or more consecutive scheduled assessments before death or progressive disease as having had an event. The company provided the results of the sensitivity analyses (see section 3.3). The company also confirmed in their response that no sensitivity analyses were conducted for the January 2024 data cut-off analysis.

EAG comment:

The EMA European Public Assessment Report (EPAR)³² for tisotumab vedotin reports that four sensitivity analyses for OS were planned but that only two of these were carried out, and it is these that the company have described and provided the results of in their response to clarification question A16. A third sensitivity analysis is reported in the EPAR³² for tisotumab vedotin but not described in the company's response to clarification question A16 ([REDACTED]). This saw OS being analysed using a restricted mean survival time (RMST) method if the proportional hazard assumption was violated (see section 3.3.5). For both OS and PFS a planned mis-stratification sensitivity analysis was not conducted and we presume that this was because the criterion for the analysis was not met. We view the sensitivity analyses as appropriate.

Source: EAG compiled tabled based on information from CS Tables 16 and 17, the InnovaTV 301 CSR and the other sources cited.

CS, company submission; CSR, clinical study report; DoR, duration of response; EAG, External Assessment Group, EORTC-QLQ-C30, European Organization for Research and Treatment Quality of Life Questionnaire Core 30; EORTC-QLQ-CX-24, European Organization for Research and Treatment Quality of Life Questionnaire Cervical Cancer Specific module; EQ-5D, EuroQol 5 Dimensions; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; ITT, Intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO FAS, patient-reported outcome final analysis set; RCT, randomised controlled trial.

The efficacy and safety analyses for the InnovaTV 204 single-arm trial used the ITT population and the statistical analyses used are summarised in CS Table 19. One enrolled participant was not included in the ITT population because they did not receive a dose of study medication (enrolled n=102, ITT population of treated participants n=101).

EAG comment on study statistical methods

The company have described the methods used in the InnovaTV 301 RCT and InnovaTV 204 single-arm trial and the EAG has no concerns about the methods used.

3.3 Critique of the results of the trials of the technology of interest

In this section we report the InnovaTV 301 RCT results for the OS, PFS, response rates, HRQoL and adverse events outcomes specified in the NICE scope and company's decision problem, along with some supporting results from the single-arm InnovaTV 204 trial where relevant. We particularly focus on the key outcomes of OS and PFS, as results for these outcomes from the InnovaTV 301 RCT informed the company's economic analyses. The company supplied the p-value thresholds used to determine the statistical significance of the OS, PFS and objective response rate results, alongside the observed p-values from the analyses of these outcomes, in clarification response A13.

3.3.1 OS

Table 8 shows the OS results from the primary and ad hoc follow-up analyses of the InnovaTV 301 RCT (dated July 2023 and January 2024, respectively), along with supporting results from the InnovaTV 204 single-arm trial. This analysis, and all other primary and ad hoc follow-up analyses, was stratified by ECOG performance status, prior bevacizumab use, and prior anti-PD(L)1 therapy, which were pre-specified stratification factors (clarification response A15). Region was not included in the primary analyses as a stratification variable as planned, due to limited data for the stratum (clarification response A15). At the time of the primary analysis, there was a statistically significant 30% reduction in the risk of death with tisotumab vedotin compared with investigator's choice of chemotherapy (hazard ratio [HR]=0.70, 95% confidence interval [CI]: 0.54, 0.89, p=0.0038). In the tisotumab vedotin arm, median OS was 11.5 months (95% CI: 9.8, 14.9) versus 9.5 months (95% CI: 7.9, 10.7) in the chemotherapy arm. The Kaplan Meier plot of OS from this analysis is shown in CS Figure 12. As the company describes in the CS, there was early separation of the tisotumab vedotin and chemotherapy curves, which was sustained over time. The estimated OS rates at 6, 12 and 18 months from the primary analysis are reported for the ITT population in CS Table 22. These show that [REDACTED]

participants randomised to tisotumab vedotin were alive at each timepoint than those randomised to investigator's choice of chemotherapy.

The OS results from the ad hoc follow-up analysis (which inform the OS estimates used in the company's base case; CS section 3.3) were similar to those obtained from the primary analysis: median OS in the tisotumab vedotin arm was 11.7 months (95% CI: 9.9, 13.1) versus 9.2 months (95% CI: 8.0, 10.3) in the chemotherapy arm. There was a 21% reduction in the risk of death among patients treated with tisotumab vedotin compared to those treated with investigator's choice of chemotherapy (HR: 0.79, 95% CI: 0.63-0.97; see Table 8) (note: these results are publicly available in the EMA EPAR³⁹). The company states that the p-value reported in Table 8 for this analysis should not be used to interpret statistical significance because the efficacy boundary was crossed during the primary analysis (clarification response A19). The Kaplan Meier plot for the ad hoc follow-up analysis is shown in CS Figure 14 (which is marked as confidential) and is publicly available in Figure 34 of the EMA EPAR.³⁹ The EAG notes that the OS curves for tisotumab vedotin and chemotherapy separate early and show sustained separation until just after 18 months, when they cross-over.

One of our clinical experts argued that the OS results from the trial are clinically meaningful, on the basis that patients with recurrent or metastatic cervical cancer that has progressed on or after systemic treatment have few other options and are often young with young families, and so any additional time alive would be seen as worthwhile by patients. The other expert did not comment on how clinically meaningful they viewed the OS results to be.

In clarification response A16, the company provided details and results of sensitivity analyses carried out of OS in the InnovaTV 301 RCT at the primary analysis July 2023 data-cut, and clarified that no sensitivity analyses were conducted at the January 2024 ad hoc follow-up analysis. The EMA EPAR³² for tisotumab vedotin reports that four sensitivity analyses were planned, and that of these, two were conducted. We describe the planned sensitivity analyses in section 3.2.4 and Table 43 in Appendix 4, and report the results in Table 8.

The company reports the results of sensitivity analyses 1 and 3 in clarification response A16. A figure note in this response states that “Only applicable sensitivity analysis are presented” (clarification response Figure 3). The EAG assumes that the results for the mis-stratification analysis (sensitivity analysis 2) were not reported because the criterion for carrying out this analysis was not met. The EMA EPAR³² reports results for sensitivity analysis 4, and these are included in Table 8.

The results of the sensitivity analyses of OS were consistent with those obtained from the main primary and ad hoc follow-up analyses of InnovaTV 301 (Table 8). The median OS estimates found with tisotumab vedotin in the two analyses of this outcome presented in the CS from the InnovaTV 204 single-arm study were also consistent with that found in the InnovaTV 301 primary and ad hoc follow-up analyses.

The EAG identified two meta-analyses of tisotumab vedotin studies,^{40, 41} both of which included the five studies identified by the company for inclusion in their systematic review (that is, no additional quantitative evidence to that already considered for inclusion in the CS is available in these meta-analyses). A meta-analysis of median overall survival, which only included the InnovaTV 301 and InnovaTV 204 trials, found a 11.83 month (95% CIs: 10.30, 13.59) survival with tisotumab vedotin.⁴⁰ The other meta-analysis found a pooled OS of 11.8 months (95% CIs: 10.2-13.5) based on three studies.⁴¹ These results are consistent with the OS findings from just the InnovaTV 301 RCT.

Table 8 OS results from the InnovaTV 301 and InnovaTV 204 trials

Trial, analysis, population, median follow-up	Tisotumab Vedotin, number of deaths n/N (%), median OS months (95% CI) (unless otherwise reported)	Chemotherapy, number of deaths n/N (%), median OS months (95% CI) (unless otherwise reported)	Stratified HR (95% CI), p-value, unless otherwise reported
InnovaTV 301, primary analysis (July 2023), ITT population, median follow-up time: 10.8 months (95% CI: 10.3, 11.6)	123/253 (48.6), 11.5 (9.8, 14.9)	140/249 (56.2), 9.5 (7.9, 10.7)	0.70 (0.54, 0.89), p=0.0038
InnovaTV 301, ad hoc follow-up analysis (January 2024), ITT population, median follow-up time: [REDACTED])	176/253 (69.6), 11.7 (9.9, 13.1)	174/249 (69.9), 9.2 (8.0, 10.3)	0.79 (0.63, 0.97), descriptive nominal 2-sided p-value = 0.0280
InnovaTV 301, primary analysis, sensitivity analysis 1 (unstratified analysis)	[REDACTED], median OS not reported	[REDACTED], median OS not reported	Unstratified HR = 0.71 (0.55, 0.90)

Trial, analysis, population, median follow-up	Tisotumab Vedotin, number of deaths n/N (%), median OS months (95% CI) (unless otherwise reported)	Chemotherapy, number of deaths n/N (%), median OS months (95% CI) (unless otherwise reported)	Stratified HR (95% CI), p-value, unless otherwise reported
InnovaTV 301, primary analysis, sensitivity analysis 3 (initiation of subsequent cancer-related therapy)	62/253 (24.5), 21.3 (9.5, -)	78/249 (31.3), 10.7 (7.2, 11.7)	0.65 (0.48, 0.88), p-value not reported
InnovaTV 301, primary analysis, sensitivity analysis 4 (RMST at 21.9 months; reported in EMA EPAR ³⁹), ITT population)	N = 253 (no. of events not reported), 12.7 (11.7, 13.7)	N = 249 (no. of events not reported), 10.8 (9.7, 11.8)	RMST difference at 21.9 months (95% CI): 1.9 (0.4, 3.4), p-value not reported
InnovaTV 204, analysis stage not reported (appears to be primary analysis), ITT population, median follow-up time: 10.0 months (IQR 6.1-13.0)	N = [REDACTED], 12.1 (9.6, 13.9)	Not applicable	Not applicable

Trial, analysis, population, median follow-up	Tisotumab Vedotin, number of deaths n/N (%), median OS months (95% CI) (unless otherwise reported)	Chemotherapy, number of deaths n/N (%), median OS months (95% CI) (unless otherwise reported)	Stratified HR (95% CI), p-value, unless otherwise reported
InnovaTV 204, final analysis, population not reported, median follow-up time not reported	Number of deaths not reported [REDACTED]	Not applicable	Not applicable

Source: Partly reproduced from CS Figures 12 and 14, clarification responses A16 and A19, InnovaTV 204 CSR,⁴² InnovaTV 301 trial CSR,³¹ EMA EPAR³² Table 69 and Coleman et al. (2021).²⁰

CI, confidence interval; EMA, European Medicines Agency; EPAR, European public assessment report; HR, hazard ratio; IQR, interquartile range; ITT, intention-to-treat; OS, overall survival; RMST, restricted mean time survival

3.3.2 PFS

Table 9 shows the PFS results from the primary and ad hoc follow-up analyses of the InnovaTV 301 RCT (dated July 2023 and January 2024, respectively), as well as the results of sensitivity analyses of PFS conducted at the primary analysis and the results for this outcome from the InnovaTV 204 single-arm trial. The InnovaTV 301 primary analysis found that the risk of disease progression or death was statistically significantly reduced by 33% among participants randomised to tisotumab vedotin versus investigator's choice of chemotherapy (HR=0.67 [95% CI: 0.54, 0.82], $p<0.0001$; Table 9). With tisotumab vedotin, median PFS was 4.2 months (95% CI: 4.0, 4.4) and in the chemotherapy arm, it was 2.9 months (95% CI: 2.6, 3.1). The PFS Kaplan-Meier (KM) plot is shown in CS Figure 13. As the company state in the CS, there is early separation of the curves, which is sustained over time.

The PFS results obtained from the ad hoc follow-up analysis of InnovaTV 301 (January 2024) were similar to those from the primary analysis (Table 9). Note that the company states that the p-value associated with the ad hoc follow-up analysis results has no strict interpretation, as the efficacy boundary was crossed during the primary analysis (clarification response A20). The KM plot is shown in CS Figure 15, with an updated version provided in clarification response A20 Figure 10.

Both the EAG's advising clinical experts were of the view that the PFS results from the trial are clinically meaningful.

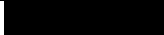
The CS did not provide details of any sensitivity analyses conducted of PFS, but this information was provided in response to clarification question A16. The results of sensitivity analyses of PFS from the InnovaTV 301 RCT (see Table 9 and section 3.2.4 for explanations of the analyses conducted and Table 9 for their results) were consistent with those of the primary analysis. We note from the EMA EPAR³² that a mis-stratification sensitivity analysis was also planned for PFS, if there was a >5% inconsistency between Randomisation and Trial Supply Management (RTSM) and electronic case report form (eCRF) in stratification factors, but as results are not presented in the EPAR or clarification response, we assume that this criterion was not met. The PFS results, from what appears to be the primary analysis of the InnovaTV 204 single-arm trial of tisotumab vedotin (as shown in Table 9), were also

consistent with those obtained from the primary, ad hoc follow-up and sensitivity analyses of InnovaTV 301. Estimates of median PFS months from the InnovaTV 204 single-arm trial were similar between the Independent Review Committee and investigator assessments of this outcome (Table 9).

CS Table 23 shows that in InnovaTV 301, there were higher rates of PFS in the tisotumab vedotin arm at 3, 6 and 9 months than in the investigator's choice of chemotherapy arm.

Of the two meta-analyses of tisotumab vedotin that the EAG identified (as mentioned in section 3.3.1),^{40, 41} one found a median PFS of 4.22 months (95% CIs: 4.03, 4.42) across the five studies included⁴⁰ and the other found a pooled median PFS of 4.2 months (95% CIs: 4.0-4.4).⁴¹ These results are consistent with those of just the InnovaTV 301 RCT.

Table 9 PFS results from the InnovaTV 301 and InnovaTV 204 trials

Trial, analysis, population, median follow-up time	Tisotumab vedotin, number of events n/N (%), median PFS months (95% CI) (unless otherwise reported)	Chemotherapy, number of events n/N (%), median PFS months (95% CI) (unless otherwise reported)	Stratified HR (95% CI), p-value (unless otherwise reported)
InnovaTV 301, primary analysis (July 2023), ITT population, median follow-up time not reported	198/253 (78.3), 4.2 (4.0, 4.4)	194/249 (77.9) 2.9 (2.6, 3.1)	0.67 (0.54, 0.82), p <0.0001
InnovaTV 301, ad hoc follow-up analysis (January 2024), ITT population, median follow-up time not reported			
InnovaTV 301, primary analysis sensitivity analysis 1a (subsequent cancer-related therapies not used as censoring reason; PD or death after starting subsequent therapy treated as PFS event), ITT population			

Trial, analysis, population, median follow-up time	Tisotumab vedotin, number of events n/N (%), median PFS months (95% CI) (unless otherwise reported)	Chemotherapy, number of events n/N (%), median PFS months (95% CI) (unless otherwise reported)	Stratified HR (95% CI), p-value (unless otherwise reported)
InnovaTV 301, primary analysis sensitivity analysis 1b (starting subsequent cancer-related therapies considered to be an event)			
InnovaTV 301, primary analysis sensitivity analysis 2 (participants missing 2 or more tumour assessments before PD or death considered to have had an event), ITT population			
InnovaTV 301, primary analysis, sensitivity analysis conducted for the EMA (EMA's preferred censoring rules; see clarification response A16), ITT population	212/253 (83.8), 4.3 (4.0, 4.5)	208/249(83.5), 2.9 (2.7, 3.1)	0.69 (0.57, 0.84)

Trial, analysis, population, median follow-up time	Tisotumab vedotin, number of events n/N (%), median PFS months (95% CI) (unless otherwise reported)	Chemotherapy, number of events n/N (%), median PFS months (95% CI) (unless otherwise reported)	Stratified HR (95% CI), p-value (unless otherwise reported)
InnovaTV 204, IRC-verified events, analysis stage not reported (appears to be primary analysis), ITT population, median follow-up time not reported	74/101 4.2 (3.0, 4.4)	Not applicable	Not applicable
InnovaTV 204, investigator-assessed PFS (appears to be primary analysis), ITT population, median follow-up time not reported	 4.1 (3.3, 4.6)	Not applicable	Not applicable

Source: Partly reproduced from CS Figure 13, CS Table 26, clarification response A16, clarification response Figure 10, Coleman et al. (2021).²⁰

CI, confidence interval; EMA, European Medicines Agency; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; PD, progressive disease; PFS, progression-free survival.

^a Percentage calculated by EAG

3.3.3 Response rates

In this section, we briefly summarise the findings for the response rates outcomes from the InnovaTV 301 RCT which are reported in the CS. We do not summarise the response rate results of the InnovaTV 204 single-arm trial, because the trial does not provide comparative data and the response rate results are not used to support the company's economic modelling. The InnovaTV 204 results are available in CS section 2.6.2.

In InnovaTV 301, the primary analysis found that:

- Objective response rate (assessed according to RECIST [Response Evaluation Criteria in Solid Tumours] v1.1 and confirmed by repeat imaging conducted four weeks or more after the initial response assessment, as confirmed in clarification response A17) was statistically significantly higher with tisotumab vedotin than with investigator's choice of chemotherapy (17.8% versus 5.2%; odds ratio [OR]=4.0 [95% CI: 2.1, 7.6], $p<0.0001$).
- Complete response, partial response, stable disease and disease control rates were [REDACTED] among participants treated with tisotumab vedotin than those treated with chemotherapy (see CS Table 24).
- [REDACTED] participants randomised to tisotumab vedotin than those randomised to chemotherapy experienced disease progression (see CS Table 24).
- Investigator assessed time to response (the time from randomisation to the first confirmed objective response) was 1.58 months in the tisotumab vedotin arm (range 1.2 to 4.5 months) and was 1.74 months (range 1.2 to 3.9 months) in the chemotherapy arm.
- Investigator assessed duration of response (the time from first confirmed objective response to the date of a first documented disease progression, measured according to the RECIST v1.1) or death from any cause) was 5.3 months (95% CI 4.2, 8.3) with tisotumab vedotin arm and 5.7 months (95% CI: 2.8, not reached) with chemotherapy.

3.3.4 HRQoL outcomes

HRQoL results for the EORTC-QLQ-C30 (but not the EORTC-QLQ-CX24) and EQ-5D visual analogue scale (VAS) (but not the EQ-5D descriptive system) are briefly reported within CS section 2.6.1 for the InnovaTV 301 RCT. None of the data presented in CS section 2.6.1 are used in the economic model because this estimates health-state utilities based on the EQ-5D-5L descriptive system (see section 4.2.7.2 of this report, CS section 3.4.1 and CS section 3.4.6). Missing data were not imputed for any the HRQoL outcomes (except in the situation that at least half of the items in a scale had been answered by a participant at a particular visit; InnovaTV 301 trial, statistical analysis plan, amendment 4 version, section 7.8.1), therefore only the HRQoL of participants remaining on treatment was captured during treatment cycle visits, the HRQoL of participants who discontinued treatment, including those who discontinued due to adverse effects of treatment, is not captured.

In the InnovaTV 204 single-arm trial the EORTC-QLQ-C30 and the EORTC-QLQ-CX24 were exploratory endpoints, the results are not reported in the CS.

3.3.4.1 EORTC-QLQ-C30 for the InnovaTV 301 RCT

In the CS, results are reported between baseline and cycle 5 (which was the median number of cycles received by participants in the tisotumab vedotin arm of the RCT). The compliance rates reported in the CSR from baseline to cycle 5 of treatment indicate that [REDACTED]

[REDACTED]. For the tisotumab vedotin arm the compliance rate was [REDACTED]
[REDACTED] In the chemotherapy arm the compliance rate was [REDACTED]

[REDACTED] Completion rates, which are calculated with the PRO FAS population as the denominator, are lower; dropping from 85.7% to 57.6% in the tisotumab vedotin arm and from 77.8% to 38.4% in the chemotherapy arm over the course of cycle 2 to cycle 5. Therefore, the evidence indicates that compliance and completion rates were lower in the chemotherapy arm than in the tisotumab vedotin arm.

The proportion of participants categorised as having a clinically meaningful change in global health status score (improvement in score of at least 10 points) [REDACTED]

[REDACTED]. In the tisotumab vedotin arm, the proportion [REDACTED] at cycle 5 was 13.9% [REDACTED]. In the chemotherapy arm the proportion [REDACTED] was 3.4% by cycle 5.

3.3.4.2 EQ-5D for the InnovaTV 301 RCT

Results are reported in the CS between baseline and cycle 5 (as they were for the EORTC-QLQ-C30). The CSR reports compliance rates from baseline to cycle 5 of treatment for the tisotumab vedotin arm of [REDACTED]% and at least [REDACTED]% in the chemotherapy arm. Completion rates [REDACTED] are lower; [REDACTED] in the tisotumab vedotin arm and [REDACTED]% in the chemotherapy arm [REDACTED]. We therefore note that that [REDACTED].

Participants were categorised as having an improved, worsened or stable score (using a 7-point threshold) on the EQ-5D VAS and the CS states that scores for both arms were stable from baseline to Cycle 5. We have not been able to verify this because it was not clear to us how the 7-point threshold was implemented, how categories of improved, worsened or stable were assigned in reference to this threshold, and we could not identify these data in the CSR. We did not find a more detailed explanation for the use of the 7-point threshold in either the protocol, statistical analysis plan or CSR for the trial. We note that the CSR table summarising EQ-5D VAS scores [REDACTED], and it is not clear to us if or how this relates to the 7-point threshold.

The company do not comment on the EQ-5D dimension results in CS section 2.6.1 but these are presented in the CSR [REDACTED]

3.3.5 Subgroup analyses

CS section 2.8.1 presents prespecified subgroup analyses from the primary (July 2023) analysis of the InnovaTV 301 RCT and CS Appendix C provides subgroup analysis of just OS from the ad hoc follow-up (January 2024) analysis. CS section 2.8.2 lists the prespecified subgroup analyses conducted for the InnovaTV 204 single-arm trial and the results of these are provided in CS Appendix C.

For the InnovaTV 301 RCT, primary analysis of confirmed objective response rate and the ad hoc follow-up analysis of OS results for all the subgroups specified in the statistical analysis plan are presented. The subgroups included the four stratification factors for the trial. Not all subgroup results were presented for the primary OS and PFS analyses: race, ethnicity and chemotherapy received subgroups were not reported for either of these outcomes; histology and number of prior relapsed/metastatic cervical cancer systemic regimens subgroups were not reported for the primary PFS analyses and these latter two results were requested and provided in response to clarification question A22.

As CS Appendix C Figure 4 shows, the OS (primary analysis) subgroup analysis point estimates for the hazard ratios are all in favour of tisotumab vedotin, except for the no prior bevacizumab administration subgroup where the hazard ratio is 1.00, indicating that there was no difference in OS between the tisotumab vedotin and chemotherapy arms for this subgroup. However, confidence intervals are wide for several subgroups (particularly those with the smallest sizes) and cross the HR=1.00 line in more than half of the subgroups examined underscoring that when HRs and their 95% confidence intervals are calculated based on low numbers of events and/or for small subgroups in a trial that was not powered to demonstrate statistically significant treatment differences according to subgroups, the results are uncertain and must be interpreted cautiously. (Note, the subgroup analysis results available in CS Appendix C Figure 4 are also publicly reported in the trial paper,¹⁸ and therefore

we report them without confidentiality marking here.) For the OS ad hoc follow-up analysis (January 2024), shown in CS Appendix C Figure 8 and Figure 9, a similar pattern of subgroup analysis results is observed, and in this case the point estimate for the hazard ratio of the no prior bevacizumab administration subgroup is 0.95 (note, the hazard ratio is publicly available in the EMA EPAR³⁹). CS Figure 9 shows the subgroup analysis results for each single chemotherapy agent received (these subgroup analysis results are not presented for the primary analysis of OS) and the hazard ratio for the vinorelbine subgroup is 1.45 (i.e. favours chemotherapy) (this value is reported in the EMA EPAR³⁹). The EAG believes, based on information available in the EPAR for tisotumab vedotin,³⁹ that investigators chose a chemotherapy for all enrolled participants prior to randomisation. The subgroup analyses for single agent chemotherapies are therefore based on the actual agent received for the chemotherapy arm of the trial and the chosen chemotherapy that participants in the tisotumab vedotin arm would have received, if they had been randomised to the chemotherapy arm. Subgroup analysis results are discussed in the EPAR for tisotumab vedotin⁴³ and it was noted there that the small subgroup for vinorelbine prevents any conclusion being drawn. Regarding prior bevacizumab use, while the InnovaTV 301 RCT found more favourable OS results for patients with prior bevacizumab exposure than among those who had not received bevacizumab (see section 3.3.5), the company states that there is no biological rationale for a difference in treatment effect (CS section 2.8.1). The EMA concluded in their assessment report for tisotumab vedotin that there is unlikely to be a true differential treatment effect according to prior bevacizumab use, in part because a literature search did not find any biologic rationale that could have explained this subgroup result.³² One of the clinical experts advising the EAG noted that, in their practice, if a patient has had previous radiotherapy then it is more likely that bevacizumab would not be used in the metastatic setting than if they had not had radiotherapy. It therefore is possible that, inadvertently, there would be more patients in the no prior bevacizumab group who have had radiotherapy and this may be a prognostic factor. However, the clinician acknowledged that the latter is uncertain. Overall, it seems likely that the finding was a chance effect from subgroup analyses.

For the PFS primary analysis, point estimates for the hazard ratios are all in favour of tisotumab vedotin, but again caution is needed in the interpretation of the results due

to some small subgroups and wide confidence intervals, some of which cross the HR=1.00 line (CS Appendix C Figure 5; results also reported in EMA EPAR³⁹).

Results for confirmed objective response rate by subgroups are presented in CS Appendix C Figure 6 and Figure 7.

3.3.6 Safety outcomes

CS section 2.11 reports the safety results from the InnovaTV 301 RCT (CS section 2.11.1) and the InnovaTV 204 single-arm trial (CS section 2.11.2). Adverse events for the InnovaTV 301 RCT are mostly reported as treatment-emergent adverse events, whereas for the InnovaTV 204 single-arm trial they are mostly reported as treatment-related adverse events. In the following sections we summarise the safety results from the two studies alongside one another and have drawn on data presented in other sources (e.g. the published papers and CSRs) to provide comparable data. It should also be noted that the median duration of exposure to tisotumab differed slightly between the InnovaTV 301 RCT and the InnovaTV 204 single-arm trial as shown in Table 10.

Table 10 Comparison of exposure to study drugs in the InnovaTV 301 RCT and InnovaTV 204 single-arm trial

Study	InnovaTV 301 RCT	InnovaTV 204 single-arm trial
Data cut-off	July 24, 2023	February 06, 2020
Median duration of exposure to tisotumab vedotin	3.65 months (range 0.4 to 18.9)	4.2 months (range: 1 – 16 months)
Median duration of exposure to chemotherapy	2.76 months (range 0.1 to 20.9)	Not applicable
Median number of cycles or doses ^a of tisotumab	5.0 cycles (range 1 to 26)	6.0 doses (range: 1 – 21)
Median number of cycles of Chemotherapy	■ cycles (range ■)	Not applicable

Source: Table created by the EAG from information presented in CS sections 2.11.1 and 2.11.2

RCT, randomised controlled trial

^a In the InnovaTV 301 RCT cycles are referred to but in the InnovaTV 204 single-arm trial doses are referred to. As far as we are aware one dose is equivalent to one cycle.

3.3.6.1 Treatment-emergent adverse events

Table 11 shows that similar proportions of participants in the tisotumab vedotin and chemotherapy arms of the InnovaTV 301 RCT experienced treatment-emergent adverse events. In the single-arm trial, where median duration of exposure was longer, the proportions of participants experiencing grade ≥ 3 TEAEs, any treatment-emergent SAE, treatment-emergent SAEs considered treatment related and TEAEs leading to death were higher than in the tisotumab vedotin arm of the RCT.

Table 11 Summary of treatment-emergent adverse events in the InnovaTV 301 RCT and the InnovaTV 204 single-arm trial

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 ^a	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)	
Treatment-emergent SAE considered treatment related			13 (13%)
TEAE leading to death	4 (1.6)	5 (2.1)	4 (4%)

Source: Reproduction of CS Table 30 with the addition of a row for the SAEs considered treatment-related and a column for the InnovaTV 204 trial for which data were sourced from the CSR and the trial publication.

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

^a In the InnovaTV 301 RCT TEAEs are defined as events that are new or worsened on or after the first dose of study treatment (tisotumab vedotin or chemotherapy) and with onset date on or before 30 days after the last dose of study treatment. In the InnovaTV 204 single-arm trial TEAEs are defined in the CSR as [REDACTED]

The most common treatment-emergent adverse events in the InnovaTV 301 RCT are listed in CS Table 31. A higher proportion of participants in the chemotherapy arm experienced anaemia, urinary tract infection, fatigue, neutropenia, increased alanine aminotransferase, and nausea than in the tisotumab vedotin arm. A grade 3 or higher decreased neutrophil count [REDACTED]. A higher proportion of participants in the tisotumab vedotin arm experienced abdominal pain, peripheral sensory neuropathy and keratitis.

In the InnovaTV 301 RCT adverse events led to 14.8% of participants discontinuing treatment with tisotumab vedotin whereas in the chemotherapy arm 3.8% of participants discontinued due to adverse events. Discontinuations were most commonly due to ocular adverse events and peripheral neuropathy adverse events.

For the InnovaTV 204 single-arm trial the most common treatment-related adverse events are reported in CS Table 36 and adverse events regardless of causality (i.e. treatment-emergent adverse events) are reported in Table S5 of the supplementary material for the published paper.⁴⁴ A wider range of treatment-emergent adverse events occurred in at least 10% of participants in the single-arm trial (25 events listed in comparison to 11 for the RCT) and eight of them were also events that commonly occurred in the RCT (nausea, fatigue, anaemia, asthenia, abdominal pain, keratitis, peripheral sensory neuropathy and urinary tract infection).

In the InnovaTV 204 single-arm trial adverse events led to 12% of patients discontinuing treatment with tisotumab vedotin. As with the RCT, discontinuations were most commonly due to ocular adverse events and peripheral neuropathy adverse events.

3.3.6.2 Serious adverse events

The CS lists the most common treatment-emergent serious adverse events during InnovaTV 301 and we have summarised these in Table 12. During InnovaTV 301 four patients (1.6%) in the tisotumab vedotin arm and five patients (2.1%) in the chemotherapy arm experienced an adverse event that led to death. In the tisotumab vedotin arm these adverse events, experienced by [REDACTED], were [REDACTED]. In the chemotherapy arm these adverse events, also experienced by [REDACTED].

Table 12 Summary of treatment-emergent serious adverse events in the InnovaTV 301 RCT

	InnovaTV 301 RCT	
	Tisotumab vedotin (n=250)	Chemotherapy (N=239)
Most common treatment-emergent SAEs (i.e. those occurring in $\geq 2\%$ of patients)	urinary tract infection 4%	urinary tract infection 7.1%
	small intestine obstruction 2.4%	anaemia 4.2%
	abdominal pain 2%	febrile neutropenia 3.3%
	sepsis 2%	hydronephrosis 2.9%
		acute kidney injury 2.1%

Source: EAG created table from text in CS section 2.11.1.

RCT, randomised controlled trial; SAEs, serious adverse events.

During InnovaTV 204 the most frequent treatment-related serious adverse events are reported in CS section 2.11.2 as pneumonia (4%), constipation (3%), and pyrexia (3%). Four participants (4%) experienced an adverse event that led to death, with one being considered treatment-related (this was due to septic shock).

The three other deaths were considered unrelated to study treatment (one case of ileus and two of unknown causes).²⁰ One further death during InnovaTV 204 was due to a non-treatment emergent cardiac arrest.

3.3.6.3 Adverse events of special interest

Three prespecified adverse events of special interest included in the CS are:

- ocular events, included because tisotumab vedotin binds to human ocular tissues³² including the human conjunctiva.⁴⁵ In the United States of America, tisotumab vedotin has a black box warning for ocular toxicity, including changes in the corneal epithelium and the conjunctiva that can result in changes in vision, including severe vision loss, and corneal ulceration. For this reason a mitigation and management strategy has been developed which aims to help reduce the risk of ocular adverse events in patients receiving tisotumab vedotin (CS Figure 16).
- bleeding events, included because bleeding risk is increased by prior use of radiotherapy or due to cervical cancer itself and because tisotumab vedotin targets tissue factors that have a role in coagulation.
- peripheral neuropathy, included because it is a known monomethyl auristatin E (MMAE)-related adverse event (MMAE is released when tisotumab vedotin is internalised by target cells). Other commonly used anticancer treatments for cervical cancer may also cause peripheral neuropathy.

In the CS the adverse events of special interest are reported slightly differently for the InnovaTV 301 RCT (CS Tables 32, 33, 35) and the InnovaTV 204 single-arm trial (CS Tables 37, 38 and 39). For the RCT, treatment-emergent adverse events are reported whereas for the single-arm trial, treatment-related adverse events are reported.

3.3.6.3.1 Ocular adverse events

In the safety analysis population of the InnovaTV 301 RCT, 132 participants (52.8%) in the tisotumab vedotin arm experienced a treatment-emergent ocular adverse event (CS Table 32) and in the InnovaTV 204 single-arm trial the same proportion of patients experienced an ocular treatment-related adverse event (54 participants [53%], CS Table 37). In comparison, in the InnovaTV 301 RCT 15 participants (6.3%) in the chemotherapy arm experienced a treatment-emergent ocular adverse event. The CSR for the RCT reports that [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED].

Most of the ocular adverse events among participants treated with tisotumab vedotin reported in CS Table 32 and CS Table 37, and all such events in participants treated with chemotherapy (CS Table 32) were Grade 1 or 2 in severity. In the RCT, 4% of the participants treated with tisotumab Vedotin had a Grade 3 ocular event. The proportion of participants experiencing a serious ocular adverse event was low (0.8% in the tisotumab vedotin arm of the InnovaTV 301 RCT and zero in the chemotherapy arm and in the InnovaTV 204 single-arm trial of tisotumab vedotin). An ocular adverse event led to the permanent discontinuation of 14 participants (5.6%) of the tisotumab vedotin arm of the InnovaTV 301 RCT but none of the chemotherapy arm. This information is not reported in the CS for the InnovaTV 204 single arm trial but Table S4 of the appendix to the published paper⁴⁴ suggests that 7 participants (6.9%) may have discontinued the trial due to an ocular adverse event.

The most common ocular treatment-related adverse events (occurring in 10% or more of participants) in the InnovaTV 204 single-arm trial were conjunctivitis, dry eye and keratitis (CS Table 37). In the InnovaTV 301 RCT the CSR reports [REDACTED] [REDACTED] were the most common in the tisotumab vedotin arm.

In the InnovaTV 301 RCT in comparison to the chemotherapy arm the median time to the first ocular adverse event onset was shorter and the median time of ocular adverse event resolution [REDACTED] in the tisotumab vedotin arm. In both RCT arms the majority of the ocular adverse events resolved or improved (CS Table 32).

3.3.6.3.2 *Bleeding adverse events*

The proportions of participants receiving tisotumab vedotin in the InnovaTV 301 RCT and in the InnovaTV 204 single-arm trial who experienced a bleeding treatment-emergent adverse event (RCT, CS Table 33) or bleeding treatment-related adverse event (single-arm trial, CS Table 39) were similar (42% and 39% respectively) and higher than in the chemotherapy arm of the RCT where 14.2% of the participants experienced a bleeding treatment-emergent adverse event. The CSR reports that the [REDACTED]

The bleeding adverse events reported in both trials (CS Table 33 and CS section 2.11.2) were mostly of Grade 1 or Grade 2 severity. Grade 3 or higher bleeding events occurred in 2.4% of participants who received tisotumab vedotin in the RCT and 2.9% of the chemotherapy arm and serious bleeding events occurred in 2.4% and 3.8% of the tisotumab vedotin and chemotherapy arms respectively. No bleeding adverse events led to permanent discontinuation in the RCT. Among the treatment-related bleeding adverse events in the single-arm trial 2% were Grade 3 or higher. CS Table 39 reports that the most common bleeding treatment-related adverse events in the single-arm trial were epistaxis (nosebleed), vaginal haemorrhage and hematuria (blood in the urine). The CSR for the RCT reports that [REDACTED]

The EAG has no further observations to highlight in relation to the remaining data presented in CS Table 33 and CS Table 39 (e.g. total number of bleeding adverse events, median time to the onset of the events, frequency of the event resolution, median time to event resolution).

3.3.6.3.3 *Peripheral neuropathy adverse events*

Some participants in both arms of the InnovaTV 301 RCT had peripheral neuropathy at baseline (CS Table 34) and [REDACTED]

In the RCT 38.4% of the participants in the tisotumab vedotin arm had a peripheral neuropathy treatment-emergent adverse event in comparison to 4.2% of the chemotherapy arm. The CSR indicates that [REDACTED]
[REDACTED]. In the single-arm trial the CSR reports [REDACTED]
[REDACTED], and CS Table 38 indicates 33% had a peripheral neuropathy adverse event that was considered treatment-related.

For most participants who experienced a peripheral neuropathy adverse event it was of Grade 1 or Grade 2 severity (CS Table 35 and CS Table 38). In the RCT the proportion of participants with a Grade 3 treatment-emergent peripheral neuropathy adverse event was 5.6% in the tisotumab vedotin arm and 0.4% in the chemotherapy arm; there were few serious peripheral neuropathy serious adverse events (CS Table 35). In the single-arm trial 7% of participants experienced a Grade 3 or greater treatment-related peripheral neuropathy adverse event (CS Table 38).

In the RCT peripheral neuropathy adverse events led to [REDACTED]
[REDACTED] some permanent discontinuations (5.6%) from tisotumab vedotin treatment [REDACTED] (CS Table 35). Fewer than half (43.8%) of the participants in the tisotumab vedotin arm with a peripheral neuropathy adverse event experienced resolution or improvement of all or some the events (CS section 2.11.1). In the single-arm trial [REDACTED] of participants had resolution of their peripheral neuropathy treatment-related adverse event (CS Table 38).

The EAG has no further observations to highlight in relation to the remaining data presented in CS Table 35 and CS Table 38 (e.g. median time to the onset of the events, median time to event resolution).

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The company state that they have not conducted an indirect treatment comparison (ITC), because the InnovaTV 301 RCT provides evidence for the efficacy of tisotumab vedotin compared with investigator's choice of chemotherapy (CS section 2.10). In clarification question A10, the EAG queried if the company had considered and explored whether there might be other trials or real-world evidence studies available that might be representative of standard care received in the NHS that could have represented a comparator arm in an indirect comparison using population matching techniques, with the InnovaTV 301 RCT tisotumab vedotin arm as the intervention arm. In response, the company state that a comprehensive systematic literature review, which was provided as part of the company's response, did not find any suitable studies to inform an ITC. The EAG believes that it is acceptable that the company has not conducted an ITC, as we conclude that the InnovaTV 301 RCT investigator's choice of chemotherapy comparator arm reasonably represents the likely efficacy of the second- and third-line single-agent chemotherapies used in NHS clinical practice in the appraisal population, including weekly paclitaxel (see section 2.3 for our reasons).

3.5 Critique of the indirect comparison or multiple treatment comparison

The company submission does not include an ITC.

3.6 Additional work on clinical effectiveness done by the EAG

The EAG has not done any additional work.

3.7 Conclusions on the clinical-effectiveness section

The company included one RCT of tisotumab vedotin versus investigator's choice of chemotherapy in the population of interest for this appraisal (InnovaTV 301) in the CS, and provided supporting data from a single-arm trial of tisotumab vedotin, also in this population (InnovaTV 204).

The CS decision problem adequately reflects the NICE scope, even though: i) the comparator specified by the company (single-agent chemotherapy; specifically either

topotecan, gemcitabine, irinotecan, vinorelbine or pemetrexed as used in the comparator arm of the InnovaTV 301 RCT) does not include weekly paclitaxel which is commonly used in clinical practice in the appraisal population, and ii) the distributions of the single agents used in the comparator arm of InnovaTV 301 do not reflect usage in clinical practice based on clinical expert advice to both the company and to us (see sections 2.2, 2.3, and 3.2.1 above and section 4.2.8.1.1 below). This is because the EAG considers that the InnovaTV 301 investigator's choice of chemotherapy arm reasonably represents the likely efficacy of the second- and third-line treatments used in practice. However, we suggest this is an uncertainty that would benefit from further discussion with clinical experts (Issue 6).

An uncertainty is whether the InnovaTV 301 chemotherapy comparator arm might adequately represent the safety of the single-agent chemotherapies used in clinical practice, given that a distribution of these used in the economic model is different to use in the trial. However, the EAG does not suggest an alternative approach.

Re-challenge with platinum doublet was not included as a comparator in either the company's decision problem or the NICE scope, but we were advised this is also a commonly used intervention in practice in this indication. Company collected data also indicates this. The EAG's clinical experts advised that it is uncertain if platinum doublet has a similar efficacy to the single-agent chemotherapies included in the company's decision problem and the InnovaTV 301 RCT. Therefore, the efficacy of this treatment may not be captured by the trial comparator. No estimates are presented in the CS of the clinical and cost-effectiveness of tisotumab vedotin versus platinum doublet. Further discussion about whether platinum doublet is a relevant comparator for tisotumab vedotin may be beneficial (we raise this as Issue 7)

Both the primary (July 2023) and ad hoc follow-up (January 2024) analyses of InnovaTV 301 found that the risk of death and the risk of disease progression or death with tisotumab vedotin was reduced compared with chemotherapy. At the ad hoc follow-up analysis (the results of which are used to inform the company's economic model; CS section 3.3), median OS was 11.7 months (95% CI: 9.9, 13.1) in the tisotumab vedotin arm and 9.2 months (95% CI: 8.0, 10.3) in the chemotherapy arm (NB. these results are reported without confidentiality marking in

the publicly available EMA EPAR³⁹). Median PFS was [REDACTED] months [REDACTED] in the tisotumab vedotin arm and [REDACTED] months [REDACTED] in the chemotherapy arm. OS and PFS findings were consistent across the primary, ad hoc follow-up and sensitivity analyses, and were consistent with the results of the InnovaTV 204 single-arm trial of tisotumab vedotin. We judged that the PFS outcome might be subject to some bias, because the InnovaTV 301 RCT was open-label and disease progression was documented by the investigator, with no central review of this outcome. However, given that the InnovaTV 204 single-arm trial analyses of PFS by independent review committee and investigator assessment found similar median PFS results, it might be argued that such a risk of bias is negligible. The EMA EPAR³² states that the OS and PFS results of the InnovaTV 301 RCT are clinically meaningful within the context of second-line and later therapies for recurrent or metastatic cervical cancer, and our clinical experts concurred with this.

In the EAG's opinion, the EORTC-QLQ-C30 and EQ-5D-5L HRQoL results from the InnovaTV 301 RCT were not clearly presented in the clinical effectiveness results section of the CS (CS section 2.6.1) and are subject to some uncertainty due to missing data. Results for the EORTC-QLQ-C30 show that a higher proportion of participants randomised to tisotumab vedotin (13.9%) were categorised as having a clinically meaningful change in global health status score at Cycle 5 than those randomised to chemotherapy (3.4%). The EAG observed [REDACTED] between the trial arms in the descriptive EQ-5D-5L results presented in the InnovaTV 301 CSR.³¹

Ocular adverse events are one of the adverse events of special interest associated with tisotumab vedotin. Of the participants in the tisotumab vedotin arm in the InnovaTV 301 trial, 52.8% experienced a treatment-emergent ocular adverse event, compared with 6.3% in the chemotherapy arm. Most of these events were Grade 1 or 2 in severity, with only 4% of the participants in the tisotumab vedotin arm experiencing a grade 3 ocular event. In the CS, the company outlines an eye care management plan to be used in the UK, [REDACTED] [REDACTED]¹⁵ (supplied in response to clarification question 3). This includes the need for an eye care professional to carry out an ophthalmic examination before the first infusion of tisotumab vedotin and as needed thereafter if the treating clinicians

assess that a patient shows symptoms and signs that warrant further evaluation by a specialist. Our advising clinical experts expressed concern about a lack of facilities in oncology departments to carry out eye examinations, a potential lack of available resources for this in eye departments, and about whether sufficient resource would be available for emergency referrals. We were told that ophthalmic examinations are not usually performed prior to chemotherapy administration, and hence this would be an additional resource requirement to deliver tisotumab vedotin. Concern was also expressed about treating clinicians assessing patients' eyes during tisotumab vedotin treatment to gauge when referral to an eye specialist is needed, as it is anticipated that this task will be challenging for non-eye specialists. We therefore suggest there is a potential practical implementation issue associated with delivering tisotumab vedotin and managing ocular adverse events in clinical practice (Issue 1).

4 Cost effectiveness

4.1 Critique of the review of cost-effectiveness evidence

The company searched for published economic evaluations and estimates of utility, resource use and costs (CS section 3.1 and Appendix E). Further information on the methods and results is provided in a draft report by the York Health Economics Consortium (YHEC), 2015.⁴⁶ The search was updated and the EAG has no concerns over the search methods. The review identified 31 economic evaluations that met the eligibility criteria (CS Appendix Table 10), only one of which was relevant to the current decision problem.

Huo et al. (2024)⁴⁷ reported a cost-utility analysis comparing tisotumab vedotin with chemotherapy for people with recurrent or metastatic cervical cancer. They used a partitioned survival model (PSM), with log-logistic extrapolations for PFS and OS fitted to digitised KM data from the InnovaTV 301 RCT, and resource use based on InnovaTV 204.^{18, 19} The company compare quality-adjusted life year (QALY) estimates from their model with those from the Huo et al. analysis (CS Table 71).

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

The company describe their economic model in CS section 3.2. We consider that their analysis is consistent with the NICE reference case (Table 13). The model uses effectiveness data from the InnovaTV 301 RCT. Based on the available evidence and based on our experts' advice, the EAG considers that it is reasonable to assume that the treatments included in the InnovaTV 301 comparator arm have similar efficacy, and that the efficacy of paclitaxel may also be reasonably represented by the InnovaTV 301 comparator arm (see section 2.3).

Table 13 NICE reference case checklist

Element of the technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and Personal Social Services	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes. Effects based on InnovaTV 301 RCT. See sections 2.3 and 3.1.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the	Yes. The QALY weighting applied for severity (CS section 3.6) is consistent with the

Element of the technology assessment	Reference case	EAG comment on company's submission
	people having the health benefit, except in specific circumstances	approach recommended by NICE. ⁴⁸ See section 5.3.1 below.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: Produced by the EAG based on data reported in the company's submission
ITC, indirect treatment comparison; QALY, Quality adjusted life year

4.2.2 Model structure

The company developed a semi-Markov economic model, implemented in Microsoft Excel® 365 with a time horizon of 30 years and cycle length of one week (CS section 3.2.2). The model structure is illustrated in CS Figure 17 (Figure 2 below).

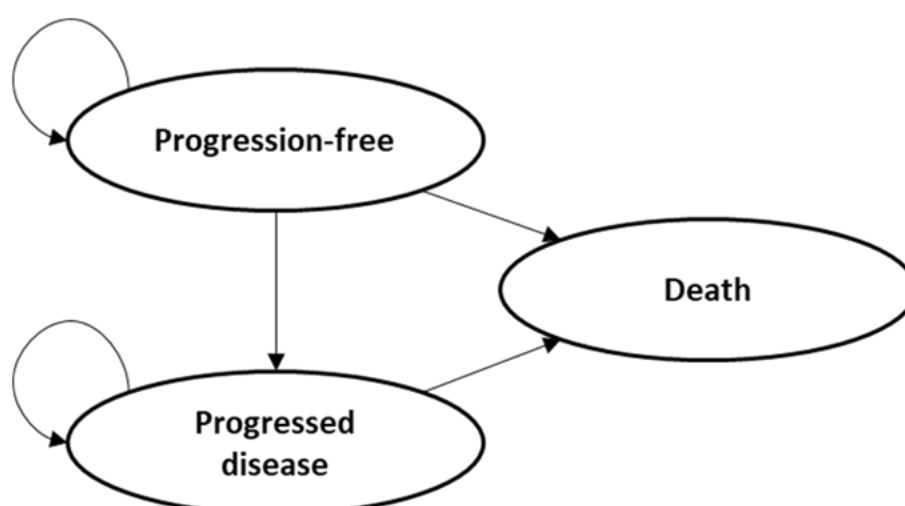


Figure 2 Model structure

Source: reproduced from CS Figure 17

The model comprises three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death. All patients enter the model in the PF state. In each weekly cycle, patients may remain in the PF state, transition to the PD state, or transition to the death state. Patients in the PD state may remain in PD or transition to death state. Transition probabilities between the three health states were estimated from InnovaTV 301 RCT data (January 2024 analysis), using a parametric multistate modelling approach. The company use trial KM data to directly estimate OS during the first 12 months, followed by the extrapolations based on the parametric multistate extrapolations (see section 4.2.6 below).

The company explain that they chose the semi-Markov design, rather than a more conventional PSM, because it enabled implementation of a clinical assumption of comparable post-progression mortality rates in both treatment arms, which clinical experts in the company's UK advisory group supported (CS section 3.2.2 and response to clarification question B1). The company's semi-Markov model requires that the risk of death after disease progression is constant. It is not possible to relax this assumption because the model does not include 'tunnel states', which would retain information about time of progression.

The company state that they explored the alternative PSM approach but rejected it due to poor clinical plausibility and external validity. Results of the company's PSM analyses are not reported, but they state that it predicted survival in the chemotherapy arm of 16–20% at two years, compared with 10–13% from clinical expert advice and an external benchmark (McLachlan et al. 2016).⁴⁹ The company concluded that the extended tail of OS in the chemotherapy arm of InnovaTV 301 and overlap between arms, was likely due to random variation as few patients remained at risk, rather than a genuine survival advantage.

In support of the Markov approach, the company also cites precedent from the NICE appraisal of pembrolizumab for relapsed, persistent or metastatic cervical cancer (TA885 and review TA939).^{8, 50} We note that in TA939, the conclusion that results from the PSM were not clinically plausible was due to 'unrealistic crossing' of the OS and PFS curves, caused by immature survival data (TA939 paragraph 3.4). It is not clear that these same concerns apply to the current appraisal. The InnovaTV 301

PFS and OS curves do not cross, and although there is uncertainty over long-term survival extrapolations, the OS data is relatively mature: median follow up [REDACTED], by which time [REDACTED] (January 2024 ITT) (see Table 8 above and CS Figure 14).

EAG comment on model structure

The EAG has concerns over the company's use of a semi-Markov model structure because we consider that the InnovaTV 301 RCT data does not support the assumption of a fixed post-progression mortality rate (see section **Error! Reference source not found.**). The alternative PSM approach is well-established and does not require this assumption. We therefore use alternative options provided in the company's model to explore the impact of a PSM approach based on direct extrapolations from InnovaTV 301 PFS and OS data in EAG scenario analysis and our preferred analysis (see sections 4.2.6.5.2 and 5.2.4).

4.2.3 EAG critique of model assumptions

The company's assumptions and justifications detailed in CS Table 65, are reviewed by the EAG below.

4.2.3.1 Assumption 1: Post-progression mortality hazard

The company apply a single post-progression survival hazard to tisotumab vedotin and chemotherapy beyond 12 months, reflecting the observed convergence of OS curves and clinical opinion that long-term outcomes should be similar once patients have progressed (CS 3.3.3). The EAG notes that imposing a shared post-progression survival hazard may underestimate or overestimate OS if post-progression effects differ between treatments. We consider that the company's assumption of a constant risk of death after disease progression, independent of previous treatment, is not supported by InnovaTV 301 RCT data (section **Error! Reference source not found.**).

4.2.3.2 Assumption 2: Use of observed OS for the first 12 months

The company combine KM data for OS in the first 12 months with parametric extrapolation thereafter (CS section 3.3.2 and response to clarification question B4). They argue that 12 months is the 'optimal cutoff', balancing use of robust data with

model stability and clinical plausibility The EAG considers that this approach may introduce structural uncertainty, as the choice of cutoff time for attachment of parametric extrapolations can influence long-term survival estimates (section 4.2.6.5.1). We report scenario analysis varying the cut-off for use of KM data (0, 9 and 15 months), see section 5.2.4.

4.2.3.3 Assumption 3: Efficacy and safety of chemotherapy drugs

The company assume equal efficacy and safety for all chemotherapy agents including weekly paclitaxel, with outcomes based on the chemotherapy arm of the InnovaTV 301 RCT. This view is supported by clinical expert advice to the company and to the EAG. The EAG considers that this is reasonable, see section 2.3.

4.2.3.4 Assumption 4: Costs for chemotherapy and subsequent treatment

For costing in the company's base case, the proportions of patients using each chemotherapy agent in the comparator arm and in subsequent treatment after disease progression was informed by a survey of eight UK clinicians involved in the management of relapsed or metastatic cervical cancer (CS 3.5.1.1 and CS 3.5.1.2). Clinical expert advice to the EAG was that the mix of comparator and subsequent treatments in the company's base case does not reflect NHS clinical practice (sections 4.2.8.1.1 and 4.2.8.1.2). We report EAG scenario analysis in section 5.2.4, based on estimates from our clinical experts, see section 2.2.2.

4.2.3.5 Assumption 5: Treatment administration costs

The model includes costs for administration of intravenous medications. Tisotumab vedotin and chemotherapies were assumed to be administered in an outpatient setting, with the same unit cost per administration for all treatments except for paclitaxel which was assumed to have a higher cost to account for prolonged infusion. Clinical advice to the EAG was that delivery of single-agent paclitaxel is similar to other chemotherapies, and that costs should not differ (section 4.2.8.1). We report EAG scenario analysis using the same administration cost for paclitaxel as for the other chemotherapy agents, see section 5.2.4.

4.2.3.6 Assumption 6: Costs for ocular assessments

The model includes costs for eye drops and ocular assessments for patients receiving tisotumab vedotin. We note uncertainty over assumptions on the frequency

and arrangements for ocular assessment based on discussion with clinical experts, as detailed in section 2.2.3.

4.2.3.7 Assumption 6: Disease management costs

Patients in the progression-free and progressed disease states were assumed to incur costs for disease management, independent of treatment type. The EAG notes that the frequencies of resource use for disease management were not consistent with advice to the EAG on UK clinical practice, see section 4.2.8.2.1. We report scenario analysis using our clinical experts' estimates, see section 5.2.4.

4.2.3.8 Assumption 7: Utilities

Health state utilities are assumed to be independent of treatment. The EAG considers that the company's assumptions around health state utilities, adverse events and disutilities are reasonable, see section 4.2.7.2.

4.2.4 Population

The modelled population consists of adult patients with recurrent or metastatic cervical cancer whose disease progressed on or after prior systemic therapy, in line with the InnovaTV 301 trial population [REDACTED]

[REDACTED]²⁹

Baseline characteristics for the base-case model cohort are provided in CS Table 40. The mean age ([REDACTED] years) was assumed to match that reported for the global InnovaTV 301 trial population. Mean body surface area (1.65 m²) and mean weight (63.31 kg), used to calculate treatment doses and corresponding drug costs, were likewise from the global InnovaTV 301 RCT data.^{51, 52}

EAG comment on the model population

The EAG considers that the company's modelled population is consistent with the NICE final scope. Clinical expert advice to the EAG is that the defined population is representative of the UK population of interest.

4.2.5 Interventions and comparators

The intervention (tisotumab) and comparator (single-agent chemotherapy) are described in the CS section 3.2.3, with the distribution of comparator chemotherapy drugs used in the cost-effectiveness analysis presented in CS Table 42.

The comparator is single-agent chemotherapy, assumed to reflect the treatments used in both the global InnovaTV 301 RCT (CS Section 2.3.1.1) and current UK clinical practice. The company's clinical experts advised that single-agent chemotherapies provide comparable efficacy for second-line / third-line relapsed or metastatic cervical cancer.¹² The company therefore use pooled efficacy data from the comparator arm of InnovaTV 301 to estimate clinical outcomes for chemotherapy in the economic model. However, costs for the chemotherapy arm in the company's base case analysis are calculated based on the distribution of single-agent chemotherapies used in UK clinical practice, estimated from their survey of eight responding clinicians, with a scenario based on the distribution in the InnovaTV 301 RCT (CS Table 42). The company excluded platinum doublet rechallenge from the model due to a lack of RCT evidence that this provides better efficacy than single-agent chemotherapies.

The EAG's clinical experts advised that the distribution of single-agent chemotherapies used in company's base case is not representative of UK clinical practice. They noted that rechallenge with a platinum-based doublet would be considered in certain cases, depending on treatment-free intervals and patient fitness, as detailed in section 2.2.2. We report additional EAG scenario analysis using the estimates from one of our clinical experts in section 5.2.4. The EAG did not include rechallenge with a platinum doublet in scenario analysis, as the comparator specified in the NICE scope is single-agent chemotherapy. The EAG scenario analysis is based on estimates provided by one clinical expert, because the second expert's opinion included a high proportion of carboplatin plus paclitaxel see Table 5. The proportion of patients who would have received a platinum doublet in the first expert's estimates used in the model was therefore re-normalised across the single-agent chemotherapy options, see Table 14.

Table 14 Comparator chemotherapy distribution used in EAG analysis

Chemotherapy agent	UK clinician survey used for costing in company's model	EAG Expert 1 estimates	Estimates used in EAG analysis model
Topotecan	4.7%	10%	11.1%
Vinorelbine	2.0%	0	0
Gemcitabine	28.4%	20%	22.1%
Irinotecan	0.3%	0	0
Pemetrexed	0.3%	0	0
Paclitaxel	64.3%	60%	66.7%
Platinum doublet	0	10%	0

Source: Partly created from CS Table 42

EAG, External Assessment Group

EAG comment on intervention and comparators

The EAG considers that the company's approach to defining comparators is broadly appropriate and consistent with the NICE scope. We consider that the company's assumption of similar efficacy across the single-agent chemotherapies, including weekly paclitaxel, is reasonable. We note that the small Genmab UK advisory board and survey (n=8 clinicians), and advice to the EAG from two clinical experts may not fully reflect national practice or regional variations. The exclusion of platinum doublet rechallenge from the comparator reflects the single-agent chemotherapy specified in the NICE scope but may underestimate real-world NHS costs. The distribution of single-agent chemotherapies used for costing is varied in the EAG scenario analysis (section 5.2.4) and adopted in our preferred assumption (section 5.2.5).

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Methods for estimation of transition probabilities

Transition probabilities for the semi-Markov model were estimated using individual patient data (IPD) from the InnovaTV 301 RCT (January 2024 data cut), and a

parametric multistate modelling approach (see CS section 3.3.1).⁵³⁻⁵⁵ This requires survival functions for each of the three health state transitions:

- Time to progression (TTP): PF to PD
- Pre-progression mortality: PF to death
- Post-progression mortality: PD to death

Standard parametric survival distributions were fitted to estimate hazards for TTP and pre-progression mortality in each treatment arm (CS section 3.3.2).⁵⁶ For post-progression mortality, the same constant hazard (exponential) distribution is assumed for both arms, estimated from pooled IPD (CS section 3.3.3). The estimated cause-specific hazards are converted to weekly transition probabilities, with adjustments to scale for the competing risks of transitions out of the PF health state (TTP and pre-progression mortality), and to ensure that the total mortality risk does not exceed that for women of the same age in the general population. The cause-specific transition probabilities are then combined to reconstruct estimates of PFS and OS, which are used to calculate health state occupancy in the model (CS section 3.3.4). For OS, the company use the trial KM estimates directly for the first 12 months, followed by fitted extrapolations over the remaining time horizon. PFS is based on fitted extrapolations across the time horizon, with a cap to prevent it exceeding OS.

We discuss the company's selection of survival curves for TTP, pre- and post-progression mortality in sections 4.2.6.2, 0 and **Error! Reference source not found.**, respectively, and critique the resulting PFS and OS extrapolations in section 4.2.6.5.

4.2.6.2 Time to progression (TTP): transitions from PF to PD

The company use a generalised gamma distribution for TTP in their base case and lognormal in a scenario, both fitted independently to the treatment arms. The company outline the reasons for this choice in CS section 3.3.2, and provide a more detailed explanation in response to clarification question B3, as summarised below:

- *Proportional hazards*: log-cumulative hazards plots (CS Appendix Figure 23) are not parallel, so separate fitting by treatment arm is appropriate.

- *Changes in risk over time:* hazards (CS Appendix Figure 22) are not monotonic in either arm, indicating that generalised gamma, lognormal or log-logistic distributions are suitable.
- *Statistical fit:* Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (CS Tables 43 and 44) statistics indicate that the generalised gamma has the best fit for both arms.
- *Visual fit:* clarification response Figures 15 and 16 show the TTP KM and parametric curves for the intervention and control arms respectively, including the numbers at risk over time. The company states that the generalised gamma captures the observed data patterns in both arms.

The above criteria follow NICE Decision Support Unit recommendations (TSD 14).⁵⁶ The company do not discuss the clinical plausibility of the TTP extrapolations, but this considered for PFS in CS section 3.13 (section 4.2.6.5 below).

The EAG notes uncertainty in the TTP extrapolations due to the periodic timing of assessments and diminishing sample size: ■ patients in the tisotumab vedotin arm and ■ in the chemotherapy arm remain at risk by month 12 (clarification response Figure 15). The AIC/ BIC statistics and the visual fit of the generalised gamma, lognormal and log-logistic distributions are all very similar (Figure 3 and Figure 4 below). From about 9 months, the generalised gamma provides a slightly better visual fit in the chemotherapy arm but appears to overestimate the proportion of patients who remain progression free in the tisotumab vedotin arm. However, these differences are small, and we consider it appropriate to use the same distribution in both arms.⁵⁶

We report EAG scenario analysis using lognormal and log-logistic extrapolations for TTP in both arms (see section 5.2.4).

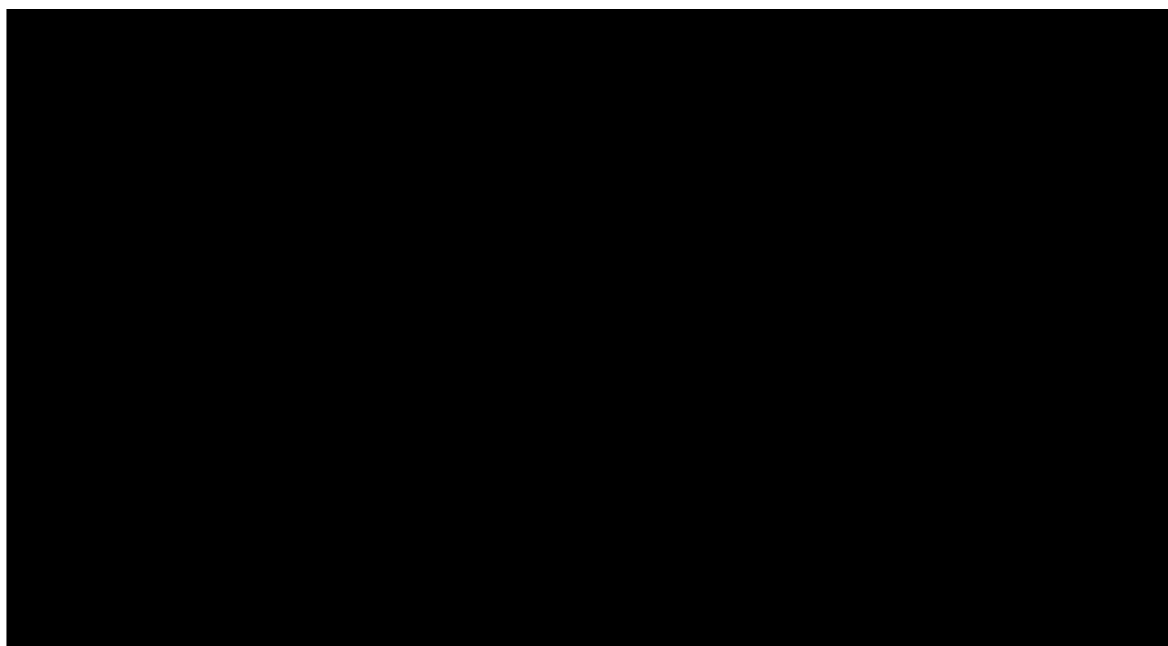


Figure 3 Time to progression: tisotumab vedotin best fit extrapolations

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

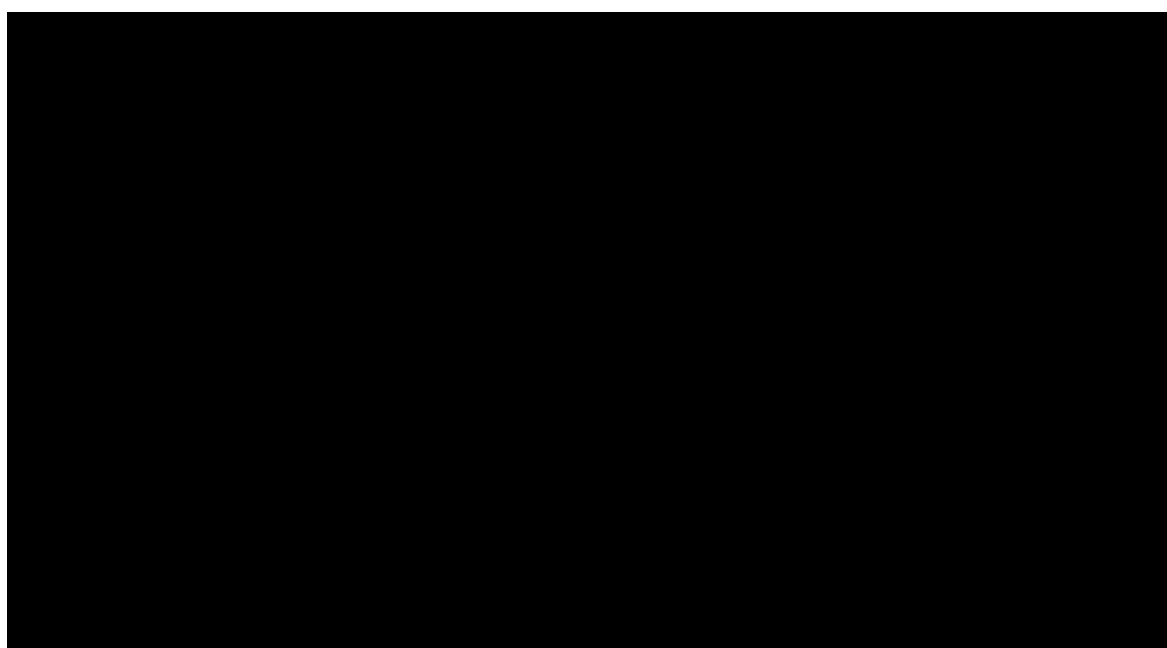


Figure 4 Time to progression: chemotherapy best fit extrapolations

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

4.2.6.3 Pre-progression mortality: transitions from PF to death

For pre-progression mortality, the company use base case distributions of Gompertz for tisotumab vedotin and lognormal for chemotherapy, based on the following considerations:

- *Proportional hazards*: log-cumulative hazards plots (CS Appendix Figure 25) are not parallel, suggesting separate fitting by treatment arm.
- *Changes in risk over time*: hazards were considered “near monotonically decreasing” for tisotumab vedotin but non-monotonic for chemotherapy (CS Appendix Figure 24).
- *Statistical fit*: Gompertz is the best fit for tisotumab vedotin and log-normal for chemotherapy, based on hazard trends and AIC/BIC (CS Tables 45 and 46).
- *Visual fit*: clarification response Figures 17 and 18 show the KM and parametric curves for the intervention and control arms respectively, including the numbers at risk over time. The company states that the use of Gompertz for tisotumab vedotin and lognormal for chemotherapy captures the observed data patterns in both arms.

We emphasise that extrapolations for pre-progression mortality are all highly uncertain, due to the low number of observed events. The hazard plots suggest a declining hazard in both arms prior to 12 months, but we consider that trends after this time cannot be assessed due to the low event rate and remaining numbers at risk (■ in the tisotumab vedotin arm and ■ in the chemotherapy arm at 12 months). Given the high level of uncertainty, we consider that the same survival distribution should be used to estimate pre-progression mortality in both arms.

None of the parametric distributions have a good visual fit to the KM curves after the first 6 months, and the goodness of fit statistics do not discriminate well between the distributions (absolute differences are small and the ranking differs by AIC and BIC). Gompertz and lognormal are in the top 3 best-fitting distributions for AIC and BIC in both arms, and exponential is the best-fitting distribution in both arms based on BIC. Figure 5 and Figure 6 illustrate pre-progression survival with Gompertz, lognormal and exponential extrapolations, alongside the KM estimates. We note that the choice

of pre-progression extrapolation has a limited impact in the company's base case model, as it applies KM OS data directly for the first 12 months, and most patients have experienced disease progression by month 12.

We report EAG scenarios with lognormal and exponential distributions for pre-progression mortality, each applied in both arms (5.2.4).

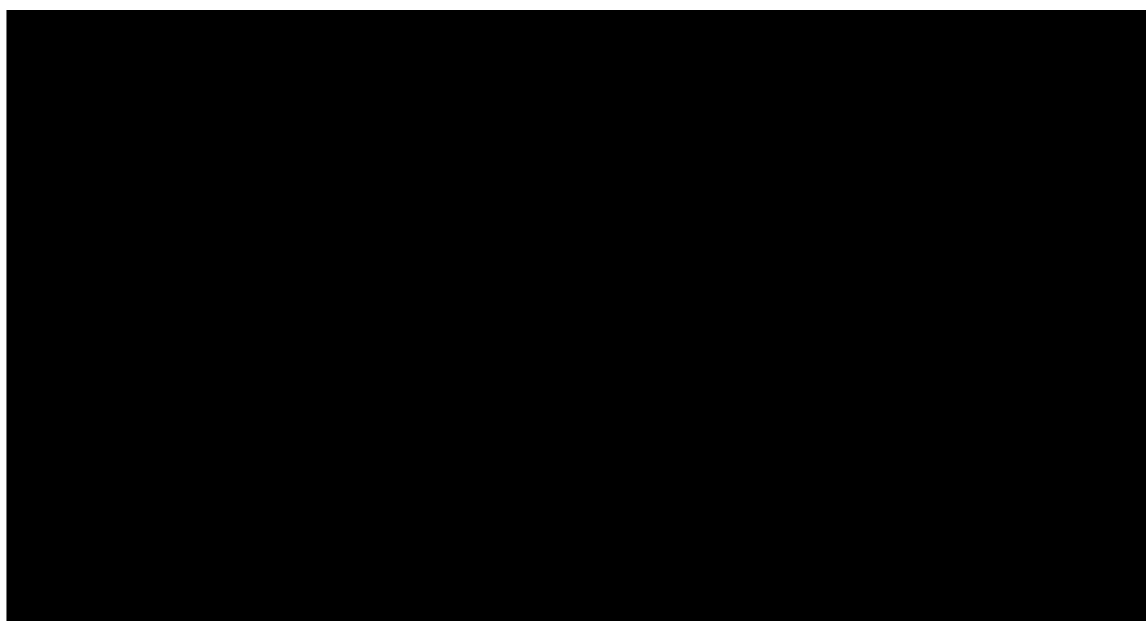


Figure 5 Pre-progression mortality: tisotumab vedotin best fit distributions

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

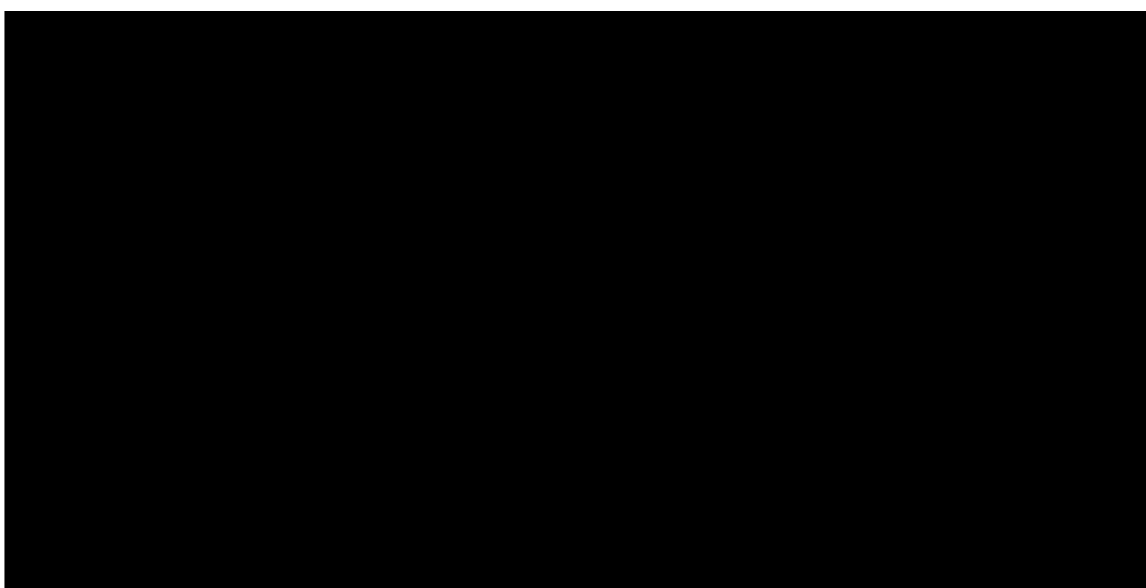


Figure 6 Pre-progression mortality: tisotumab vedotin best fit distributions

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

4.2.6.4 Post-progression mortality: transitions from PD to death

The company assume a constant (exponential) hazard for post-progression mortality, with the same value applied in both treatment arms (CS section 3.3.3).

This rate is estimated using individual-level patient data on post-progression survival, pooled from the tisotumab vedotin and chemotherapy arms of the InnovaTV 301 RCT.

4.2.6.4.1 Constant post-progression mortality hazard

The company put forward the following arguments for use of a constant post-progression mortality rate (CS section 3.3.3 and clarification response B3):

- It simplifies the model structure, as tunnel states are not required to track the time since entry to the PD health state, which would be necessary with alternative parametric survival distributions.
- A time-varying hazard function was not considered necessary, given the short post-progression survival time.
- The exponential model has a good visual fit to observed data (CS Figure 24), supported by the Cox-snell residual plots (CS Appendix Figure 26).

The EAG considers that the empirical evidence from the InnovaTV 301 RCT does not support the assumption of a constant post-progression mortality risk. In response to clarification question B5, the company provided hazard and log-cumulative hazard plots for post-progression survival, pooled across the treatment arms (clarification response Figure 26 and Figure 27). These show that the hazard [REDACTED]

The company's model includes AIC and BIC statistics for the standard parametric distributions fitted to pooled post-progression survival data from InnovaTV 301 (summarised in Table 15) below. [REDACTED]

Table 15 Goodness of fit (AIC and BIC) for post-progression survival (pooled)

Functional form	AIC (rank)	BIC (rank)
Exponential		
Weibull		
Lognormal		
Log-Logistic		
Gompertz		
Gamma		
Generalized Gamma		

Source: Produced by the EAG from data in the company's model

AIC, Akaike information criterion; BIC, Bayesian information criterion

4.2.6.4.2 Common post-progression mortality hazard

The company cite clinical advice that once patients have transitioned to subsequent treatments, their survival trajectories are comparable and no longer influenced by the initial treatment (CS section 3.3.3). The hazard and log-cumulative hazard plots for post-progression mortality by treatment arm are reported in the company's response to clarification question B5 (response Figures 24 and 25). [REDACTED]

The company argues that these trends deviate from clinical expectations and external evidence, and that this is likely related to statistical uncertainty.

In conclusion, the EAG has concerns about the assumption of a constant risk of death after disease progression, independent of prior treatment. Other assumptions cannot be explored in the company's semi-Markov model, due to the lack of tunnel states, we therefore consider other options to explore uncertainty over long-term survival, as described in the following section.

4.2.6.5 PFS and OS extrapolations

The OS and PFS curves from the company's base case parametric multistate model are shown in CS Figures 26 and 27 respectively (CS section 3.3.4). The OS curves follow the KM plots for the first 12 months, with an adjustment to ensure that the risk of death cannot be lower than for women of the same age in the general population.

4.2.6.5.1 *Use of observed KM data for OS prior to month 12*

The company explain their reasons for using raw KM data to model OS in the first 12 months in response to clarification question B4. They argue that empirical inspection and clinical validation showed that the fitted curves overestimated OS for chemotherapy and underestimated OS for tisotumab vedotin (clarification response Figure 21). Regarding the choice of for the cutoff date, the company argues that this maximises the use of robust empirical data before applying the fitted curves: by 12 months, few patients remained on randomised treatment (■■■ in the tisotumab vedotin arm and ■■■ in the chemotherapy arm), but the number at risk was 'still meaningful' (■■■ in the tisotumab vedotin arm and ■■■ in the chemotherapy arm, CS Figure 14). The company report ICERs for scenarios with 9- and 15-month cutoffs for use of OS KM data in the response to clarification question B4.

The EAG considers that the raw KM data is subject to uncertainty from trial-specific factors and random variation, and that there is a risk of bias due to the post-hoc choice of timepoint to switch from KM to fitted curves. We report EAG scenarios with no KM data (cutoff at month 0), as well as with cutoffs of 9 and 15 months (section 5.2.4). We do not use KM data directly in the EAG preferred analysis.

4.2.6.5.2 *Partitioned survival approach*

As noted above, the EAG has concerns over the assumptions that the mortality risk after disease progression is constant and independent of previous treatment. The effect of the constant post-progression survival hazard cannot be tested in the current model structure. The company state that they have explored the alternative PSM approach but did not adopt this due to a lack of clinical and external validity (company response to clarification question B1). Further information is not provided in the CS or clarification responses. The EAG has therefore used options provided in the company's model to investigate a PSM approach. The model includes directly fitted OS and PFS curves that can be used to implement a PSM, and two alternatives 'mortality capping' methods to avoid unrealistic crossover of the OS curves:

- Dependent models for the treatment arms (proportional hazards or failure time ratios)

- Common mortality rate once the OS curves for the treatment arms converge (hazard for tisotumab vedotin equal to that for chemotherapy).

The company report a scenario with dependent models: fitted parametric distributions for chemotherapy (PFS generalised gamma and OS lognormal), adjusted for tisotumab vedotin using a hazard ratio (CS Table 70). However, the failure time ratios for this analysis have not been justified, and the company have not reported log-cumulative hazards plots for PFS or OS.

For EAG preferred analysis, we use a PSM with the assumption of a common mortality rate for the treatment arms when the OS curves converge (section 5.2.4).

4.2.6.5.2.1 PFS direct extrapolation

We report AIC and BIC statistics for PFS extrapolations in Table 16. The lognormal, log-logistic and generalised gamma distributions have a similar statistical fit (top three for AIC and BIC in both arms, with similar numerical values). They also have a good visual fit with similar extrapolations (Figure 7 and Figure 8). The flexible spline extrapolations are similar to the parametric distributions. For comparison, we include the best-fit spline model, the log-logistic single knot, in Figure 7 and Figure 8. For the EAG preferred PSM analysis, we prefer the parametric log-logistic distribution for PFS with the same distribution in both arms, independently fitted. We report scenarios with lognormal and generalised gamma extrapolations of PFS.

Table 16 PFS extrapolations: goodness of fit statistics

Distribution	Tisotumab vedotin		Chemotherapy	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Parametric				
Exponential				
Weibull				
Lognormal				
Log-Logistic				
Gompertz				
Gamma				
Gen Gamma				

Flexible spline				
1 knot - Weibull				
1-knot - Log-logistic				
1-knot - Lognormal				
2 knot - Weibull				
2-knot - Log-logistic				
2-knot - Lognormal				

Source: Produced by the EAG from data in the company's model

AIC, Akaike information criterion; BIC, Bayesian information criterion

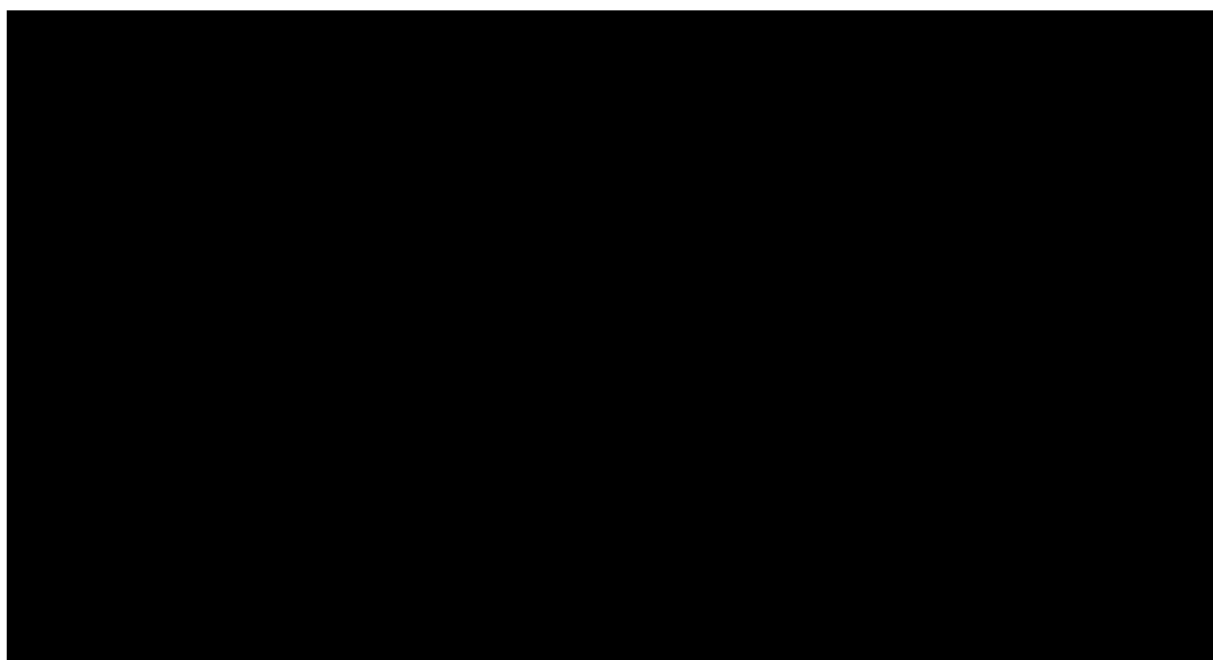


Figure 7 PFS KM and extrapolations for tisotumab vedotin

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

KM, Kaplan-Meier; TV, tisotumab vedotin; PFS, progression free survival

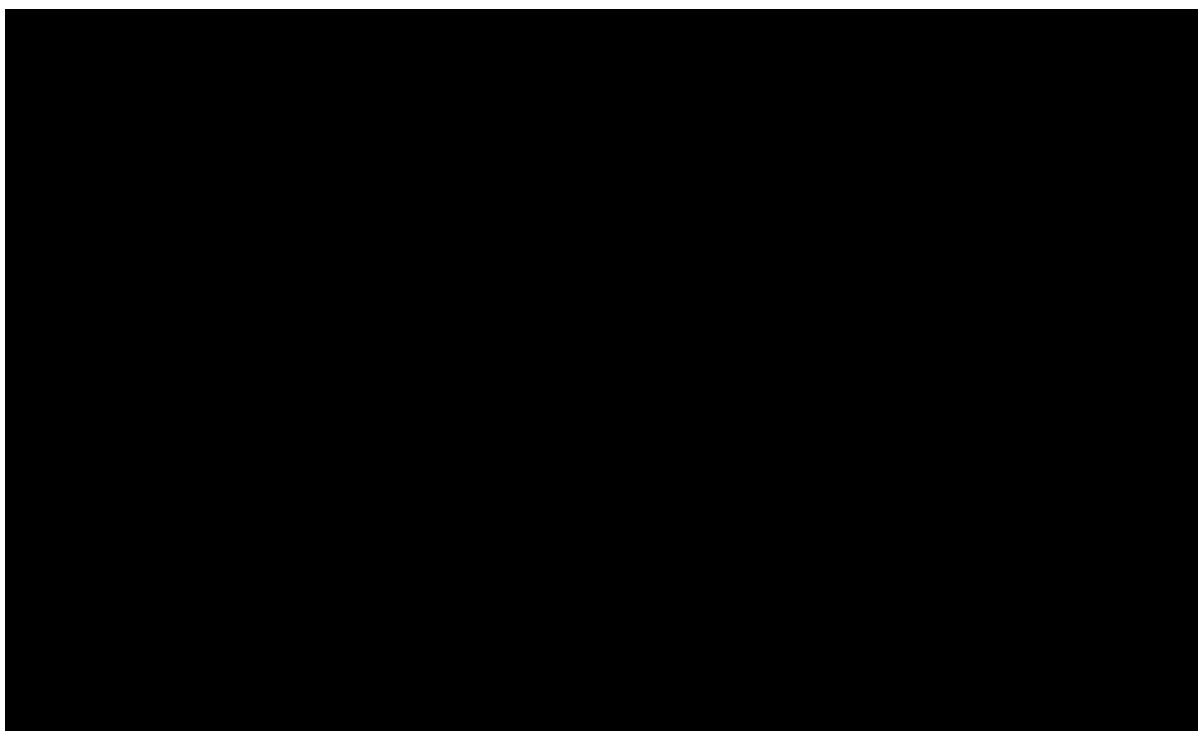


Figure 8 PFS KM and extrapolations for chemotherapy

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

KM, Kaplan-Meier; CHEM, chemotherapy; PFS, progression free survival

4.2.6.5.2.2 OS direct extrapolation for partitioned survival

AIC/BIC statistics for OS are reported in Table 17. We show selected OS curves in Figure 9 and Figure 10: log-logistic (best statistical fit for chemotherapy); Weibull (best statistical fit for tisotumab vedotin); gamma, generalised gamma and the 1-knot log-logistic spline (good statistical fit in both arms). We consider that the log-logistic and log-logistic 1-knot spline have the best visual fit for tisotumab vedotin. The log-logistic and generalised gamma provide a good visual fit for chemotherapy. For the EAG preferred PSM analysis, we use log-logistic extrapolations for OS in both arms, independently fitted, with two alternative scenarios: generalised gamma in both arms, independently fitted; and Weibull for tisotumab vedotin and log-logistic for chemotherapy.

Table 17 OS extrapolations: goodness of fit statistics

Distribution	Tisotumab vedotin		Chemotherapy	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)

Parametric				
Exponential				
Weibull				
Lognormal				
Log-logistic				
Gompertz				
Gamma				
Gen Gamma				
Flexible spline				
1 knot - Weibull				
1-knot - Log-logistic				
1-knot - Lognormal				
2 knot - Weibull				
2-knot - Log-logistic				
2-knot - Lognormal				

Source: Produced by the EAG from data in the company's model

AIC, Akaike information criterion; BIC, Bayesian information criterion

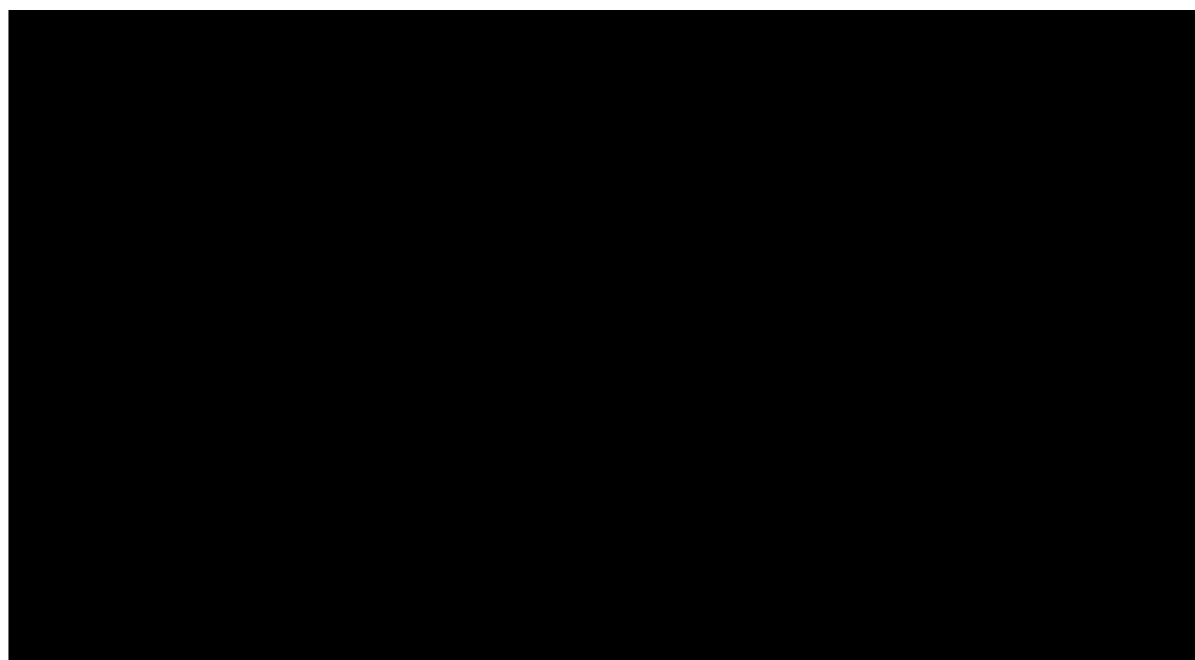


Figure 9 OS extrapolations for tisotumab vedotin

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

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

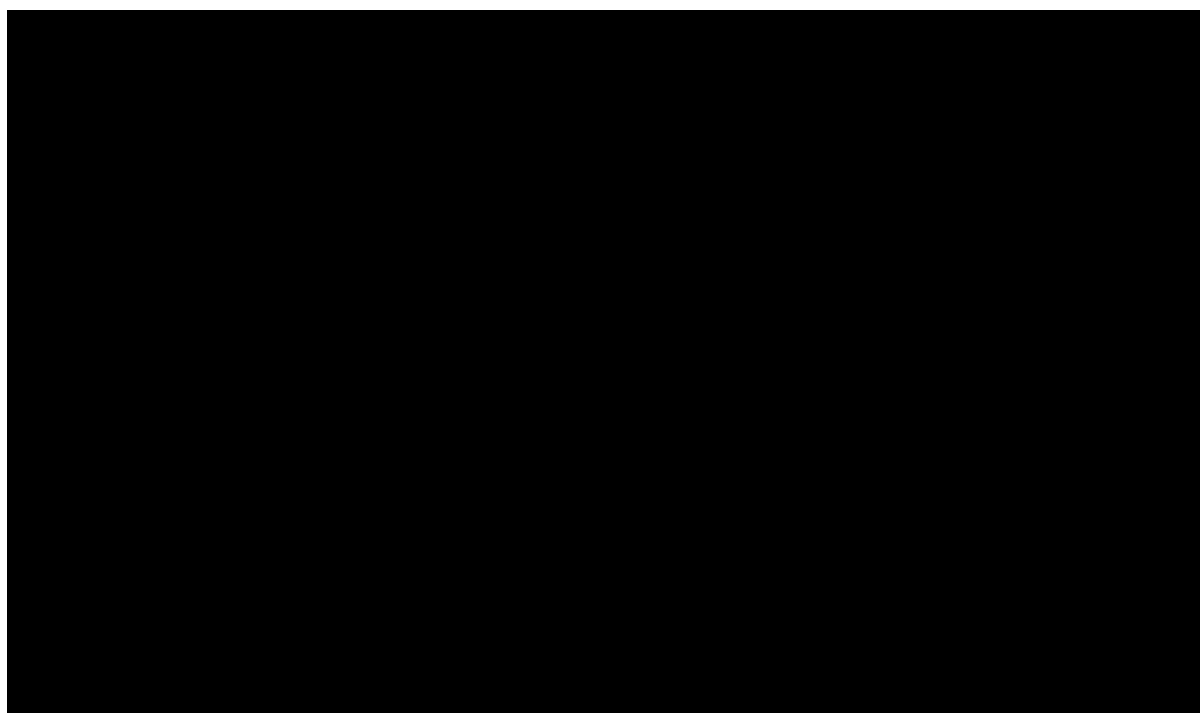


Figure 10 OS extrapolations for chemotherapy

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

CHEM, chemotherapy; KM, Kaplan-Meier; OS, overall survival

EAG comment on treatment effectiveness and extrapolation

The EAG has a number of concerns over the company's approach to modelling treatment effectiveness.

We report EAG scenario analysis to explore uncertainty related to the choice of extrapolations in the company's semi-Markov model, including lognormal or log-logistic extrapolations for time to progression; use of the same distributional form (lognormal or exponential) for pre-progression mortality; and we test the impact of the different cutoff times for direct use of OS KM data (0, 9 and 15 months).

We consider that the assumption of a constant mortality risk after disease progression, and the assumption that this is the same in each treatment arm are not supported by evidence of hazard trends from the InnovaTV RCT. It is not possible to explore the impact of time-varying hazards for post-progression survival, given the current model structure. We therefore prefer

to use a partitioned survival approach for EAG analysis, with an assumption that the risk of mortality is the same for tisotumab vedotin and chemotherapy when the OS curves converge, and no direct use of KM data.

For the EAG preferred PSM analysis, we use log-logistic extrapolations for PFS and OS, independently fitted in each arm. We report scenario analysis with alternative PFS and OS extrapolations.

4.2.7 Health-related quality of life (HRQoL)

4.2.7.1 Systematic literature review of utilities

The company conducted a systematic literature review to identify sources for utility estimates (CS section 3.4.5 and Appendix E).⁴⁶ The EAG have no concerns over the search methods. The review identified nine primary studies that elicited utility data (CS Appendix Table 11), and 13 secondary studies citing utility estimates from other sources (CS Appendix Table 12). None of the included studies met NICE reference case criteria (patient reported EQ-5D with valuation from a representative sample of the UK population).⁴⁸

The company report scenario analyses with health state utility values from two published sources (CS Table 70), but neither of these sources relate to the population of interest in this appraisal:

- **Zheng et al. (2023)**⁵⁷ reported a cost-effectiveness analysis of pembrolizumab for patients with recurrent or metastatic cervical cancer, but quote health state utility values for breast cancer.⁵⁸⁻⁶⁰
- **Liu et al. (2023)**⁶¹ used health state utilities from a cost-effectiveness analysis by Thurgar et al. (2021), which relate to a population with previously treated deficient mismatch repair or high microsatellite instability unresectable or metastatic endometrial cancer.⁶²

We note that suitable estimates of utility are not available from current published NICE technology appraisals for cervical cancer. In TA183 (topotecan), base case utilities were derived from a disease specific outcome measure (Functional Assessment of Cancer Therapy, FACT-G) mapped to utility using a published

algorithm, and scenarios were based on a breast cancer population.⁵ In TA885 and TA939 (pembrolizumab) utilities were estimated from trial EQ-5D-5L data and appropriately mapped to UK values, but the values are redacted in the available documentation.^{8, 10}

4.2.7.2 Study-based health related quality of life

For their base case, the company used health state utilities estimated from EQ-5D-5L data from patients in the InnovaTV 301 RCT (January 2024 data cut): see CS Table 53. The methods used to analyse the trial data are described in CS section 3.4.1. The company used appropriate methods to map from EQ-5D-5L to UK EQ-5D-3L utility values, as recommended by NICE.^{48, 63, 64} A generalised estimating equation (GEE) model was used to analyse the utility data, with an assumption of a constant correlation between timepoints for each patient. The base case GEE model included health status (pre-progression / post-progression) as the only independent variable. The company reports the impact of adding other covariates in CS Table 49, and state that these were deemed to have limited impact. They note that baseline ECOG status was statistically significant, but that the absolute impact on the utility estimate was small. The company also report an alternative mixed effects analysis used for scenario analysis, which includes between-patient and within-patient variation (random intercept and random slope): see CS section 3.4.3.

We note that the company did not impute missing EQ-5D data. As noted in section 3.3.4.2, it is difficult to assess the proportion of EQ-5D-5L VAS data that is missing based on reporting in the CSR, [REDACTED]

[REDACTED]. CS Table 48 reports the number of patients with at least one EQ-5D utility in the pre-progression and post-progression health states, and the total number of assessments in each state (including repeat assessments). We cannot infer the volume of missing data from these results or assess if there is a difference in the proportion of data that is missing by treatment arm. We therefore consider that missing data is a potential source of bias but cannot assess the size or direction of this bias.

4.2.7.3 Health state utilities used in the economic analysis

Table 18 summarises the health state utilities used in the company's base case (GEE model) and scenarios (mixed effects model, Liu et al. and Zheng et al.). We also include two scenarios based on the 95% confidence limits for the GEE means, as reported in CS Table 53: pre-progression [REDACTED] (95% CI: [REDACTED]); and post-progression [REDACTED] (95% CI: [REDACTED]).

Table 18 Health state utility estimates used in company analysis

Scenario	PF	PD	Difference	Source
GEE (base case)	[REDACTED]	[REDACTED]	[REDACTED]	InnovaTV 301
Mixed effects	[REDACTED]	[REDACTED]	[REDACTED]	InnovaTV 301
Liu scenario	0.817	0.779	0.038	Liu et al. 2023 ⁶¹
Zheng scenario	0.850	0.520	0.330	Zheng et al. 2023 ⁵⁷
GEE lower 95% limits	[REDACTED]	[REDACTED]	0.15	InnovaTV 301
GEE upper 95% limits	[REDACTED]	[REDACTED]	0.14	InnovaTV 301

Source: Produced by the EAG using information from CS Tables 48 and 52

GEE, generalised estimating equation; PD, progressed disease; PF, progression free.

Health state utilities are appropriately adjusted in the economic model to reflect the decline in utility with age in the general population, based on estimates reported by McNamara et al. (2023).⁶⁵

EAG comment on health state utilities

We agree with the methods used to estimate health state utilities from InnovaTV 301 EQ-5D-5L data, including mapping and use of the GEE model estimate values for the base case analysis. Utility is appropriately adjusted for aging. The published utilities that the company use for scenario analysis are not based on data from the population of interest in this appraisal, people with cervical cancer, and were not derived using NICE reference case methods.^{57, 61} We therefore use another approach to illustrate sensitivity of the cost-effectiveness results to the health state utilities, with scenarios based on the lower and upper confidence limits from the company's base case GEE model.

4.2.8 Resources and costs

The company conducted a systematic literature review to identify data on healthcare resource use and costs associated with the treatment of previously treated, relapsed or metastatic cervical cancer (CS section 3.5).⁴⁶ A description of the review including the search strategy and study selection is provided in CS Appendix E.

The following cost components were included in the company's economic model: pre-progression treatment costs, pre-medication costs for tisotumab vedotin, post-progression treatment costs, adverse event costs, disease management costs and terminal care costs. All costs were reported in 2024 Pounds Sterling. Published estimates based on prior years were adjusted to 2024 Pound Sterling using the Personal Social Services Research Unit (PSSRU) Inflation Index.^{66 67}

4.2.8.1 Intervention and comparators' costs and resource use

4.2.8.1.1 *Pre-progression treatment costs*

4.2.8.1.1.1 *Drug acquisition and administration costs*

The company assume that the pre-progression treatment costs, drug acquisition and administration costs for tisotumab vedotin and the comparator chemotherapies, would only be incurred while patients are on treatment and progression-free.

Drug acquisition costs are calculated as a function of unit drug prices, dosing schedules, relative dose intensity (RDI), duration of treatment (DoT), and patient weight / body surface area (BSA) distributions from the InnovaTV 301 RCT with an assumption of drug wastage (no vial sharing) in the base case model.⁵² The distribution of chemotherapy drugs is based on the UK survey of eight oncology specialists involved in managing recurrent or metastatic cervical cancer, shown in CS Table 42.

Dosing schedules and RDIs for tisotumab vedotin and chemotherapy are taken from the InnovaTV 301 RCT.^{52, 68} Unit drug prices for chemotherapy agents were sourced from the drugs and pharmaceutical electronic market information tool (eMIT).^{52, 68-74} The unit cost of tisotumab vedotin (██████████) includes a confidential (██████████) Patient Access Scheme (PAS) discount offered by the company on the UK list price of

██████████. Drug acquisition costs for both tisotumab vedotin and chemotherapy are presented in Table 19 below (CS Table 54).

The company assumed that all treatments are administered in an outpatient setting, with costs calculated from NHS reference costs (CS Tables 55 and 56).⁷⁵ The EAG notes that the company assumes a higher cost for administration of paclitaxel (£352 for complex chemotherapy including prolonged infusion, SB14Z), than for the simple chemotherapy agents pemetrexed, gemcitabine, topotecan, irinotecan, vinorelbine (£152, SB12Z). However, clinical experts advised the EAG that while issues of allergies regarding giving paclitaxel could introduce complexities in drug administration, single-agent paclitaxel is typically administered as a relatively short infusion around one hour and should not differ from other chemotherapies.

The EAG reports a scenario analysis using the cost of simple parenteral administration for paclitaxel (section 5.2.4), and we use this in our preferred analysis (section 5.2.5).

Table 19 Dosing schedules and drug acquisition costs for tisotumab vedotin and chemotherapy (company base case)

Drug	Dosing schedule (Descriptive)	Proportion in treatment arm	RDI	Unit cost (2024)	Unit size (mg)	Units per day
Tisotumab Vedotin	2.0 mg/kg Q3W	100%	████	██████████	40	3
Chemotherapy						
Topotecan	1 or 1.25 mg/m ² on days 1 to 5, Q3W	5.0%	████	£41.64	4	1
Vinorelbine	30 mg/m ² on days 1 and 8, Q3W	2.0%	████	£17.55	50	1
Gemcitabine	1000 mg/m ² on Days 1 and 8, Q3W	28.0%	████	£19.74	2000	1
Irinotecan	100 or 125 mg/m ² weekly for 28 days, Q6W	0.0%	████	£16.59	500	1
Pemetrexed	500 mg/m ² on day 1, Q3W	0.0%	████	£47.25	850	1
Paclitaxel	80 mg/m ² on day 1, QW	64.0%	████	£19.46	150	1

Source: reproduced from company submission Table 54

Q3W, every 3 weeks; Q6W, every 6 weeks; RDI, relative dose intensity; mg, milligram; ml, millilitres; kg, kilograms

Proportion in treatment arm are rounded up to whole numbers (%)

4.2.8.1.1.2 *Costs for prevention and management of ocular events*

Patients allocated to tisotumab vedotin are assumed to undergo an ocular assessment prior to treatment initiation, comprising a full eye examination (visual acuity and slit-lamp exam; CS Table 61), at an estimated cost of £169. To reduce the incidence and severity of ocular adverse events, patients treated with tisotumab vedotin are also assumed to receive pre-medication with dexamethasone and brimonidine tartrate eye drops (CS section 3.5.1.1.1 and Table 57). The EAG notes that the model does not include costs for topical preservative-free lubricating eye drops or cooling eye pads, which are specified in the company's eye care management plan [REDACTED] (see 2.2.3 above).

After treatment initiation, costs are included for an eye examination at each subsequent tisotumab vedotin cycle for patients who experience a grade 3/4 ocular adverse event in a prior cycle (4% of patients; CS Table 61).

Clinical experts advised the EAG that managing ocular toxicity would be difficult due to limited ophthalmic capacity in oncology settings, increased costs and patient burden from mandatory eye assessments, and challenges in providing timely specialist care (see section 2.2.3).

4.2.8.1.1.3 *Duration of treatment*

The company estimated the duration of treatment (DoT) for tisotumab vedotin and chemotherapy using IPD from the InnovaTV 301 RCT (CS Figure 28 and CS Figure 29). They fitted standard parametric models independently to the tisotumab vedotin and chemotherapy DoT curves and selected best-fit models for the base case (CS Figure 30). The company selected the generalised gamma distribution for tisotumab vedotin (as they assume that the log-logistic overestimated DoT beyond month 6) and log-logistic for chemotherapy (based on lowest AIC/BIC). DoT was constrained not to exceed PFS at any time.

4.2.8.1.2 *Post-progression treatment costs*

The company report the post progression treatment options and usage in CS Table 58. The company estimated the proportion of patients that received post-progression treatment among those who progressed ([REDACTED]) based on pooled data from the

tisotumab vedotin and chemotherapy arms of the InnovaTV 301 RCT.⁵² For each treatment, the company estimated an aggregate post-progression treatment cost based on treatment costs (drug acquisition and administration costs) per week and mean duration as observed in the InnovaTV 301 RCT.⁵²

One of the EAG clinical experts advised that the company's estimated proportion of patients receiving post progression treatment is reasonable, but another considered that a third would better reflect UK clinical practice, as many patients are too unwell to have further treatment. The clinical experts also noted that paclitaxel would be used more frequently than the other single-agent subsequent treatments (60% paclitaxel, 30% gemcitabine, 10% topotecan), and one expert highlighted that paclitaxel is often used as part of combination treatment. We explore the expert's estimates for subsequent therapy in scenario analyses (section 5.2.4), and adopt our expert's estimated distribution of patients receiving each subsequent treatment regimen in our base case analysis (section 5.2.5).

4.2.8.1.3 *Adverse reaction unit costs and resource use*

The company included costs and disutility for grade 3+ adverse events, reported in $\geq 5\%$ of patients in either treatment arm in the model. Adverse event costs were calculated separately for each arm using adverse event incidence rates (CS Table 47) and unit costs per event (CS Table 59). The company applied a one-off, weighted mean adverse event cost (CS Table 60) for tisotumab vedotin and chemotherapy at treatment initiation. No inpatient management was assumed. Outpatient adverse event costs were sourced from NHS reference costs⁷⁵ and the NICE technology appraisal of pembrolizumab for recurrent or metastatic cervical cancer (TA939).⁸

The EAG notes that the 52.8% incidence of grade 3+ ocular adverse events reported in CS Table 47, differs from the 4% used in the model. In response to clarification question B6, the company explained that 52.8% represents all-grade events, and that this is appropriate for costing as even mild cases may require eye examinations. The 4% rate reflects grade 3+ events for applying the QALY disutility (-0.04), as mild events have minimal quality-of-life impact. The EAG implements the company's response as a correction to their economic model (see section 5.2.3).

4.2.8.2 Health-state unit costs and resource use

4.2.8.2.1 Disease management costs

The model includes costs for routine disease management, with the assumption that the same costs apply equally before and after progression, due to the lack of state-specific data. In addition to the initial ocular assessment, eye examinations before treatment administrations (as discussed in sections 4.2.8.1.1.2 and 4.2.8.1.3 above, costs are included for follow-up consultations and tests, as listed in CS Table 61.

Clinical experts advising the EAG stated that the company's follow-up assumptions did not reflect UK clinical practice. They noted that colposcopy, X-Ray, positron emission tomography (PET) and magnetic resonance imaging (MRI) are not used in follow-up, and that patients are typically reviewed every three months with computed tomography (CT) imaging and often accompanied by blood tests and oncologist visits and a 6 monthly CT scan follow up depending on health. One expert highlighted that few patients remain on treatment beyond year three, by which time most will have transitioned to palliative care. This expert commented that the company's resource estimates appeared more consistent with radical chemoradiotherapy rather than metastatic disease management. Company and EAG clinical expert estimates of resource use for disease management are summarised in Table 20. We use the EAG clinicians estimates in scenario analyses (section 5.2.4), and in the EAG preferred analysis (section 5.2.5).

Table 20 Annual frequency of resource use for disease management

	Company estimates			EAG experts' estimates		
	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

Source: *Adapted from CS Table 61*

4.2.8.2.2 *Terminal care costs*

In the model, the company applied a one-time terminal care cost of £5,490.14 for each patient who died.⁷⁶

EAG comment on resources and costs

The EAG considers that the company's overall approach to estimating resource use and costs is broadly reasonable and generally consistent with methods used in previous NICE appraisals for recurrent or metastatic cervical cancer. However, we received advice from clinical experts that UK practice differs from the company's resource use assumptions in several respects: including the proportion of patients receiving subsequent treatment, and the types of treatment used after disease progression; and routine disease management. We test the impact of the EAG clinical experts' estimates in scenario analysis and adopt them in our preferred analysis.

We note that comparator drug prices in the company's model were based on a previous edition of eMIT (period 1 July 2024 to 30 June 2025; revised 22 July 2025). Updated prices (period 1 July 2024 to 30 June 2025; revised 24 July 2025), and confidential price discounts are applied in the EAG analysis within the confidential PAS appendix.

5 Cost-effectiveness results

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

The company's base case deterministic cost-effectiveness results are shown in CS Table 66 (reproduced in Table 21 below). Based on the calculated QALY shortfall, the results include a severity modifier with a QALY weighting of 1.7 (section 5.3.1). The ICER with (and without) severity modifier is £47,046 (£79,978) per QALY.

All results in this report include a confidential PAS price discount of [REDACTED] for tisotumab vedotin, with comparator and subsequent therapies costed at list price. We report results including price discounts for comparator and subsequent treatments in a confidential addendum to this report (see section 5.4).

Table 21 Company's deterministic base-case cost-effectiveness results with and without severity weighting (x1.7)

Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Chemotherapy	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£79,978 (£47,046)
Tisotumab Vedotin	[REDACTED]	[REDACTED]	-	-	-

Source: Reproduced from CS Table 66

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

5.1.2 Deterministic sensitivity analyses

The company presented deterministic sensitivity analysis (DSA) results in a tornado diagram (CS Figure 33), illustrating the 10 most influential parameters. Parameters were varied within their 95% confidence intervals or, where variance data were not available, by applying a standard error of $\pm 10\%$ around base-case values. A full list of parameters and assumptions tested is provided in CS Appendix J. The company reported that the model was generally robust to parameter variation, and that the key

drivers of the ICER were chemotherapy administration costs, pre-progression utility, and post-progression treatment costs for chemotherapy.

5.1.3 Scenario analysis

The company presented results of their scenario analyses for tisotumab vedotin vs single agent chemotherapy in CS Table 70. The EAG was able to replicate all reported scenarios. Scenarios tested included treatment efficacy, chemotherapy treatment distribution, adverse event costs, and adverse event-related utility/disutility. The company reported ICERs including a QALY weighting of 1.7, ranging from £34,471 per QALY (using dependent models for tisotumab vedotin and chemotherapy) to £59,667 per QALY gained (chemotherapy treatment distribution from the InnovaTV 301 RCT). The key drivers were the use of the global trial-based chemotherapy treatment distribution, modelling of post-progression survival, and application of alternative parametric curve distributions for progression-free to post-progression and progression-free to death transitions.

5.1.4 Probabilistic sensitivity analysis

The company presented probabilistic sensitivity analysis (PSA) results in CS Table 69 reproduced in Table 22. The mean probabilistic ICER is £46,660 per QALY (with QALY weighting), which is consistent with the deterministic base case results. At the WTP thresholds of £20,000 and £30,000 per QALY, the probability of tisotumab vedotin being cost-effective is 0% compared with chemotherapy.

This result was based on 200 Monte Carlo iterations (with 150 iterations considered sufficient for ICER convergence). The severity modifier was applied in the PSA, using the median of modifiers generated from the chemotherapy arm to ensure weighting values of 1.7, rather than an average. Modelled parameters, distributions, and uncertainty assumptions are summarised in CS Table 68, CS Table 21, and CS Appendix J. The EAG considers the distributions used in the PSA to be appropriate.

Results for tisotumab vedotin versus chemotherapy were presented as a cost-effectiveness scatter plot CS Figure 32 and a cost-effectiveness acceptability curves CS Figure 31.

Table 22 Company's probabilistic base-case cost-effectiveness results with and without severity weighting (x1.7)

Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Chemotherapy	██████	██████	██████	██████ ██████	██████ ██████
Tisotumab Vedotin	██████	██████			

Source: Source: reproduced from CS Table 69

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

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The company report quality control procedures used in the development and testing of their economic model in CS section 3.13.1.1.

The EAG also conducted a range of face validity and verification checks on the company's model, following our quality assurance log. This included:

- Checking that the values of all input parameters are consistent between the cited source, values stated in CS and those used in the model.
- Verification of model coding, using 'white box' checks of formulae linking model inputs, calculations and outputs.
- A series of 'black box' tests to assess face validity by checking that the model responds as expected to change in parameters and assumptions.
- We also obtained clinical expert advice on the plausibility and relevance to UK practice of key model parameters and assumptions, as well as model outcomes.

We consider that the model is technically well-implemented, and we only identified a few minor errors, see section 5.2.3 for EAG corrections. The clinical experts who we

spoke with disagreed with some assumptions regarding current UK practice, which we tested in EAG scenario analysis and include in our preferred assumptions where we consider it appropriate (5.2.4 and 5.2.5).

5.2.2 Validation of survival predictions

The company report validation of their base case survival predictions in CS section 3.13, by comparing with observed outcomes from three clinical trials, see discussion below. Landmark survival estimates and graphs illustrating the predicted and observed PFS and KM are reported in CS Appendix H.

5.2.2.1 Comparison with the InnovaTV 301 trial (both arms)

The company compare OS predictions from their base case model with KM estimates from the InnovaTV 301 RCT (CS Appendix Figure 13 and Table 13). They conclude that there is a strong fit for OS in the tisotumab vedotin arm, with predicted values close to the observed values. For chemotherapy, the company note divergence between observed and predicted OS towards the tails of the curves. They attribute this to the small remaining sample size and argue that the predicted 24-month survival of █████ for chemotherapy is consistent with the 10% estimate from their clinical experts. We also note that in response to clarification question B1, the company cite a figure of 13% 24-month survival for a cohort of patients receiving second-line chemotherapy at the Royal Marsden Hospital (McLachlan et al. 2017).⁴⁹ PFS has a good fit in both arms (CS Appendix Figure 14 and Table 14).

5.2.2.2 Comparison with the InnovaTV 204 trial (tisotumab vedotin only)

The company compare their base case OS and PFS predictions for tisotumab vedotin with results from the phase 2 InnovaTV 204 single-arm trial (CS Appendix Figures 15-16 and Tables 15-16).⁴² They state that patients in InnovaTV 204 and InnovaTV are comparable, and that InnovaTV 204 has longer follow-up. The EAG has not been able to verify the population or median survival for the InnovaTV 204 final analysis (see Table 8).⁷⁷ The company states that the model predictions align well with estimates from InnovaTV 204, and that although the PFS and OS predictions were slightly lower than the trial KM at the tails, the predictions were within 95% confidence limits from the trial (CS 3.13.1.2). The EAG notes that the

model predictions fall below the lower 95% confidence limits, but that the numbers of patients at risk are not reported.

5.2.2.3 Comparison with EMPOWER Cervical-1 (chemotherapy only)

The company use results from the control arm of the EMPOWER-Cervical 1 trial to validate their base case predictions for chemotherapy OS and PFS. EMPOWER-Cervical 1 was a phase 3 trial of cemiplimab compared with a control arm of investigator's choice single-agent chemotherapy (n=304) for patients with recurrent or metastatic cervical cancer that had progressed on or after platinum-containing chemotherapy (ECOG $\leq$ 1).^{78, 79} The final analysis (median follow up 47.3 months) reported median OS of 8.5 months for the control arm, with 34.2% alive at 12 months, and 11.9% at 24 months (Oaknin et al. 2025).⁷⁹ The KM data used for the company's validation (CS Appendix Figure 17) appears to have been digitised from a previous data cut with median follow up of 30.2 months (CS 3.13.1.2). The company conclude that the model predictions of PFS and OS aligned well with the EMPOWER-Cervical 1 data, and they note the similarity of the 24-month estimates.

5.2.2.4 Comparison of company and EAG OS predictions

Figure 11 and Figure 12 show the OS predictions from the company's base case model and the EAG's preferred log-logistic model, respectively. We consider that the EAG's preferred model has a better visual fit to the InnovaTV 301 RCT data. However, it might be considered that predicted survival with chemotherapy in our preferred model is unrealistically high (████ at 24 months), compared with 11.9% in the EMPOWER-Cervical 1 comparator arm, 13% from the Royal Marsden cohort.⁴⁹ An alternative EAG scenario, with generalised gamma extrapolations in both arms (Figure 13) predicts █████ 24-month survival, but we consider that this has a less good visual fit to the InnovaTV 301 KM than the log-logistic model.

In addition to the plausibility of the chemotherapy estimate, the other major consideration in comparing alternative survival models is the plausibility of the projected treatment benefit for tisotumab vedotin beyond █████, where the InnovaTV 301 KM curves from converge. Figure 14 illustrates a less favourable scenario with a Weibull extrapolation for tisotumab vedotin, which merges with the log-logistic extrapolation for chemotherapy shortly after the KM curves meet.

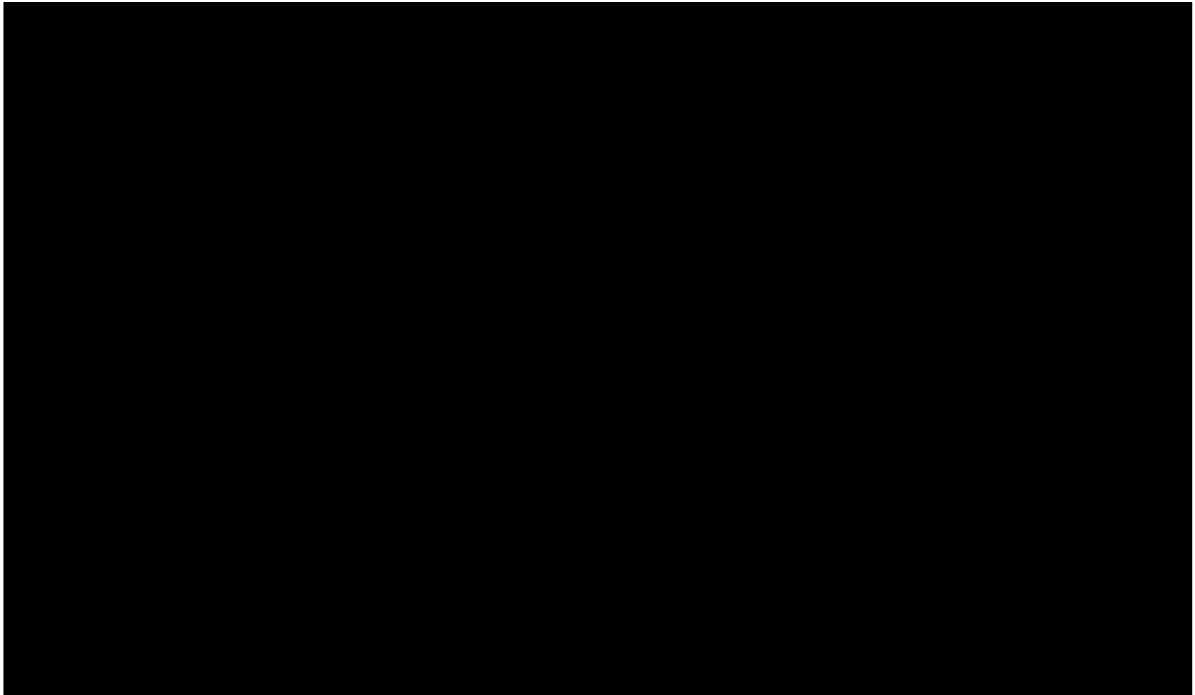


Figure 11 Company base case (semi-Markov), with InnovaTV 301 KM

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

CHEM, chemotherapy; KM, Kaplan-Meier, TV, tisotumab vedotin

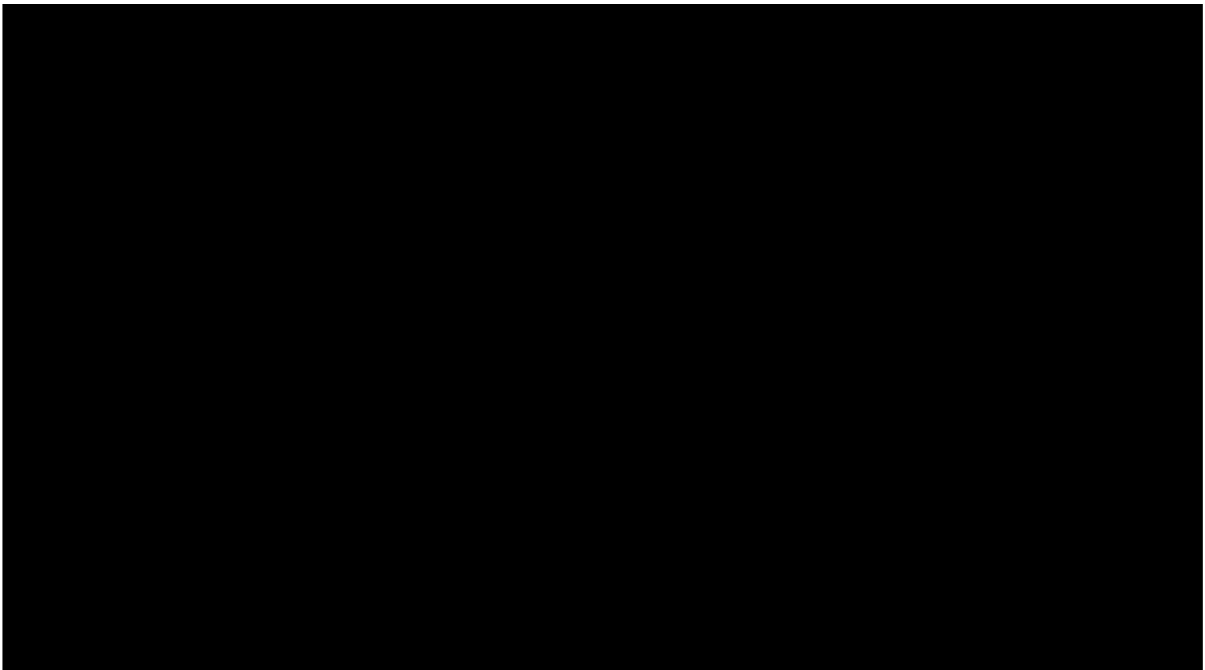


Figure 12 EAG base case (log-logistic OS), with InnovaTV 301 KM

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

CHEM, chemotherapy; KM, Kaplan-Meier, TV, tisotumab vedotin

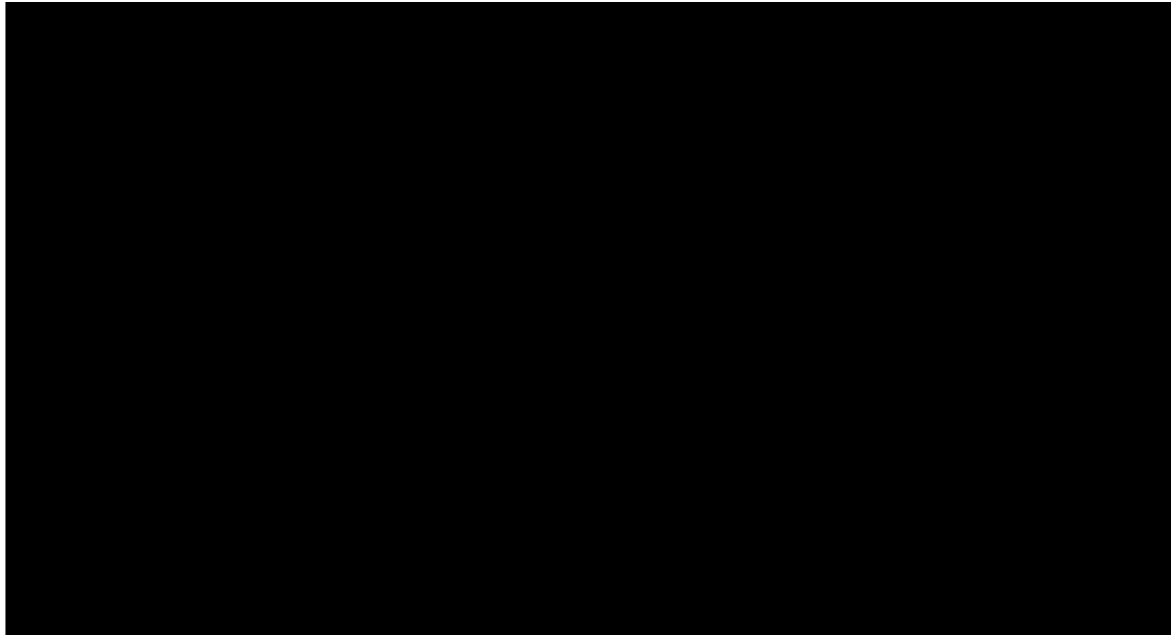


Figure 13 EAG scenario (generalised gamma OS), with InnovaTV301 KM

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

CHEM, chemotherapy; KM, Kaplan-Meier, TV, tisotumab vedotin

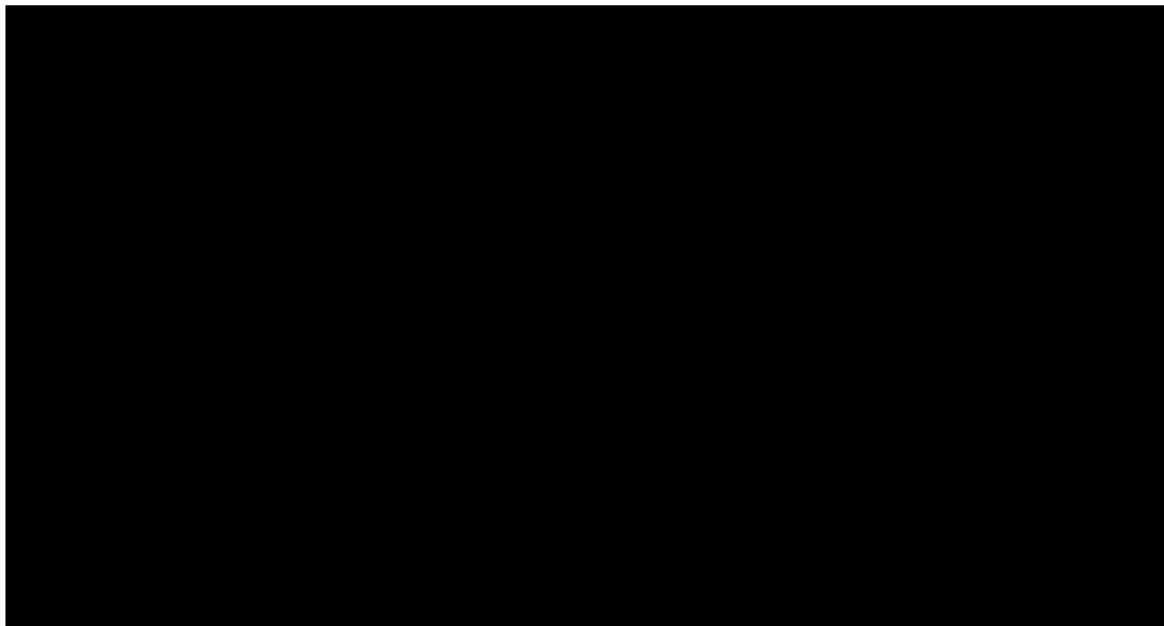


Figure 14 EAG scenario (Weibull for tisotumab vedotin, log-logistic for chemotherapy, with InnovaTV301 KM)

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

CHEM, chemotherapy; KM, Kaplan-Meier, TV, tisotumab vedotin

Table 23 Landmark OS estimates for tisotumab vedotin

	3 m	6 m	12 m	24 m	36 m	48 m
InnovaTV 301 trial	████	████	████	████	████	████
InnovaTV 204 trial	████	████	████	████	████	████
EMPOWER-Cervical 1	N/A	N/A	N/A	N/A	N/A	N/A
Company base case	████	████	████	████	████	████
Company– PSM	████	████	████	████	████	████
Company - 9m KM	████	████	████	████	████	████
Company - 15m KM	████	████	████	████	████	████
EAG preferred log-logistic	████	████	████	████	████	████
EAG generalised gamma	████	████	████	████	████	████
EAG Weibull / log-logistic	████	████	████	████	████	████

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

KM, Kaplan-Meier; m, month; N/A, not available; PSM, partitioned survival model with dependent PFS and OS

Table 24 Landmark OS estimates for chemotherapy

	3 m	6 m	12 m	24 m	36 m	48 m
InnovaTV 301 trial	████	████	████	████	████	████
InnovaTV 204 trial	N/A	N/A	N/A	N/A	N/A	N/A
EMPOWER-Cervical 1	86.4%	66.3%	34.3%	11.3%	7.2%	N/A
Company base case	████	████	████	████	████	████
Company– PSM	████	████	████	████	████	████
Company - 9m KM	████	████	████	████	████	████
Company - 15m KM	████	████	████	████	████	████
EAG preferred log-logistic	████	████	████	████	████	████
EAG generalised gamma	████	████	████	████	████	████
EAG Weibull / log-logistic	████	████	████	████	████	████

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

KM, Kaplan-Meier; N/A, not available; PSM, partitioned survival model with dependent PFS and OS

5.2.3 EAG corrections to the company model

The EAG identified four coding problems in the company's economic model:

1. **Selection of the methods and source for PFS and OS curves:** The controls to select the method of extrapolation (parametric functions, splines or hazard ratio) and trials (InnovaTV 204, InnovaTV 301 and EMPOWER trials) have broken references ("Effectiveness" sheet, cells G19, G20, G49, G50, I19, and I20 using the "Data validation" menu option). We replace the missing information pointing to cell Var!L174 ("Apply the same risk of death after progression for TV and chemotherapy"). This does not affect the company's base-case results but allows the EAG to explore scenarios.
2. **PFS should be capped by the OS:** on "tx1" and "tx2" sheets, we have the PFS estimate in column I and the OS estimate in column K for tisotumab and the comparator, respectively. Both these estimates are calculated and treated in the "Effectiveness_Calc" sheet. However, when the model assumes a KM curve in the initial months for the OS curve, it can lead to PFS estimates exceeding OS estimates because the PFS is capped when we consider only the fitted OS, not the KM curve. We included a cap in the PFS estimates in "tx1" and "tx2" sheets. This has a marginal impact (less than £1) with the selected distributions.
3. **Resource use per week estimates for colposcopy:** There is a typo in "Raw_MedCost" sheet, cells from C9 to G9, where the year is considered to have 365.27 days. All other formulae in the model considered a year of 365.25 days. This does not affect the results, but we amended the model for completeness.
4. **Rate for ocular adverse event:** The rate for ocular adverse event applied in the company's model is corrected in "Disease Management Costs!E36" to reflect the company's response to clarification question B6 (see section 4.2.8.1.3). This increases the company's base case ICER by £3,383.

Table 25 shows the company's corrected base case results including the EAG corrections listed above.

Table 25 Company's base-case results with EAG corrections, with and without severity weighting (x1.7), deterministic analysis

Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Chemotherapy	████████	████████	████████	████████	£83,360 (£49,035)
Tisotumab Vedotin	████████	████████			

Source: company's corrected economic model

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

Table 26 Company's base-case results with EAG corrections, with and without severity weighting (x1.7), probabilistic analysis

Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Chemotherapy	████████	████████	████████	████████	£79,220 (£46,600)
Tisotumab Vedotin	████████	████████			

Source: company's corrected economic model

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

5.2.4 EAG's exploratory analyses using company's base case

A full summary of EAG observations on key aspects of the company's economic model which are explored through scenario analysis are presented in Table 27

Table 27 Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1 & 2	PF to PD: generalised gamma	Lognormal or log-logistic, in both arms	Extrapolations have similar fit as base case	Section 4.2.6.2
3 & 4	PF to death: Gompertz (TV) and lognormal (chemo)	Exponential or lognormal, in both arms	High uncertainty, use same curve for both arms	Section 4.2.6.3
5 to 7	OS based on KM data for first 12 months	OS KM for 0, 9 or 15 months	Avoids risk of bias from choice of cutoff	Section 4.2.6.5.1
8	Semi-Markov model	EAG PSM: equal mortality when curves converge, log-logistic for PFS and OS (both arms)	EAG preferred extrapolations, good fit to PFS and OS KM in both arms	Section 4.2.6.5.2
9	Semi-Markov model	EAG PSM: OS scenario with generalised gamma in both arms for OS	Alternative OS extrapolations with good fit to both arms	Section 4.2.6.5.2
10	Semi-Markov model	EAG PSM: OS scenario with Weibull for TV, log-logistic for chemotherapy	Best fit OS extrapolations for each arm	Section 4.2.6.5.2

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
11 & 12	Semi-Markov model	EAG PSM: PFS scenarios with log-normal or gen. gamma in both arms	To illustrate sensitivity to of PSM to PFS extrapolation	Section 4.2.6.5.2
13	Administration cost for paclitaxel: complex chemotherapy, prolonged infusion (£352)	Administration cost for paclitaxel based on simple parenteral chemotherapy (£152)	EAG clinical experts estimates to reflect UK clinical practice	Section 4.2.8.1.1
14	Single agent chemotherapy mix, see Table 14	Single agent chemotherapy mix (EAG's Expert 1; see Table 14)	EAG clinical expert's' estimate to reflect UK clinical practice	Section 4.2.5
15	Subsequent therapy: 53%	Subsequent therapy: 33%	EAG clinical experts' estimate to reflect UK clinical practice	Section 4.2.8.1.2
16	Subsequent therapy mix: 33% each for topotecan, gemcitabine and paclitaxel	Subsequent therapy mix: 10% topotecan, 30% gemcitabine and 60% paclitaxel	EAG clinical experts' estimates to reflect UK clinical practice	Section 4.2.8.1.2

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
17	Disease management resource use, see Table 20	Disease management resource use, see Table 20	EAG clinical experts' estimates to reflect the UK clinical practice	Section 4.2.8.2.1
18 & 19	Utilities: GEE estimates from trial EQ-5D-5L: [REDACTED] (CS Table 53)	95% CI limits: [REDACTED] and [REDACTED]	To explore sensitivity, in the absence of other relevant estimates	Section 4.2.7

Source: EAG created table

CS, company submission; EQ-5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; GEE, generalised estimating equation; KM, Kaplan-Meier; OS, overall survival; PD, progressed-disease; PF, progression-free; PFS, progression-free survival; PSM, partitioned survival model; TV, tisotumab vedotin

Table 28 presents the deterministic results for the EAG's exploratory scenario analyses with each scenario applied, one at a time, to the EAG-corrected company's base case. We report deterministic results for convenience. The company's deterministic and probabilistic base-case results were consistent: the ICER decreased by approximately £386 in the probabilistic analysis. Similarly, if the results from the scenario analysis were presented probabilistically, the ICERs would be expected to decrease slightly.

We note that the appropriate QALY weight differs between the scenarios (x1.2 or x1.7).

The ICER ranges from £80,814 (without severity modifier) when the single agent chemotherapy mix based on EAG experts' estimates is applied, to £135,322 (without

a severity modifier) when the model structure was revised to a PSM with generalised gamma curve for PFS and OS in both treatment arms.

Using the unweighted ICERs as the results have different QALY weight applied to them (x1.2 or x1.7 severity modifier), the ICER is most sensitive to the PSM OS modelling assumptions (scenarios 9 and 10). Also, the result in scenario 13 indicates a meaningful influence of treatment delivery costs on the ICER.

Table 28 Results of EAG's exploratory analyses using company's base case with EAG corrections

Number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weight)	ICER £/QALY (x1.2 or 1.7 weight)
	Company base case (EAG corrections)	████████	████████	£83,360 (£49,035 ^b)
1	PF to PD: Lognormal (both arms)	████████	████████	£103,920 (£61,129 ^b)
2	PF to PD: Log-logistic (both arms)	████████	████████	£96,566 (£56,804 ^b)
3	PF to death: Exponential (both arms)	████████	████████	£97,573 (£57,396 ^b)
4	PF to death: Lognormal (both arms)	████████	████████	£91,452 (£53,795 ^b)
5	Do not use the OS KM data with the OS fitted curve	████████	████████	£100,691 (£59,230 ^b)
6	Use OS KM data for the first 9 months	████████	████████	£87,419 (£51,423 ^b)

Number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weight)	ICER £/QALY (x1.2 or 1.7 weight)
7	Use the OS KM data for the first 15 months	████████	████████	£81,713 (£48,067 ^b)
8	EAG PSM: OS scenario with log-logistic in both arms (no OS KM)	████████	████████	£111,826 (£93,188 ^a)
9	EAG PSM: OS scenario with generalised gamma in both arms (no OS KM)	████████	████████	£135,322 (£79,601 ^b)
10	EAG PSM: OS scenario with Weibull for TV and log-logistic for chemo (no OS KM)	████████	████████	£129,136 (£75,962 ^b)
11	EAG PSM: PFS scenarios with log-normal in both arms	████████	████████	£116,038 (96,698 ^a)
12	EAG PSM: PFS scenarios with gen. gamma in both arms	████████	████████	£112,764 (£93,970 ^a)
13	Administration cost for paclitaxel based on simple parenteral chemotherapy	████████	████████	£99,434 (£58,490 ^b)

Number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weight)	ICER £/QALY (x1.2 or 1.7 weight)
14	Single agent chemotherapy mix based on experts' estimates	████████	████████	£80,814 (£47,538 ^b)
15	Subsequent Therapy proportion based on EAG expert's estimate	████████	████████	£83,453 (£49,090 ^b)
16	Subsequent therapy distribution based on the EAG experts' estimates	████████	████████	£83,353 (£49,031 ^b)
17	Disease management resource use	████████	████████	£81,954 (£48,208 ^b)
18	Pre and post progression utilities from lower limits of 95% CI (0.69, 0.54)	████████	████████	£82,265 (£50,744 ^b)
19	Pre and post progression utilities from upper limits of 95% CI (0.73, 0.59)	████████	████████	£81,126 (£47,721 ^b)

Source: EAG created table

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

a QALY weight of 1.2

b QALY weight of 1.7

5.2.5 EAG's preferred assumptions

Based on the EAG critique of the company's model in section 4.2, we have identified the following aspects of the company base case with which we disagree. Our preferred model assumptions are:

- OS curve: We do not consider the OS Kaplan Meier data in the OS selected curve (see section 4.2.6.5.1).
- Partitioned survival model: we change the model structure from a semi-Markov model to a 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 (see section 4.2.6.5.2).
- Cost for administration of paclitaxel: we use a reduced cost for simple parenteral administration of paclitaxel (see section 4.2.8.1.1).
- Chemotherapy mix: we use the EAG expert estimates for single-agent chemotherapy mix (see section 4.2.5).
- Subsequent treatment mix: we use the EAG expert estimates for subsequent therapy mix (see section 4.2.8.1.2)
- Healthcare management costs: we use the EAG expert estimates for single agent chemotherapy mix (see section 4.2.8.2.1).

The cumulative cost-effectiveness results from applying the EAG preferred model assumptions to the company's post clarification base case ICER are shown in Table 29, with a PAS discount for tisotumab vedotin and list price for the other treatments. We provide a separate EAG confidential cPAS addendum with all treatments costed with their confidential price discounts. Incorporating all the EAG assumptions, the deterministic ICER for tisotumab vedotin compared with chemotherapy increases to £108,169 (£129,803) per QALY with (and without) a x1.2 severity modifier.

Excluding the use of observed KM OS data increased in the cumulative ICER by £17,331 per QALY, and changing the model structure to a PSM reduced the severity modifier from x1.7 to x1.2. The model results are most sensitive to the reducing in the assume administration cost for paclitaxel. The EAG considers that a disease severity modifier of 1.2 is appropriate see section 5.3.1.

Table 29 Results using EAG's preferred model assumptions with and without severity weighting

Preferred assumption	Treatment	Exploratory analysis number	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.2 or x1.7 weighting)	Cumulative ICER £/QALY (x1.2 or x1.7 weighting)
Company's base case	Chemotherapy	NA	████████	████████	████████	████████	£79,978 (£47,046) ^b
	Tisotumab vedotin		████████	████████			
EAG's corrected company base case	Chemotherapy	NA	████████	████████	████████	████████	£83,360 (£49,035) ^b
	Tisotumab vedotin		████████	████████			
Consider only OS fitted curve (no OS KM data)	Chemotherapy	5	████████	████████	████████	████████	£100,691 (£59,230) ^b
	Tisotumab vedotin	5	████████	████████			
PSM: Log-logistic for PFS and OS in both arms	Chemotherapy	8	████████	████████	████████	████████	£111,826 (£93,188) ^a
	Tisotumab vedotin	8	████████	████████			
Administration cost for paclitaxel based on simple parenteral chemotherapy	Chemotherapy	13	████████	████████	████████	████████	£133,918 (£111,598) ^a
	Tisotumab vedotin	13	████████	████████			

Preferred assumption	Treatment	Exploratory analysis number	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.2 or x1.7 weighting)	Cumulative ICER £/QALY (x1.2 or x1.7 weighting)
Single agent chemotherapy mix based on the EAG experts' estimates	Chemotherapy	14	██████	██████	██████	██████	£131,243 (£109,369) ^a
	Tisotumab vedotin	14	██████	██████			
Subsequent treatment mix based on the EAG experts' estimates	Chemotherapy	16	██████	██████	██████	██████	£131,256 (£109,380) ^a
	Tisotumab vedotin	16	██████	██████			
Healthcare disease management cost based on the EAG experts' estimates	Chemotherapy	17	██████	██████	██████	██████	£129,803 (£108,169) ^a
	Tisotumab vedotin	17	██████	██████			
EAG Base Case	Chemotherapy	NA	██████	██████	██████	██████	£129,803 (£108,169) ^a
	Tisotumab vedotin	NA	██████	██████			

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

^a QALY weight of 1.2, ^b QALY weight of 1.7

The probabilistic results with the EAG's preferred assumptions are presented in Table 30 below. From the 200 PSA iterations, 68.5% had a QALY weighting of 1.2 and 31.5% had a 1.7 QALY weighting. Considering the average total QALY in the chemotherapy arm of [REDACTED], we calculate that the QALY weight for the EAG's base case probabilistic result of 1.2.

Table 30 EAG's probabilistic preferred assumptions cost-effectiveness results with and without severity weighting (x1.7)

Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Chemotherapy	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£110,120 (£91,767)
Tisotumab Vedotin	[REDACTED]	[REDACTED]	-	-	-

Source: Reproduced from CS Table 66

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

5.2.6 Company's sensitivity and scenario analyses

The company's deterministic sensitivity analysis 5.1.2, probabilistic sensitivity analysis 5.1.4 and scenario analysis 5.1.3 are reported in CS section 3.11. The EAG was able to replicate all the company's scenario analysis from CS Table 70. Table 32 presents the results (with and without a severity modifier) from the two selected company's scenarios, as summarised in Table 31, on our base case.

Table 31 Summary of selected company scenario analyses using EAG's preferred assumptions

	EAG's base-case assumption	Company's scenario
1	Partitional Survival Model with lognormal distribution to fit the PFS curve and log-logistic distribution to fit the OS curve	Use dependent models for tisotumab vedotin and chemotherapy (PSM approach) PFS: Generalised gamma, OS: Lognormal

	EAG's base-case assumption	Company's scenario
2	Proportion of the single agent chemotherapy distribution based on EAG expert estimates	Chemotherapy treatment distribution from the InnovaTV 301 RCT

Source: EAG created Table

EAG external assessment group; OS, overall survival; PFS, progression free survival; PSM, partitioned survival model; RCT, randomised controlled trial

Table 32 Results of company's scenario analyses using EAG's preferred assumptions with and without severity modifiers

	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (x1.2 or x1.7 weighting)	ICER £/QALY (x1.2 or x1.7 weighting)
	EAG base case			£129,803 (£108,169) ^a
1	Use dependent models for tisotumab vedotin and chemotherapy (PSM approach) PFS: Generalised gamma, OS: Lognormal			£74,081 (£43,577) ^b
2	Chemotherapy treatment distribution from the InnovaTV 301 RCT			£139,913 (£116,594) ^a

Source: EAG created Table

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PFS, progression free survival; OS, overall survival; PSM, partitioned survival model; EAG external assessment group

^a QALY weight of 1.2

^b QALY weight of 1.7

5.2.7 Scenario analyses using EAG's preferred assumptions

Table 33 summarises the scenario analyses applied to the EAG base case preferred analysis. The deterministic results are presented in Table 34. The results were most sensitive to revising the model structure to a PSM: using generalised gamma in both arms for OS. The ICERs ranged from £106,866 per QALY (administration of paclitaxel based on complex chemotherapy, including prolonged infusion treatment cost) to £156,995 per QALY (PSM: OS scenario with generalised gamma in both arms for OS).

Table 33 EAG scenario analyses applied to the EAG's preferred analysis

-	EAG's base case assumptions	EAG's scenario
1	Administration cost for paclitaxel based on simple parenteral chemotherapy	Based on complex chemotherapy, including prolonged infusion treatment cost (company's assumption)
2	Proportion of the single agent chemotherapy distribution based on EAG experts' estimates	Proportion of the single-agent chemotherapy distribution based on the company's UK expert estimates (company's assumption)
3	Subsequent treatment mix based on the EAG experts' estimates	Subsequent treatment mix based on the company expert estimates (company's assumption)
4	Healthcare management costs based on the EAG experts' estimates for single agent chemotherapy mix	Healthcare management costs based on the company's expert estimates for single agent chemotherapy mix
5	Partitional Survival Model with log-logistic distribution to fit the PFS and OS curves in both arms	Semi-Markov model with generalised gamma for PF-PD, Gompertz for the PF-Death for TV and lognormal for PF-Death in chemotherapy arm (company assumption)

-	EAG's base case assumptions	EAG's scenario
6 to 9	Partitional Survival Model with log-logistic distribution to fit the PFS and OS curves in both arms	PSM with alternative distributions (see EAG exploratory scenarios 9 to 12)
10	Do not consider the KM curve for the OS	Consider KM curve for the first 12 months. (company's assumption)
11 & 12	Utilities	Using the 95% CI (EAG exploratory scenarios)

Source: EAG created table.

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

Table 34 Results of scenario analyses applied to the EAG's preferred analysis

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weighting)	ICER £/QALY (x1.2 or 1.7 weighting)
	EAG base case	████████	████████	£129,803 (£108,169) ^a
1	Administration costs for paclitaxel assuming prolonged infusion (company's assumption)	████████	████████	£106,866 (£89,055) ^a
2	Chemotherapy treatment mix based on company expert estimates (company's assumption)	████████	████████	£132,478 (£110,398) ^a

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weighting)	ICER £/QALY (x1.2 or 1.7 weighting)
3	Subsequent treatment mix based on the company expert estimates (company's assumption)	████████	████████	£129,789 (£108,158) ^a
4	Healthcare management costs based on company expert estimates for single agent chemotherapy	████████	████████	£131,256 (£109,380) ^a
5	Semi-Markov model with generalised gamma for PF-PD and Gompertz for PF-Death for TV; lognormal for PF-Death in chemotherapy arm (company assumption)	████████	████████	£116,615 (£68,597) ^b
6	EAG PSM: OS scenario with generalised gamma in both arms for OS	████████	████████	£156,995 (£92,350) ^b
7	EAG PSM: OS scenario with Weibull for TV and log-logistic for chemo	████████	████████	£149,593 (£87,996) ^b
8	EAG PSM: PFS scenario with log-normal in both arms	████████	████████	£133,278 (£111,065) ^a

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weighting)	ICER £/QALY (x1.2 or 1.7 weighting)
9	EAG PSM: PFS scenario with generalised gamma in both arms	██████████	██████████	£129,922 (£108,268) ^a
10	Consider OS KM curve for the first 12 months. (company's assumption)	██████████	██████████	£126,007 (£105,006) ^a
11	Pre and post progression utility from ██████████ ██████████ (EAG exploratory scenario)	██████████	██████████	£134,035 (£111,696) ^a
12	Pre and post progression utility ██████████ ██████████ (EAG exploratory scenario)	██████████	██████████	£126,691 (£105,576) ^a

Source: EAG created the table based on the results from the company's model 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
a QALY weight of 1.2, b QALY weight of 1.7

The EAG considers the disease severity modifier of 1.2 or 1.7 is appropriate.

5.2.8 EAG summary of key issues and additional analyses

See section 5.5 below.

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The criteria for applying QALY weights for severity are shown in Table 35.⁴⁸

Table 35 Criteria for severity modifier

QALY weight	Proportional shortfall	Absolute shortfall
x1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Source: NICE methods manual

The company apply a QALY weight of 1.7 in their base case and scenario analyses. They explain their approach to calculating the QALY shortfall in CS section 3.6, and further information about the assumptions and sources are available in the company's economic model.

The assumptions used to calculate the general population QALY shortfall estimates are summarised in Table 36. The EAG agrees that these assumptions are appropriate. The company has not reported economic analysis for any population subgroups, and the model only includes one comparator: single-agent chemotherapy. Although this is a blended comparator (comprising a weighted mix of chemotherapy treatments), the company assume that the treatments have equivalent clinical effects, and the EAG agrees that this assumption is appropriate. There is therefore no need for different QALY shortfall estimates by patient subgroup or comparator treatment.

Table 36 Summary of company's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (CS Table 62)	Reference to section in submission or rationale
Sex distribution	100% female	Epidemiology: CS section 1.3.2

Factor	Value or source (CS Table 62)	Reference to section in submission or rationale
Starting age	■	Patient population CS section 3.2.1
Expected years of life	ONS UK life tables 2021- 2023 ⁸⁰	CS section 3.6 & model (Raw_life_Table)
Quality of life by age	McNamara et al. 2023 ⁶⁵	CS section 3.6 & model (General population)
Discount rate	Not stated by company, but results are consistent with 3.5% per year	EAG verification of results based on the company's assumptions

Source: CS section 3.6, Table 62 and company model

The EAG's preferred assumptions used to determine the QALY shortfall estimates for standard care are summarised in Table 37, and the company's assumptions are summarised in Table 38. The company's assumptions with which the EAG disagrees are applied as scenarios to the EAGs base case in (section 5.2.5).

Table 37 Summary of EAG's preferred assumptions for standard-care QALY shortfall estimates

Modelled input	Assumption or value (reference to appropriate table or figure in submission or EAR)	Rationale or justification
Kaplan Meier data for modelling OS	No observed Kaplan Meier data used in the selected OS curve (section 4.2.6.5.1)	Avoids risk of bias from choice of cutoff
Model structure	PSM with direct extrapolations of log-logistic distribution for PFS and OS in both arms (section 4.2.6.5.2)	Mortality risk after progression should not be assumed constant or independent of prior treatment

Modelled input	Assumption or value (reference to appropriate table or figure in submission or EAR)	Rationale or justification
Administration cost for paclitaxel	Simple parenteral administration of paclitaxel (section 4.2.8.1.1).	Reflects current NHS clinical practice
Single agent chemotherapy mix	EAG expert estimates (section 4.2.5).	Reflects current NHS clinical practice
Subsequent treatment distribution	EAG expert estimates (section 4.2.8.1.2)	Reflects current NHS clinical practice
Healthcare management resource use	EAG expert estimates (see section 4.2.8.2.1).	Reflects current NHS clinical practice

Source: EAG created table

Abbreviations: QALY, quality-adjusted life year; PSM, partitioned survival model; PFS, progression free survival; OS, overall survival; NHS, national health service; EAG external assessment group; EAR, external assessment report

Table 38 Summary of company's preferred assumptions for standard-care QALY shortfall estimates

Modelled input	Assumption or value (reference to appropriate table or figure in submission or EAR)	Rationale or justification
Treatment efficacy	Efficacy from InnovaTV 301 (CS Table 65)	Generalisable treatment efficacy for treatments from clinical trial to the

Modelled input	Assumption or value (reference to appropriate table or figure in submission or EAR)	Rationale or justification
		target population in England and Wales
Chemotherapy comparator proportions	Genmab survey of 8 UK clinicians involved in the management of r/m CC in the UK (CS Table 65)	Generalisable chemotherapy mix to the UK population as informed by the survey of the 8 UK clinicians
Efficacy and safety of chemotherapy	Comparable efficacy of all single agent chemotherapies, including weekly paclitaxel (CS Table 65)	Efficacy and safety for all chemotherapy agents were assumed equivalent, based on the InnovaTV 301 trial, with no evidence supporting different outcomes for UK regimens such as weekly paclitaxel
Health state transitions	PD TO Death; no difference in post- progression mortality after month 12 (CS Table 65)	Observed convergence of OS curves and clinical opinion that long-term outcomes should be similar once patients have progressed
Health state utilities	Health-state utilities dependent health states (CS Table 65)	Health-state utilities were dependent only on health states and independent of treatment arms
Adverse events	Grade 3/4 AEs (CS Table 65)	Grade 3/4 AEs in more than 5% of any

Modelled input	Assumption or value (reference to appropriate table or figure in submission or EAR)	Rationale or justification
		intervention or comparator arm, plus all ocular events of grade 3/4
Disutilities	Grade 3/4 AEs (CS Table 65)	Only patients with severe AEs (grade 3+)
Relevant costs	Drug acquisition and administration cost, AE costs and disease management costs (CS Table 65)	Patients in progression-free and progressed disease states incur cost independent of treatment
Premedication costs	Applied to only patients receiving tisotumab vedotin (CS Table 65)	Only patients treated with tisotumab vedotin require eye-drop pre-medication and ophthalmic monitoring.
Costs associated with mortality	All patients (CS Table 65)	All patients would incur terminal care costs before death

Source: reproduced from company submission Table 65

Abbreviations: QALY, quality-adjusted life year; AEs, adverse events

CS, company submission; OS, overall survival; PD, progressed-disease; PF, progression-free; r/m CC, recurrent /metastatic cervical cancer; EAR, external assessment report; CS, company submission

Table 39 Summary of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

	Expected total QALYs for the general population	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	14.45				1.7
EAG's base case	14.45				1.2

Produced by the EAG using information from the company's model

5.3.2 Uncaptured benefits

The company note that cervical cancer often affects young women who are often raising families (CS section 3.12). The impact on family members has not been included in the economic evaluation, to align with the NICE reference case.

5.3.3 Health inequalities

The company comments on equality considerations in CS section 1.4. They note that cervical cancer is a disease that affects young women in their productive and family-raising years, it is more prevalent in socioeconomically deprived populations, and evidence, though scarce, does suggest that HPV screening uptake is lower in more deprived and non-white ethnic populations.

The company concludes state that these factors demonstrate current inequalities in burden and impact of cervical cancer, and in access to interventions in England,

The company have not reported cost-effectiveness analysis for subgroups by age, indicators of socioeconomic status or ethnicity.

5.4 Confidential comparator and subsequent treatment prices

All results in this report include a confidential PAS price discount of [REDACTED] for tisotumab vedotin, with comparator and subsequent therapies costed at list price. Results including additional price discounts for comparator and subsequent treatments and including current eMIT prices in a confidential addendum to this report.

5.5 Conclusions of the cost-effectiveness section

5.5.1 Decision problem

The EAG considers that the decision problem addressed in the company's cost-effectiveness analysis is consistent with the NICE scope for this appraisal. The population in the model and the pivotal InnovaTV 301 trial are representative of the UK population of interest (sections 4.2.4), and we consider it reasonable to assume similar efficacy for the single-agent chemotherapies in the InnovaTV 301 comparator arm, and for paclitaxel which is commonly used in UK practice (section 2.3 and 4.2.5).

5.5.2 Model structure (Issue 2)

The EAG has concerns over potential bias in the company's base case semi-Markov model. This model uses clinical effectiveness estimates for time to progression, pre-progression survival and post-progression survival extrapolated from InnovaTV 301 trial data (section 4.2.2). Importantly, the model requires an assumption that the risk of death after disease progression is constant over time, because the model does not retain information about time of progression. The company also assume that the post-progression mortality rate is the same for both treatment arms, estimated from pooled trial data. The EAG considers that the information provided by the company does not support the use of a constant risk of death after progression, or that this rate is independent of previous treatment (see discussion in section **Error! Reference source not found.**). We also note that there is high uncertainty over pre-progression survival, because the number of deaths prior to disease progression in the clinical trial was low (see 4.2.6.3).

The company's model includes options that allow it to be run as a conventional partitioned survival model (PSM): based on extrapolations of PFS and OS data

from the InnovaTV 301 trial, and options to prevent unrealistic crossover of the tails of the OS curves. The company state that they explored the PSM approach but rejected it due to poor clinical plausibility and external validity (response to clarification question B1). They report results for a PSM scenario with dependent accelerated failure time models for PFS and OS, but we consider that the assumptions required for this analysis have not been justified, and the assumption of a persistent survival benefit for tisotumab vedotin does not appear plausible based on KM results from the clinical trial. The EAG therefore prefers a PSM approach applied with an assumption that the mortality rate is the same for tisotumab vedotin and chemotherapy when the OS curves for the treatment arms converge (see section 4.2.6.5.2).

The ICER is sensitive to the use of a PSM model, rather than semi-Markov model (see scenarios 8-10 in Table 28).

5.5.3 OS extrapolations – use of KM data, and distributions (Issue 3)

There is uncertainty over the OS extrapolations due to the diminishing sample size at the tails of the InnovaTV 301 KM. The KM curves start to converge [REDACTED] and overlap [REDACTED] when few patients remain at risk (CS Figure 14). The company argue that empirical inspection and clinical validation shows that the OS curves derived from their preferred semi-Markov model overestimate survival OS for chemotherapy and underestimate survival for tisotumab vedotin, which they attribute to random variation caused by the diminishing sample size (clarification response B4). To produce what they consider to be more plausible extrapolations, the company use KM data from InnovaTV 301 to override modelled OS for the first 12 months. They argue that the 12 month cutoff is appropriate as it maximises the use of robust empirical data before applying the fitted curves.

The EAG agrees that the overlap of the KM plots for OS is likely to be related to the diminishing sample size. However, we note that this uncertainty applies in both arms, and that an alternative interpretation of the OS results from the trial is that the survival advantage of tisotumab vedotin wanes, and does not persist beyond the point where the KM curves converge. We also suggest that there is a risk of bias from the post-hoc decision to use KM data to override the model predictions, and

the choice of timepoint to switch from KM to the fitted curves. We report EAG scenarios with no KM data (cutoff at month 0), in addition to cutoffs of 9 and 15 months which the company report (Table 28). We do not use KM data directly in our preferred analysis.

The choice of distributions for OS is not clear-cut (see section 5.2.2.4). The company report validation of predicted survival from their base case against observed data sources (CS section 3.13). We compare observed predictions from the company's base case and the three EAG PSM scenarios (8, 9 and 10 in Table 28) with observed OS from InnovaTV 301 (section 5.2.2.4). We suggest that there is a trade-off between model fit to InnovaTV 301 data, consistency with chemotherapy estimates from external sources (11.9% to 13% survival at two years),⁷⁹⁴⁹ and the plausibility of projected persistence of the survival advantage with tisotumab vedotin.

The ICER is sensitive the use of KM data to override modelled OS in the company's semi-Markov model (scenario 5 in Table 28), and to the OS survival distribution in the PSM model (scenarios 8-10 in Table 28).

5.5.4 Time to progression and pre-progression survival (Issue 4)

ICERs for the company's semi-Markov model are sensitive to the choice of survival distribution for time to treatment progression (TTP), and pre-progression survival in the company's semi-Markov model (scenarios 1-2 in Table 28). This reflects structural dependency between these outcomes and overall survival, as well as variation. There is a high degree of uncertainty over the pre-progression survival extrapolations, due to the low numbers of observed events in the InnovaTV 301 trial.

The ICER is not sensitive to the choice of PFS extrapolation in the EAG PSM model, (scenarios 8 and 9 Table 38).

5.5.5 Administration cost for paclitaxel (Issue 5)

The ICER is sensitive to the assumed cost per administering paclitaxel, see section 4.2.8.1.1.1 (scenario 13 in Table 28). For EAG analysis, we assume the same cost

for paclitaxel as for other chemotherapy agents, based on advice to the EAG from clinical experts.

5.5.6 Other resource use assumptions

Without the assumption of the higher cost for administration of paclitaxel, the ICER is insensitive to the assumed mix of comparator chemotherapy drugs used for costing (Table 14), see scenarios 1-2 in Table 34. The ICER is also insensitive to the assumed mix of subsequent treatments (section 4.2.8.1.2), and other healthcare resource use for follow up and monitoring (section 4.2.8.2.1), see scenarios 3 and 4 in in Table 34.

5.5.7 Health state utilities

The EAG agrees with the company's base case health state utilities used in the company's base case analysis (Table 18), see section 4.2.7.2 for EAG critique. The ICER is not sensitive to health state utility scenarios tested by the company (CS Table 70) or EAG (Table 28)

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7 Appendices

Appendix 1 Evidence to support an assumption of clinical efficacy equivalence between single-agent chemotherapies

In this Appendix, we consider in detail the evidence supplied by the company to support the assumption of clinical efficacy equivalence between the single-agent chemotherapies included in the comparator arm of the InnovaTV 301 RCT (topotecan, gemcitabine, irinotecan, vinorelbine, and pemetrexed) and the clinical efficacy equivalence of these single agents and weekly paclitaxel. We also detail and consider some evidence identified by the EAG.

Table 40 EAG summary and critique of the evidence provided by the company to support an assumption that single-agent chemotherapies have similar efficacy to each other and to weekly paclitaxel

Evidence supplied by company	EAG's comments
In CS Table 5, the company has summarised the findings of some studies of the efficacy of single-agent chemotherapies at second-line treatment, including gemcitabine, irinotecan, nab-paclitaxel, pemetrexed, and topotecan.	The company do not outline how these studies were identified and selected for presentation in CS Table 5, so it is unclear how representative the results are of the wider evidence base and thus there may be a risk of bias associated with their selection. The data shown in CS Table 5 suggest that gemcitabine, pemetrexed and topotecan have similar efficacy in terms of OS and PFS (based on one study for each agent). OS and PFS rates found in the nab-paclitaxel study were more favourable than those reported in CS Table 5 for the other agents listed, except that a study of irinotecan found a higher median PFS rate than was found for nab-paclitaxel. However, we were informed by our clinical experts that nab-paclitaxel is

Evidence supplied by company	EAG's comments
	not the same agent as paclitaxel (it is paclitaxel bound to albumin) and thus the findings of this study are not relevant to this appraisal. The EAG notes that the cited studies of gemcitabine, irinotecan, nab-paclitaxel, pemetrexed and topotecan in CS Table 5 included small participant numbers (ranging from 18 to 42 participants) and thus the findings are limited and likely subject to uncertainty.
In clarification response A8, the company states that no published meta-analyses or pooled analyses are available that directly compare the efficacy of pemetrexed, gemcitabine, topotecan, irinotecan and vinorelbine single-agent chemotherapies.	None.
In clarification response A8, the company highlights that InnovaTV 301 RCT subgroup analyses by single-agent chemotherapy of OS and PFS show that confidence intervals overlap across the chemotherapies, indicating no difference in efficacy.	The EAG agrees with this interpretation (based on the PFS subgroup results provided in clarification response Figure 2 [PFS from the ad-hoc, follow-up analysis] and CS Appendix C Figure 9 [OS from the ad-hoc, follow-up analysis]), but notes that some of the subgroups included small numbers of participants which means that the findings are likely uncertain. We also note that subgroup analyses of OS and PFS by single-

Evidence supplied by company	EAG's comments
	agent chemotherapy were not provided in the CS from the primary analysis of the InnovaTV 301 RCT.
In clarification question A9, the company supplied a full version of the CS clinical systematic literature review (an abbreviated copy had originally been provided with the CS). ¹⁷ [REDACTED].	In the EAG's opinion, [REDACTED] the conclusion above about similar efficacy of topotecan and the other chemotherapy single agents (in terms of PFS and OS).
The full report of the CS clinical systematic literature review, ¹⁷ included [REDACTED] [REDACTED] [REDACTED] [REDACTED]	In the [REDACTED] [REDACTED] [REDACTED]. However, as noted above, nab-paclitaxel is not the same agent as paclitaxel and thus is not a relevant comparator in this appraisal. [REDACTED] [REDACTED], and, therefore, again, the findings are limited and likely subject to uncertainty.
In clarification response A8, the company references two studies ^{49, 85} providing data on the efficacy of paclitaxel: one was [REDACTED] Homesley et al. (2008) ⁸⁵ [REDACTED]	The EAG has looked at both studies. One ⁴⁹ provides information on the proportion of patients with recurrent or metastatic cervical cancer receiving second-line treatment at one centre who experienced a partial response or had stable disease while receiving paclitaxel, and provides results for the

Evidence supplied by company	EAG's comments
██████████ and the other was a retrospective review at one study centre,⁴⁹ which the EAG discusses further below).	same outcomes for patients receiving other second-line treatments. Only 15 participants in this study received weekly paclitaxel and small numbers of participants (one to 12) received each of the other treatments. The other study⁸⁵ included participants (n = 20) with squamous cell cancer of the cervix who were receiving weekly paclitaxel as a second-line treatment and reports complete and partial response rates. While the company concludes in clarification response A8 that the results from the studies demonstrate that paclitaxel has similar efficacy to single-agent chemotherapies in the appraisal population, the EAG does not concur. The numbers of participants receiving each therapy in the studies was small (one to 20) and the numbers experiencing partial response, stable disease or complete response were also small (none to eight participants), limiting any conclusions that might be drawn.

Source: EAG created table, informed by the sources cited in the table.

CS, company submission; EAG, External Assessment Group; OS, overall survival; PFS, progression-free survival.

In addition to the evidence presented in Table 40, the EAG found a publication⁸⁷ that summarises historical data on the efficacy of single-agent chemotherapies, including paclitaxel, in the second-line treatment of persistent, recurrent or metastatic cervical cancer. Reported objective response rates in this paper for topotecan, gemcitabine, vinorelbine and pemetrexed ranged from 8.0% to 15.0% in the overall population. The paper also reports objective response rates of 4.5%, 7.1% and 31% for gemcitabine, vinorelbine and paclitaxel, respectively, specifically in a non-squamous cell carcinoma population; the latter results may not be generalisable to the wider population of interest in this appraisal.

Overall, in the absence of more convincing data and based on our experts' advice (as outlined in section 2.3), it seems reasonable to assume that the agents included in the InnovaTV 301 comparator arm have similar efficacy and that the efficacy of paclitaxel may also be reasonably represented by the InnovaTV 301 comparator arm.

The conclusion that the InnovaTV 301 RCT comparator arm may reasonably represent the efficacy of the second-line therapies used in clinical practice is further supported by the retrospective review at one UK centre⁴⁹ (cited by the company in clarification response A8 and mentioned in Table 40 above) of 75 patients who had recurrent or metastatic cervical cancer and had received at least one prior line of therapy.⁴⁹ In this study, 28.3% of the patients had been treated with weekly paclitaxel and the remaining patients with other agents, including carboplatin-based chemotherapy (24.5%), docetaxel-based chemotherapy (13.2%), topotecan (9.4%) and gemcitabine (1.9%), at second-line therapy. The median OS and median PFS rates found in the whole study population were similar to those found in the InnovaTV 301 RCT (retrospective review median OS 9.3 months [95% CIs: 6.4, 12.5] versus InnovaTV 301 RCT chemotherapy arm median OS at the primary analysis 9.5 months [95% CIs: 7.9, 10.7]; retrospective review median PFS 3.2 months [95% CIs: 2.1, 4.3] versus InnovaTV 301 RCT chemotherapy arm median PFS at the primary analysis 2.9 months [95% CIs 2.6, 3.1]). Although, again, caution needs to be applied when interpreting these results due to the small number patients of included in the retrospective review and the findings being based on treatment at one centre.

Appendix 2 EAG appraisal of systematic review methods

Table 41 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The clinical SLR objective is stated in CS Appendix B 1.1 “to identify, review and report the efficacy of second line or later treatments for previously treated, persistent/ recurrent or metastatic cervical cancer” and this is further defined by the PICOD framework used to summarise the review eligibility criteria (CS Appendix B 1.1 Table 1).
Were appropriate sources of literature searched?	Yes	The literature sources searched were comprehensive and are listed in CS Appendix 1.1 Table 2. The sources searched included Medline ALL, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, relevant clinical trial registries and selected relevant conferences.
What time period did the searches span and was this appropriate?	Yes	The searches spanned from database inception to January 2019, supplemented by regular update searches, the last of which was in May 2025. Although the search span was appropriate, we note that the inclusion/exclusion criteria included limits as discussed below.

Systematic review components and processes	EAG response	EAG comments
Were appropriate search terms used and combined correctly?	Yes	Searches were accurate and consistent and not likely to miss any studies. Search strategies are reported in CS Appendix 1.1 Figure 1 with the 2025 search strategies reported in Appendix A of the clinical SLR. ⁸⁸

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Inclusion and exclusion criteria are specified in CS Appendix 1.1 Table 1. The criteria for the comparator are broader than the decision problem (e.g. studies whose participants had received second-line combination therapy were eligible for inclusion and the comparators could be any systemic intervention or combination of interventions at second-line or later). Eligible studies were not limited to RCTs. However, limits were placed on the criteria: only studies published since 2003 were eligible (the searches did not include a date limit) and studies with fewer than 10 patients with the eligible histologies were excluded. Because no rationale was given for these limits, we asked the company to provide this (clarification question A4). The 2003 cut-off was selected because cisplatin-based doublet regimens became the first-line standard of care from 2004 onwards for patients with recurrent or metastatic cervical cancer. This also meant studies less relevant to current clinical practice, because of improvements in supportive care and treatment practices, were excluded. This seems appropriate. The exclusion of studies with fewer than 10 eligible

Systematic review components and processes	EAG response	EAG comments
		patients aimed to help minimise the influence of case reports and very small studies with the aim of achieving a robust and generalisable evidence base. We feel this is acceptable in this case.
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix 1.1 states that two reviewers independently assessed the titles and records that remained after a single reviewer removed any records deemed obviously ineligible, for example because the participants were children or the disease was ineligible. Full texts were independently assessed by two reviewers.
Was data extraction performed by two or more reviewers independently?	No, but a second reviewer independently checked extracted data	The CS did not state how data extraction for the clinical effectiveness review was performed. In response to clarification question A5 the company state this task was conducted by one reviewer and independently checked by a second reviewer.

Systematic review components and processes	EAG response	EAG comments
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	A summary of the risk of bias assessment results is presented in CS section 2.5, Table 20 and Table 21. Full details of the assessments are provided in CS Appendix B 1.3 Table 5 and Table 6. In response to clarification question A6 the company state the tool used for the assessment of RCTs was the Cochrane Risk of Bias (ROB 1) tool and the appropriate CRD checklist was used for non-randomised studies. However, in this response the company describe the InnovaTV 204 single-arm trial as a randomised controlled trial (when it is single-arm study) and say they used the Cochrane Risk of Bias tool to critically appraise it. Our assumption is that the company used the CRD checklist for case series to assess the InnovaTV 204 single-arm trial.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No, but a second reviewer independently checked the assessment.	The CS did not state how the risk of bias assessments for the clinical effectiveness review were undertaken. In response to clarification question A5 the company state this task was conducted by one reviewer and independently checked by a second reviewer.

Systematic review components and processes	EAG response	EAG comments
Is sufficient detail on the individual studies presented?	Yes	The CS included: • details for the PICOD (CS Table 6) • a summary of study designs in CS section 2.3.1 (including CS Table 7 and CS Table 8) • the baseline demographic and clinical characteristics in CS section 2.3.2 (including CS Table 9, CS Table 10, CS Table 11, Table 12, Table 13) • Statistical analysis for individual trials in CS section 2.4 • Critical appraisal in CS section 2.5 • Clinical effectiveness results in CS section 2.6 • Subsequent treatment information in CS section 2.7 • Subgroup analysis in CS section 2.8 • Adverse reactions information in CS section 2.11
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not applicable	No statistical evidence synthesis was undertaken and we believe that this is acceptable.

Source: EAG created table

CRD, Centre for Reviews and Dissemination; CS, company submission; PICOD, Population-Intervention-Comparator-Outcome-Design; RCT, randomised controlled trial; SLR, systematic literature review

Appendix 3 List of studies identified for inclusion in the CS clinical effectiveness systematic literature review and the EAG's comments on these

Table 42 Studies identified for inclusion in the clinical systematic literature review

Study identifier	Primary Publication	Intervention	EAG comment
InnovaTV 301	Vergote et al. (2024) ¹⁸	Tisotumab vedotin	Included in CS.
InnovaTV 201	Hong et al. (2020) ¹⁹	Tisotumab vedotin	A phase 1/2 dose escalation and expansion study; primary objective was to assess safety and tolerability; no comparator; included a cohort of 55 participants with locally advanced or metastatic cervical cancer who had progressed on or who were ineligible for standard treatments; ¹⁹ appropriate not to include in CS.
InnovaTV 204	Coleman et al. (2021) ²⁰	Tisotumab vedotin	Included in CS.
InnovaTV 206	Yonemori et al. (2022) ²¹	Tisotumab vedotin	A phase 1/2 single arm dose escalation and expansion study in Japanese participants; no comparator; included 6 participants with locally advanced or metastatic cervical cancer who had disease progression on standard therapy or were not eligible for it in part 1; included 17 participants with extrapelvic recurrent or metastatic cervical cancer who had disease progression on or after previous treatment in part 2 and some efficacy data provided for these participants; ²¹ appropriate to not include in CS.

Study identifier	Primary Publication	Intervention	EAG comment
InnovaTV 205 ENGOT-Cx8 GOG-3024	Vergote et al. (2023) ²²	Tisotumab vedotin + pembrolizumab	Does not evaluate tisotumab vedotin monotherapy; appropriate to not include in CS.

Source: Partly reproduced from CS Appendix Table 3, with EAG comments added and additional information sourced from Hong et al. (2020)¹⁹ and Yonemori et al. (2022).²¹

CS, company submission; EAG, External Assessment Group.

Appendix 4 Planned OS sensitivity analyses in the InnovaTV 301 RCT

Table 43 Planned OS sensitivity analyses in the InnovaTV 301 RCT

Sensitivity analysis no.	Short description	Details of analysis
1	Unstratified analysis	Treatment arms compared via unstratified log-rank test; unstratified Cox regression model used to estimate HR and CIs for treatment effect; primary analysis censoring method applied.
2	Mis-stratification	If there was a >5% inconsistency between the stratification factors from the RTSM and eCRF, those from the eCRF were to be used in the stratified log-rank test and stratified Cox proportional hazards regression model.
3	Initiation of subsequent cancer-related therapy	Sensitivity analysis using inverse probability of censoring weights method. Participants who received subsequent therapy were censored at the time of starting this, with participants weighted by the probability that they would receive subsequent therapy.
4	Non-proportional hazard	If the proportional hazard assumption was not met, OS was to be analysed using RMST, to show average survival time up to a specific time point.

Source: Partly reproduced from clarification response A16, with information also sourced from EMA EPAR³⁹

CI, confidence interval; eCRF, electronic case report form; EMA, European Medicines Agency; EPAR, European Public Assessment Report; HR, hazard ratio; OS, overall survival; RMST, restricted mean survival time; RTSM, Randomisation and Trial Supply Management.

Appendix 5 Critical appraisal of the InnovaTV 301 RCT

Table 44 Company and EAG critical appraisal of the InnovaTV 301 RCT

Question	Company judgement	Company description	EAG response	EAG comments
Was the allocation sequence adequately generated?	Yes	Randomization and Trial Supply Management (RTSM) systems	Yes	A central randomisation and trial supply management system was used.
Was the concealment of treatment allocation adequate?	Yes	Randomization and Trial Supply Management (RTSM) systems	Yes	A central randomisation and trial supply management system was used.
Was knowledge of the allocated interventions adequately concealed from participants and personnel	No	Open label study	No	Open label study.
Was knowledge of the allocated	No	Open label study	No	Open label study.

Question	Company judgement	Company description	EAG response	EAG comments
interventions adequately concealed from outcome assessors				
Were incomplete outcome data adequately addressed?	Yes	ITT analysis was used for the primary and secondary outcomes while safety data was limited to patients who took at least one dose of the study drug	Yes (except HRQoL)	Efficacy end points (except HRQoL) were analysed using the intention-to-treat population. All randomised participants who received any amount of study treatment were included in the safety analyses.
Are reports of the study free of suggestion of selective outcome reporting?	Unclear	Noted that EQ-5D is reported in the protocol, however no results for this tool have been made available	Yes (for this appraisal)	Results for most outcomes listed in the protocol are presented in the published paper. Some data are only available in the CSR which is not publicly available (EQ-5D-5L dimensions from the descriptive system, EORTC-QLQ-CX24, pharmacokinetics analysis and data on

Question	Company judgement	Company description	EAG response	EAG comments
				anti-drug antibodies). It is not clear if these data will be published at a future date.
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	-	Yes	We have not identified any additional problems that would increase the susceptibility of the trial to bias.

Source: CS Appendix B 1.3 Table 5 with additional columns for the EAG response and EAG comments.

CSR, clinical study report; EAG, External Assessment Group; EQ-5D, European Quality of Life Working Group Health Status Measure 5 Dimensions, EORTC-QLQ-C30, European Organization for Research and Treatment Quality of Life Questionnaire Core 30; EORTC-QLQ-CX24, European Organization for Research and Treatment Quality of Life Questionnaire Cervical Cancer Specific module; RTSM, Randomisation and Trial Supply Management

Appendix 6 Patient-reported outcome measures (InnovaTV 301 RCT)

Table 45 Description of the patient-reported outcome measures used in the InnovaTV 301 RCT

Measure	Description
EQ-5D-5L	The EQ-5D-5L is a global measure of HRQoL that includes a short descriptive system questionnaire and a VAS. The descriptive system measures five dimensions of HRQoL (mobility, self-care, usual activities, pain/discomfort and anxiety and depression) by asking the participant to select from five responses: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. Each response is scored and an index score is then derived from these scores that ranges from zero (representing a health state equivalent to dead) to one (representing full health). The VAS is a vertical scale that ranges from 'the best health you can imagine' to 'the worst health you can imagine' and the participant marks a point between those two extremes to indicate their perception of their own overall health.⁸⁹ The company provides limited results from the EQ-5D VAS score (using a 7-point threshold to define the score as improved, worsened or stable) in CS section 2.6.1. In response to clarification question A18 the company state that a 0.07 change on a 0-1 scale has been identified as a minimally important difference in both chronic illness and general population samples⁹⁰ but it is not clear if the 7-point minimally important difference threshold for the EQ-5D VAS is validated in this population.⁹¹ The EQ-5D-5L data were used to estimate health-state utilities for the company's economic model (with the EQ-5D-5L data being mapped to the EQ-5D-3L value set prior to utility values being derived for the model, CS section 3.4.1).

Measure	Description
EORTC-QLQ-C30	The EORTC developed the 30-item QLQ-C30 core questionnaire to assess the quality of life of cancer patients. ⁹² The questionnaire covers global health status, functional scales (e.g. physical functioning, social functioning) and symptom scales or items (e.g. fatigue, appetite loss, financial difficulties). ⁹³ Raw scores are converted to a standardised score range of zero to one hundred with a higher score indicating either a better level of functioning or a worse level of symptoms. The company have used a 10-point threshold to define a clinically meaningful change in score. Although this is a commonly used threshold, and one said to be generally recommended for interpreting group differences and changes as clinically meaningful, ⁹⁴ based on work by Osoba et al., ⁹⁵ we have not been able to find a reference supporting this threshold specifically in cervical cancer, however this threshold has been used in other trials in cervical cancer. ⁹⁶ The company state that in oncology, this 10-point minimum important difference is a widely accepted benchmark for interpreting changes in quality-of-life (see response to clarification A18 for more detail and additional references).
EORTC-QLQ-CX24	This is a supplementary questionnaire module used in conjunction with the EORTC-QLQ C30 described above. This module assessed symptom experience, body image and sexual/vaginal functioning. The scoring ranges from zero to one hundred with a high score either representing a high level of symptoms or a high level of functioning. ⁹⁷ Results from this module are not presented in the CS but are available in the CSR.

Source: EAG table created from information within the references cited in the table and CS section 2.6.1.

CS, company submission; CSR, clinical study report; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-3L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 levels; EQ-5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 levels; HRQoL, health-related quality of life; QLQ-C30, quality of life questionnaire-

Core 30; QLQ-CX24, quality of life questionnaire cervical cancer module; VAS, visual analogue scale.

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**External Assessment Group Report commissioned by the
NIHR Evidence Synthesis Programme on behalf of NICE**

**Tisotumab vedotin for treating recurrent or metastatic
cervical cancer that has progressed on or after systemic
treatment – Addendum 2**

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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1 INTRODUCTION

The EAG prepared this addendum to investigate the impact of additional information on EAR key issue 5, provided by the company on 18/12/2025, after the Factual Accuracy Check. In EAR key issue 5, the EAG discussed the appropriate currency code for the administration cost of paclitaxel. Table 1 below shows alternative codes for the administration of simple or complex chemotherapy. The company used the code SB14Z for the base case in their original submission (see CS 3.5.1.1), whereas we used the code SB12Z for EAG preferred analysis (EAR 4.2.8.1.1.1 and key issue 5). The company has subsequently suggested that code SB13Z is appropriate, citing two local NHS protocols available online which indicate that single-agent paclitaxel requires pre-medication 30 minutes prior to infusion, followed by 60-minute paclitaxel infusion; and that the NHS payment scheme for 2025/26 indicates that chemotherapy regimens requiring 60 minutes of nurse time and up to 120 minutes of chair time should be assigned to code SB13Z. The company also refer to the National Tariff Chemotherapy Regimens Workbook (2017/18) which allocated the paclitaxel 7-day regimen to administration code SB13Z.

Table 1 Administration costs for paclitaxel

Currency code	Description	Explanation	Cost per unit/hour
SB12Z	Deliver Simple Parenteral Chemotherapy at First Attendance	Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.	£152
SB13Z	Deliver more Complex Parenteral Chemotherapy at First Attendance	Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.	£202
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle.	£352

Source: 2023/2024 National Cost Collection Data and 2025/2026 NHS Payment Scheme – Annex B: guidance on currencies

In this addendum, we report scenarios based on the tables from EAR Chapter 5, with the currency code for administration of paclitaxel changed to SB13Z. All analyses use the PAS discounted price for tisotumab vedotin provided in the company submission, and list price for the remaining drugs.

2 COMPANY'S COST-EFFECTIVENESS RESULTS

2.1 Scenario with paclitaxel administration cost SB13Z applied to the company's deterministic base-case analysis

Table 2 shows results for the scenario with the SB13Z cost for paclitaxel administration (£202) applied to the EAG-corrected company's base case. In this scenario, the ICER without QALY weighting increases to £95,415, compared with £86,360 in the company's original base case (administration of paclitaxel, £352).

Table 2 Company's base-case results with EAG corrections, and currency code SB13Z for paclitaxel's administration cost, with and without severity weighting (x1.7), deterministic analysis

Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Chemotherapy	██████	██████	██████	██████	£95,415 (£56,127)
Tisotumab Vedotin	██████	██████			

Source: company's corrected economic model

Note: EAR Table 25 + administration cost SB13Z for paclitaxel instead of SB14Z

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

Table 3 shows that the reduced cost for paclitaxel administration in the scenario reduces total costs in both arms. This is because paclitaxel is included as a subsequent treatment after disease progression in the tisotumab vedotin arm. However, the reduction in total costs is larger in the chemotherapy arm than in the tisotumab arm. Hence, the net effect is an increase in the incremental cost, and an increase in the ICER.

Table 3 Difference in costs between company base case and scenario using administration cost code SB13Z for paclitaxel

Administrati on cost code for paclitaxel	Treatment	Pre- progression treatment costs	Post- progression treatment costs	Other costs	Total costs
SB14Z (company's base case)	Chemotherapy	██████	██████	██████	██████
	Tisotumab	██████	██████	██████	██████
Code SB13Z (scenario)	Chemotherapy	██████	██████	██████	██████
	Tisotumab	██████	██████	██████	██████

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

2.2 Company's probabilistic results

Table 4 shows the probabilistic results for the scenario with the company base case and code SB13Z for the paclitaxel administration cost.

Table 4 Company's base-case results with EAG corrections considering the currency code SB13Z for paclitaxel's administration cost, with and without severity weighting (x1.7), probabilistic analysis

Treatment	Total costs	Total QALYs	Incrementa l costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Chemotherapy	██████	██████	██████	██████	£90,461 (£53,212)
Tisotumab Vedotin	██████	██████			

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

Note: EAR Table 26 + administration cost SB13Z for paclitaxel instead of SB14Z

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

3 EAG'S ADDITIONAL ANALYSES

3.1 EAG's exploratory analyses using company's base case

The results of the EAG's exploratory analyses conducted using the EAG-corrected company base case (see description in EAR section 5.2.4, Table 27) are presented in the EAR Table 28. Table 5 below shows the scenarios in EAR Table 28 applied with the currency code SB13Z for paclitaxel administration.

Table 5 Results of EAG's exploratory analyses using company's base case with EAG corrections and change to the cost of paclitaxel administration cost (SB13Z)

Number	Scenario applied to company's base case + code SB13Z for paclitaxel's administration cost	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weight)	ICER £/QALY (x1.2 or 1.7 weight)
	Company base case (EAG corrections) and admin cost for paclitaxel SB13Z			£95,415 (£56,127) ^b
1	PF to PD: Lognormal (both arms)			£118,043 (£69,437) ^b
2	PF to PD: Log-logistic (both arms)			£110,445 (£64,968) ^b
3	PF to death: Exponential (both arms)			£111,502 (£65,590) ^b
4	PF to death: Lognormal (both arms)			£104,709 (£61,594) ^b
5	Do not use the OS KM data with the OS fitted curve			£115,373 (£67,867) ^b
6	Use OS KM data for the first 9 months			£100,090 (£58,876) ^b
7	Use the OS KM data for the first 15 months			£93,519 (£55,011) ^b
8	EAG PSM: OS scenario with log-logistic in both arms (no OS KM)			£128,395 (£106,996) ^a
9	EAG PSM: OS scenario with generalised gamma in both arms (no OS KM)			£155,043 (£91,202) ^b
10	EAG PSM: OS scenario with Weibull for TV and log-logistic for chemo (no OS KM)			£147,846 (£86,968) ^b

Number	Scenario applied to company's base case + code SB13Z for paclitaxel's administration cost	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weight)	ICER £/QALY (x1.2 or 1.7 weight)
11	EAG PSM: PFS scenarios with log-normal in both arms	████████	████████ ████████	£132,009 (£110, 008) ^a
12	EAG PSM: PFS scenarios with gen. gamma in both arms	████████	████████ ████████	£128,625 (£107,187) ^a
13	Administration cost for paclitaxel based on simple parenteral chemotherapy (SB12Z)	████████	████████ ████████	£99,434 (£58,490) ^b
14	Single agent chemotherapy mix based on experts' estimates	████████	████████ ████████	£93,319 (54,893) ^b
15	Subsequent Therapy proportion based on EAG expert's estimate	████████	████████ ████████	£95,491 (£56,171) ^b
16	Subsequent therapy distribution based on the EAG experts' estimates	████████	████████ ████████	£95,422 (£56,131) ^b
17	Disease management resource use	████████	████████ ████████	£94,010 (£55,300) ^b
18	Pre and post progression utilities from lower limits of 95% CI (0.69, 0.54)	████████	████████ ████████	£98,741 (£58,083) ^b
19	Pre and post progression utilities from upper limits of 95% CI (0.73, 0.59)	████████	████████ ████████	£92,858 (54,622) ^b

Source: EAG created table

Note: EAR Table 28 + administration cost SB13Z for paclitaxel instead of SB14Z

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

a QALY weight of 1.2

b QALY weight of 1.7

3.2 Scenario on EAG's preferred assumptions

Table 6 below shows how the EAG-corrected company base case with the SB13Z paclitaxel administration cost changes with the addition of EAG preferred assumptions.

Table 6 Scenarios using EAG's preferred model assumptions with and without severity weighting

Preferred assumption	Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.2 or x1.7 weighting)	Cumulative ICER £/QALY (x1.2 or x1.7 weighting)
Company's base case	Chemotherapy	██████	██████	██████	██████	£79,978 (£47,046) ^b
	Tisotumab vedotin	██████	██████			
EAG's corrected company base case with SB13Z	Chemotherapy	██████	██████	██████	██████	£95,415 (£56,127) ^b
	Tisotumab vedotin	██████	██████			
EAG preferred assumptions with SB13Z	Chemotherapy	██████	██████	██████	██████	£124,070 (£103,392) ^a
	Tisotumab vedotin	██████	██████			

Source: EAG created table

Note: EAR Table 29 + administration cost SB13Z for paclitaxel instead of SB12Z

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

^a QALY weight of 1.2,^b QALY weight of 1.7

3.3 EAG scenario analyses using EAG preferred assumptions and the cost of paclitaxel administration (SB13Z)

Results of selected company scenarios conducted using the EAG preferred analysis (EAR section 5.2.6, Table 31) are presented in EAR Table 32. Table 7 below shows the two scenarios from EAR Table 32 with the currency code SB13Z for paclitaxel administration applied.

Table 7 Results of the company's scenario analyses using EAG's preferred assumptions and applying code SB13Z to paclitaxel administration cost with and without severity modifiers

	Scenario applied to EAG's base case + code SB13Z for paclitaxel's administration cost	Incremental costs (£)	Incremental QALYs (x1.2 or x1.7 weighting)	ICER £/QALY (x1.2 or x1.7 weighting)
	EAG base case + code SB13Z for paclitaxel administration cost			£124,070 (£103,392) ^a
1	Use dependent models for tisotumab vedotin and chemotherapy (PSM approach) PFS: Generalised gamma, OS: Lognormal			£70,929 (£41,723) ^b
2	Chemotherapy treatment distribution from the InnovaTV 301 RCT			£139,902 (£116,585) ^a

Source: EAG created table

Note: EAR Table 32 + administration cost SB13Z for paclitaxel instead of SB12Z

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PFS, progression free survival; OS, overall survival; PSM, partitioned survival model; EAG external assessment group

^a QALY weight of 1.2

^b QALY weight of 1.7

Results of the EAG's scenario analyses conducted using the EAG's preferred assumptions (see description in EAR section 5.2.7, Table 33) are presented in the EAR Table 34. Table 8 below shows the scenarios in EAR Table 34 applied with the currency cost code SB13Z for paclitaxel administration.

Table 8 Results of scenario analyses applied to the EAG's preferred analysis

Scenario analysis number	Scenario applied to EAG's base case + code SB13Z for paclitaxel's administration cost	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weighting)	ICER £/QALY (x1.2 or 1.7 weighting)
	EAG base case and assuming code SB13Z for paclitaxel's administration cost			£124,070 (£103,392) ^a
1	Administration costs for paclitaxel assuming prolonged infusion (company's assumption: SB14Z)			£106,867 (£89,056) ^a
2	Chemotherapy treatment mix based on company expert estimates (company's assumption)			£126,591 (£105,792) ^a
3	Subsequent treatment mix based on the company expert estimates (company's assumption)			£124,062 (£103,385) ^a
4	Healthcare management costs based on company expert estimates for single agent chemotherapy			£125,522 (£104,602) ^a
5	Semi-Markov model with generalised gamma for PF-PD and Gompertz for PF-Death for TV; lognormal for PF-Death in chemotherapy arm (company assumption)			£111,535 (£65,609) ^b
6	EAG PSM: OS scenario with generalised gamma in both arms for OS			£150,171 (£88,336) ^b
7	EAG PSM: OS scenario with Weibull for TV and log-logistic for chemo			£143,119 (£84,188) ^b

Scenario analysis number	Scenario applied to EAG's base case + code SB13Z for paclitaxel's administration cost	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weighting)	ICER £/QALY (x1.2 or 1.7 weighting)
8	EAG PSM: PFS scenario with log-normal in both arms			£127,752 (£106,460) ^a
9	EAG PSM: PFS scenario with generalised gamma in both arms			£124,434 (£103,695) ^a
10	Consider OS KM curve for the first 12 months. (company's assumption)			£120,444 (£100,370) ^a
11	Pre and post progression utility from the lower values of the 95% CI (0.69, 0.54) (EAG exploratory scenario)			£128,115 (£106,763) ^a
12	Pre and post progression utility from the upper 95% CI values (0.73, 0.59) (EAG exploratory scenario)			£121,095 (£100,913) ^a

Source: EAG created the table based on the results from the company's model

Note: EAR Table 34 + administration cost SB13Z for paclitaxel instead of SB12Z

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

a QALY weight of 1.2, b QALY weight of 1.7

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 25 November 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Description of the issue with the direct use of KM data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 8: In the table outlining Issue 3, against the subheading “Issue 3 Uncertainty over survival predictions: impact of direct use of KM data and selection of survival distributions”, the EAG report states “<i>The company state that empirical inspection and clinical validation shows that the OS predictions from the semi-Markov model overestimate survival for chemotherapy and underestimate survival for tisotumab vedotin, which they attribute to random variation caused by the diminishing sample size (clarification response B4).</i>”	Revise “<i>which they attribute to random variation caused by the diminishing sample size (clarification response B4).</i>” to “<i>The company notes that the OS predictions from the semi-Markov model overestimate survival for chemotherapy and underestimate survival for tisotumab vedotin for the initial period, which has lead the company’s decision to use observed data up to 12 months, which allows the optimisation of robust empirical data while the number at risk remained meaningful [REDACTED]</i>”.	In the clarification response, the company state “[REDACTED]” The current wording of Issue 3 may be misinterpreted as the company attributing the differences in projected and observed OS to random variation caused by a diminishing sample size. However, this was not the intended meaning as the sample size is sufficiently large for the first 12 months. The company’s position is that the number at risk remained sufficiently large during the first 12 months to support the direct use of	Not a factual inaccuracy. The purpose of the wording in the key issues section is to highlight the underlying issue rather than restate the company’s rationale for its chosen approach.

		Kaplan-Meier (KM) data. The company does not believe that using extrapolated results—derived from the observed data—would reduce random variation or provide a more reliable representation of survival than the observed data when the number at risk is still reasonably high.	

Issue 2 Severity modifier description in Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9: In the table outlining Issue 3, against the subheading “Issue 3 Uncertainty over survival predictions: impact of direct use of KM data and selection of survival distributions”, the EAG report states “We note that the QALY multiplier differs between these scenarios (x1.7 for the company’s	Please rephrase to “All scenarios are reported without (with) adjustment for severity, with a QALY multiplier of x1.7.”	All three EAG scenarios described in issue 3 have a severity modifier of 1.7.	We have removed the text relating to the QALY multipliers for EAG scenarios from the table for Issue 3. These referenced the wrong EAG scenario numbers; however, there is no need to refer to them here. The three scenarios cited in the Issue 3 table are all

base case and EAG scenarios 2 and 3, x1.2 for EAG scenario 1)."			applied to the company's base case and use the same 1.7 multiplier.

Issue 3 EAG clinical experts' advice regarding the use of paclitaxel in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, Issue 6, page 14 highlights that the EAG's clinical experts advised that <i>'paclitaxel...is the most commonly used second-line or later therapy in clinical practice.'</i> However, there are some areas of the EAG report (pages 24 and 28) where it is stated that: <i>'paclitaxel is the most commonly used second-line therapy in clinical practice.'</i> There is therefore some inconsistency as to whether the EAG's clinical experts consider paclitaxel the most commonly used second and	Please provide clarification as to whether paclitaxel <i>'is the most commonly used second-line therapy'</i> or <i>'the most commonly used second and later-line therapy'</i> in clinical practice throughout the EAG report. Relevant areas of the report which highlight this information include: pages 14, 24, 25, and 28).	To ensure consistency in the reporting of the EAG's clinical expert advice regarding the use of paclitaxel in current clinical practice.	Thank you for highlighting this. We have reviewed instances of this in our report and we have amended text to state that paclitaxel is the most commonly used second-line or later therapy in clinical practice. Amendments made in: paragraph four in section 2.2.2; the text under the 'EAG comment' heading following section 2.2.4; and, the 'Comparators' row / 'EAG comments' column of Table 3 in section 2.3.

later-line therapy or just the most commonly used second-line therapy in current clinical practice.			

Issue 4 Severity modifier in EAG scenarios

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17: In Table 2, the severity modifiers used in EAG scenarios are either 1.7 or 1.2 but the table header states “x1.7”	Propose revising the table to state “(x1.7)” to “(x1.2 or 1.7 weight)”	To correctly reflect the severity modifiers used by EAG	The header for Table 2 has been revised, and a footnote added to ensure clarity and consistency over the QALY weights applied.

Issue 5 Clarity surrounding first-line treatment options for recurrent or metastatic cervical cancer

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21: The EAG outlines the treatment options for recurrent or metastatic disease ‘may include	Propose rewording sentence to provide further clarity: ‘Options may include salvage surgery where recurrence is confined to the cervix or upper vagina	Alignment to CS section 1.3.4.2.	We have amended the text as follows to add the rationale for use of salvage surgery, as set

<i>salvage surgery or chemotherapy and/or radiotherapy if the disease has not been controlled by initial surgery.⁷</i> The rationale for utilisation of salvage surgery is not provided.	<i>and where chemotherapy has failed or further chemotherapy and/or radiotherapy if the disease has not been controlled by initial surgery.⁷</i>		out in the NICE Clinical Knowledge Summary for cervical cancer and HPV (reference 7 in our report): “Options may include salvage surgery if relapse occurs only in the central pelvis and if chemoradiotherapy has been unsuccessful, or chemotherapy and/or radiotherapy if the disease has not been controlled by initial surgery.”

Issue 6 Alignment of tisotumab vedotin positioning to CS in Section 2.2.3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26, The EAG report that CS Table 2 states: <i>‘tisotumab vedotin is expected to be indicated as a monotherapy to treat adults with recurrent or metastatic cervical cancer</i>	Propose rewording sentence to align with exact wording in CS Table 2: <i>‘tisotumab vedotin is expected to be indicated as a monotherapy to treat adults with recurrent or metastatic cervical cancer with disease</i>	Alignment of wording CS Table 2.	Amended - the amended wording has been copied from CS Table 2. Quotation marks have been placed around the text, which has also been italicised, to make it clear

<i>with disease progression during or subsequent to systemic therapy.'</i> This wording does not exactly match what was stated in CS Table 2.	<i>progression on or after systemic therapy.'</i>		this is a direct quote from the CS.

Issue 7 Specification of the duration of infusion in the draft MHRA SmPC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26, the EAG notes that the [REDACTED].' This should be corrected since the draft MHRA SmPC does mention the duration of the infusion on page 5: [REDACTED].'	Rewording of sentence to specify that the draft SmPC does include mention of the duration of infusion: [REDACTED] <i>the draft MHRA SmPC.'</i>	Reporting of incorrect statement.	The text of the EAG report has been corrected.

Issue 8 Pre-progression mortality (PF->death) fitting

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 99: when discussing visual fit of pre-progression mortality in Section 4.2.6.3, the EAG report mentions “The company states that the generalised gamma captures the observed data patterns in both arms.”	Revise to “The company states Gompertz should be used for tisotumab vedotin and log-normal should be used for chemotherapy”.	EAG might have mistakenly copied the statement from 4.2.6.2 to 4.2.6.3 section.	Thank you; this was an error. We have revised the comment under the bullet point “Visual fit” in section 4.2.6.3 to “The company states that the use of Gompertz for tisotumab vedotin and lognormal for chemotherapy captures the observed data patterns in both arms.”

Issue 9 Fit statistics for PFS extrapolations

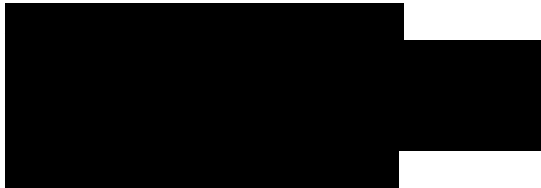
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 104: Fit statistics for PFS extrapolations based on the spline models are missing in Table 16. However, the following figures (Figures 7-8) present PFS curves based on spline	Pleaes consider adding fit statistics for PFS extrapolations based on the spline models	An update would ensure consistency across Table 16 and Figures 7-8	As stated in the text above Table 16, the flexible spline extrapolations are similar to the parametric extrapolations. For clarity, we only included

log-logistic single knot model and Table 17 presents fit statistics for spline models in OS extrapolations			selected parametric models with a good fit and the best-fitting spline model in Figures 7 and 8 (log-logistic single knot, which has the lowest BIC in both arms). For completeness, we have added the AIC/BIC statistics for spline models to Table 16, and we have adjusted the text under the section 4.2.6.5.2.1 heading to reflect this. We have also made a correction to EAR Figure 10, as we had omitted the log-logistic single knot extrapolation from the legend.

Issue 10 Resource use for disease management

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 117: Chemistry panel is missing in Table 20.	Please add annual frequency for chemistry panel in Table 20.	Chemistry panel is considered in the model but has been omitted in the EAG report.	The annual frequency of chemistry panel use has been added to Table 20.

Issue 11 Formatting of confidential markup for list and PAS price of tisotumab vedotin

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			

Issue 12 EAG scenario with Weibull for tisotumab vedotin and loglogistic for chemotherapy for OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 125: In Figure 14, the predicted OS curves of tisotumab vedotin and chemotherapy should be updated to reflect the same mortality after OS converges. The landmark OS estimates in the “EAG Weibull/ log-logistic” row in Tables 23 and 24 are as indicated, however, Figure 14, is not.	Please update Figure 14 to apply the same approach used to generate the values in Tables 23 and 24.	Figure 14 does not reflect the approach used by the EAG in their analysis and is inconsistent with the results presented in Tables 23 and 24.	EAG Figure 14 has been updated to reflect the EAG assumptions presented in Tables 23 and 24.

Issue 13 Assumption of proportional hazards

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 104: The EAG report states “<i>The company report a scenario with dependent models: fitted parametric distributions for chemotherapy (PFS</i>	<i>“The company report a scenario with dependent models: fitted parametric distributions for chemotherapy (PFS generalised gamma and OS</i>	In the dependent modeling approach using generalized gamma or log-normal distributions, both are specified under the accelerated failure time	Thank you for pointing out this error. We have made the requested edit in EAG section 4.2.6.5.2. We note that the company's dependent

<i>generalised gamma and OS lognormal), adjusted for tisotumab vedotin using a hazard ratio (CS Table 70). However, the assumption of proportional hazards required for this analysis has not been justified: the company have not reported log-cumulative hazards plots for PFS or OS.”</i> However, both generalized gamma and lognormal distributions are accelerated failure time models and do not require the proportional hazards assumption	<i>lognormal) using dependent models (CS Table 70)”</i> Please consider removing statements referring to hazard ratios or proportional hazards, as these concepts are not applicable in this context. Wording can be replaced with failure time ratios for accuracy.	(AFT) framework. Therefore, there is no proportional hazards assumption, and the hazard ratio can vary over time. For the dependent generalized gamma model, we are fitting it under AFT framework, both arms are assumed to share the same shape parameters, and the relative treatment effect is represented by a time ratio, which means one treatment’s survival curve is a stretched or compressed version of the other along the time axis. However, the two groups don’t necessarily have proportional hazards to hold. For the dependent log-normal model, both arms also share the same hazard shape, but the hazard ratio is inherently time-dependent because the log-normal distribution does not satisfy	model scenario is referred to in CS Table 70 as a proportional hazards approach. We have made additional corrections to clarify this point in the table for Issue 2, section 4.2.6.5.2, 5.1.3, tables 23, 24, 31 and 32, and section 5.5.2.

		the proportional hazards property. For both, they do not require hazard ratio or proportional hazard assumptions.	

Issue 14 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 7: The EAG report three PSM scenarios, including <i>'Weibull for tisotumab vedotin and loglogistic for chemotherapy.'</i> This sentence is missing hyphenation for <i>'loglogistic'</i>.	<i>'Weibull for tisotumab vedotin and log-logistic for chemotherapy.'</i>	Correction of typographical error.	The hyphenation for log-logistic has been included across the EAG report.
Page 17: Bullet (2) PFS should be capped by the OS states <i>'Correcting this has a marginal impact (less than £1) on ICER'</i>.	<i>'Correcting this has a marginal impact (less than £1) on the ICER'.</i>	Correction of typographical error.	The EAGs comment has been revised as "Correcting this has a marginal impact (less than £1) on the ICER".

Typographical error due to absence of the word 'the'.			
Page 17: States <i>'The corrections above [REDACTED] the company's base case ICER from £79,978 (£47,046) to £83,360 (£49,035) per QALY gained, with and with the 1.7 QALY severity weighting.'</i> Typographical error in latter part of sentence: <i>'with and with the 1.7 QALY severity weighting.'</i>	<i>'The corrections above [REDACTED] the company's base case ICER from £79,978 (£47,046) to £83,360 (£49,035) per QALY gained, with and without the 1.7 QALY severity weighting.'</i>	Correction of typographical error.	The EAGs comment has been revised as "The corrections above increase the company's base case ICER from £79,978 (£47,046) to £83,360 (£49,035) per QALY gained, with and without the 1.7 QALY severity weighting."
Page 19: <i>'Most cases of cervical cancer are caused by a persistent Human Papilloma Virus (HPV) infection with one of the high-risk HPV types.'</i> Typographical error in the reporting of <i>'Human Papilloma Virus (HPV)'</i> - should be one word.	<i>'Most cases of cervical cancer are caused by a persistent Human Papillomavirus (HPV) infection with one of the high-risk HPV types.'</i>	Correction of typographical error.	Amended as suggested. We have also amended this in the List of Abbreviations at the beginning of the EAG report.

Page 29: <i>'The company provided some evidence in the CS and their clarification response to support of an assumption of clinical efficacy equivalence between the single-agent chemotherapies included in the InnovaTV 301 RCT comparator with each other, as well as with paclitaxel.'</i> Typographical error within <i>'to support of an assumption of clinical efficacy'</i>, specifically removal of the word 'of'.	<i>'The company provided some evidence in the CS and their clarification response to support an assumption of clinical efficacy equivalence between the single-agent chemotherapies included in the InnovaTV 301 RCT comparator with each other, as well as with paclitaxel.'</i>	Correction of typographical error.	This typographical error has been corrected.
Page 47: <i>'InnovaTV 204 (also known as GCT1015-04; NCT03438396) is a single-arm, phase 2, multicentre trial of tisotumab vedotin which enrolled 102 participants from the United States and Europe who had previously treated</i>	<i>'InnovaTV 204 (also known as GCT1015-04; NCT03438396) was a single-arm, phase 2, multicentre trial of tisotumab vedotin which enrolled 102 participants from the United States and Europe who had previously treated recurrent or metastatic cervical cancer with disease progression during or after</i>	Correction of typographical error.	This typographical error has been corrected.

<i>recurrent or metastatic cervical cancer with disease progression during or after doublet chemotherapy (paclitaxel plus either platinum or topotecan) with bevacizumab (if eligible by local standards) (CS Table 8 and Coleman et al., 2021²⁰).'</i> The InnovaTV 204 trial is not currently ongoing, therefore sentence should be updated to reflect this: <i>'InnovaTV 204 (also known as GCT1015-04; NCT03438396) is a single-arm, phase 2, multicentre trial...'</i>	<i>doublet chemotherapy (paclitaxel plus either platinum or topotecan) with bevacizumab (if eligible by local standards) (CS Table 8 and Coleman et al., 2021²⁰).'</i>		
Page 57, outlines that: <i>'Censoring rules for time-to-event outcomes are not described in the CS but are available from the publicly available statistical analysis plan.'</i>³⁸	Suggest clarifying that information regarding statistical analysis is available as part of the pivotal trial publication: <i>'Censoring rules for time-to-event outcomes are not described in the CS but are</i>	Reporting of incorrect statement.	This is not an incorrect statement. The statistical analysis plan is available to the public from the trial record on clinicaltrials.gov. The link to this statistical analysis plan is provided in reference 38 https://cdn.clinicaltrials.gov/large-

The company's statistical analysis plan was submitted as Data on File and therefore is not publicly available.	<i>detailed in the publicly available pivotal trial publication.³⁸</i>		docs/28/NCT04697628/SAP_001.pdf . No change made.
Page 57: The EAG comment on the handling of missing data states: <i>'For the most part missing data were not imputed and censoring rules appear follow censoring rules seen in other cancer treatment trials'</i> Sentence contains typographical error: <i>'censoring rules appear follow censoring rules seen in other cancer treatment trials'</i>	<i>'For the most part missing data were not imputed and censoring rules appear to follow censoring rules seen in other cancer treatment trials'</i>	Correction of typographical error.	Typographical error corrected.
Page 61. Typographical error in the following sentence: <i>'A meta-analysis of median overall, which only included the InnovaTV 301 and InnovaTV 204 trials, found</i>	Clarity that the meta-analysis relates to median overall survival (OS): <i>'A meta-analysis of median overall survival, which only included the InnovaTV 301 and InnovaTV 204 trials, found a 11.83</i>	Correction of typographical error.	This typographical error has been corrected.

<i>a 11.83 month (95% CIs: 10.30, 13.59) survival with tisotumab vedotin.⁴⁰</i>	<i>month (95% CIs: 10.30, 13.59) survival with tisotumab vedotin.⁴⁰</i>		
Page 66, the following sentence misses the word 'of': <i>'Estimates median PFS months from the InnovaTV 204 single-arm trial were similar between the Independent Review Committee and investigator assessments of this outcome (Error! Reference source not found.).'</i>	<i>'Estimates of median PFS months from the InnovaTV 204 single-arm trial were similar between the Independent Review Committee and investigator assessments of this outcome (Error! Reference source not found.).'</i>	Correction of typographical error.	This typographical error has been corrected.
Table 10, page 75 requires superscript in the following table row: <i>'Median number of cycles or dosesa of tisotumab'</i>	<i>'Median number of cycles or doses^a of tisotumab'</i>	Correction of typographical error.	Superscript for the footnote has been reinstated.
Page 84 states: <i>'Both the primary (July 2023) and ad hoc follow-up (January 2024) analyses of InnovaTV 301 found that the risk of death or of</i>	<i>'Both the primary (July 2023) and ad hoc follow-up (January 2024) analyses of InnovaTV 301 found that the risk of death or of disease progression with tisotumab vedotin was statistically significantly</i>	Correction of typographical error.	This is not a typographical error, but we have revised this sentence so that it reads: "Both the primary (July 2023) and ad hoc follow-up (January 2024) analyses of

<i>disease progression or death with tisotumab vedotin was statistically significantly reduced compared with chemotherapy.'</i> Typographical error in: 'that the risk of death or of disease progression or death with tisotumab vedotin'	<i>reduced compared with chemotherapy.'</i>		InnovaTV 301 found that the risk of death and the risk of disease progression or death with tisotumab vedotin was reduced compared with chemotherapy.” We have amended the sentence in this way to: a) clarify our intended meaning (that is, that we are referring to both the overall survival and progression-free survival outcomes), and b) to remove reference to statistical significance, because we note that the p-values for the ad hoc follow-up analyses should not be used to infer statistical significance.
Page 119 states: 'The ICER with (and without) severity modifier is [REDACTED] ([REDACTED]) per QALY.' The ICER with severity modifier contains a decimal point rather than a comma in the value: [REDACTED]	'The ICER with (and without) severity modifier is [REDACTED] ([REDACTED]) per QALY.'	Correction of typographical error.	The ICER without severity modifier has been corrected to include a comma not a decimal point.

Issue 15 Incorrect marking of confidential information

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.5, page 17 states: 'This [REDACTED] the company's base case ICER by £3,383. The corrections above [REDACTED] the company's base case ICER from £79,978 (£47,046) to £83,360 (£49,035) per QALY gained, with and with the 1.7 QALY severity weighting.' Page 127 also states: 'This [REDACTED] the company's base case ICER by £3,383.'	Markup on 'increase' can be removed since the company's base case ICER is not marked up in the CS.	'This increases the company's base case ICER by £3,383. The corrections above increase the company's base case ICER from £79,978 (£47,046) to £83,360 (£49,035) per QALY gained, with and with the 1.7 QALY severity weighting.' Markup should also be removed for these sentences on page 17 and page 127.	The confidential marking used for the word "increase" in sections 1.5 and 5.2.3 has been removed.
Pages 26 has confidential markup for: [REDACTED]. Pages 26, 40, 48, 85, and 115 have confidential markup for: [REDACTED].	The phrases 'draft SmPC' or 'draft MHRA SmPC' can be unmarked throughout the EAG report.	'Draft SmPC' and 'draft MHRA SmPC' can be unmarked on pages 26, 40, 48, 85, and 115.	Confidential mark up for 'draft SmPC' and 'draft MHRA SmPC' has been removed where not part of wider confidentiality marking.

Table 4, page 44 mentions the duration of OS median follow-up for the InnovaTV 301 RCT as: '██████████ (ad-hoc follow-up analysis dated ██████████ January 2024; company data on file, ³⁰ page 1).'	Markup on '██████████ January 2024' can be removed since this is publicly known information.	██████████ (ad-hoc follow-up analysis dated 16th January 2024; company data on file, ³⁰ page 1).'	Confidential mark up has been removed.
Table 4, page 44 states the number of participants from the UK in InnovaTV 301: '██████████ participants from the UK were enrolled (██████████ in each arm).'	Markup required since information is from the InnovaTV 301 CSR.	██████████ participants from the UK were enrolled (██████████ in each arm).'	Confidential mark up has been reinstated (a technical glitch led to the loss of this mark up in the submitted version of our report). We note that the figures to which the company refer were not marked up as confidential in the first column of this FAC table (i.e. under 'Location of incorrect marking'), so the EAG has added confidentiality marking to the figures in this column here.
Table 5, page 45 includes confidential markup for the	Table markup can be removed to align with CS.	Markup in Table 5 can be removed for the following	Mark up has been removed.

number of participants (%) in InnovaTV 301 who received investigator's choice of chemotherapy.		comparators: pemetrexed, gemcitabine, topotecan, irinotecan, vinorelbine.	
Page 47 states: <i>'We note that 50.2% and 43.4% of participants in the tisotumab vedotin and chemotherapy arms received subsequent anti-cancer therapies, respectively, 18 [REDACTED] [REDACTED]'</i>	Markup required for the number of participants in the tisotumab vedotin and chemotherapy arms who received subsequent anti-cancer therapies. Markup can be removed when referencing CSR source: '[REDACTED]'	<i>'We note that [REDACTED]% and [REDACTED]% of participants in the tisotumab vedotin and chemotherapy arms received subsequent anti-cancer therapies, respectively, 18 [REDACTED] [REDACTED] (InnovaTV 301 RCT CSR, 31 Table 14.2.6).'</i>	The proportion of participants in the trial arms who received subsequent therapies was calculated from Figure 1 in the Vergote et al. trial publication (127/253 participants in the tisotumab arm and 108/249 participants in the chemotherapy arm). The trial publication has been referenced for this information which is in the public domain and therefore no mark up is required. Mark up for the CSR source has been removed.
Page 58. Confidential markup has been added for some of the abbreviation list.	Markup can be removed for all abbreviations.	<i>'CS, company submission; CSR, clinical study report; DoR, duration of response; EAG, External Assessment Group, EORTC-QLQ-C30,</i>	Confidential markup has been removed from the abbreviations list.

		European Organization for Research and Treatment Quality of Life Questionnaire Core 30; EORTC-QLQ-CX-24, European Organization for Research and Treatment Quality of Life Questionnaire Cervical Cancer Specific module; EQ-5D, EuroQol 5 Dimensions; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; ITT, Intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO FAS, patient-reported outcome final analysis set; RCT, randomised controlled trial.'	
Table 11, page 76 contains confidential markup for the following table row: ' <i>TEAE leading to death.</i> '	Markup of TEAE leading to death values in Table 11 for both the tisotumab vedotin and chemotherapy arms can be removed to align with markup in the CS.	Table 11: <i>TEAE leading to death –</i> <i>Tisotumab vedotin: '4 (1.6)'</i> <i>Chemotherapy: '5 (2.1)'</i>	Confidential markup for the row 'TEAE leading to death' in Table 11 has been removed.

Page 119 states: <i>'The ICER with (and without) severity modifier is [REDACTED] ([REDACTED]) per QALY.'</i>	Markup on values can be removed since ICERs per QALY are not marked up in the CS.	<i>'The ICER with (and without) severity modifier is £47,046 (£79,978) per QALY.'</i>	The confidential marking in the company's base case ICER (with and without) severity modifier has been removed.