Medicinrådet

Bilag til Medicinrådets vurdering af tisotumab vedotin til behandling af recidiverende eller metastatisk livmoderhals-kræft med sygdomsprogression under eller efter systemisk behandling

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. tisotumab vedotin
2. Forhandlingsnotat fra Amgros vedr. tisotumab vedotin
3. Ansøgers endelige ansøgning vedr. tisotumab vedotin

Genmab

Til: Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

Den 28. april 2026

Notat vedrørende Medicinrådets vurdering af tisotumab vedotin til tidligere behandlet recidiverende eller metastatisk cervixcancer (r/m CC).

Genmab A/S takker Medicinrådet for den konstruktive dialog og det løbende samarbejde igennem vurderingsprocessen. Overordnet set repræsenterer Medicinrådets rapport en fair og afbalanceret evaluering. Der er dog to forhold, som giver anledning til bekymring, idet de har væsentlig indflydelse på resultaterne for omkostningseffektiviteten og synes at afvige fra både tidligere praksis inden for dette terapiområde og almindelig klinisk forståelse.

Antagelser om patientkarakteristika

Antagelsen om kropsvægt der er anvendt i den sundhedsøkonomiske model, er ikke forankret i den kliniske evidens og er ikke konsistent med Medicinrådets egen praksis inden for dette sygdomsområde.

I vurderingen af pembrolizumab til førstelinjebehandling af r/m CC accepterede Medicinrådet i 2023 en gennemsnitlig kropsvægt på 64,7 kg, svarende til patientpopulationen i KEYNOTE-826. I den aktuelle vurdering har Medicinrådet imidlertid valgt at anvende den gennemsnitlige kropsvægt for kvinder i den danske befolkning på 70 kg frem for at anvende samme tilgang og acceptere den observerede forsøgsbaserede vægt på 63,6 kg fra innovaTV 301-studiet. Den anvendte vægt er hverken baseret på danske sygdomsspecifikke data for r/m CC eller understøttet af en klinisk begrundelse for netop denne patientpopulation. Valget medfører signifikant overestimerede lægemiddelomkostninger i modellen, da tisotumab vedotin doseres efter kropsvægt.

Kvinder med tidligere behandlet r/m CC, som modtager anden- eller tredjelinjebehandling, udgør en særlig patientgruppe, hvis kropsvægt adskiller sig væsentligt fra den generelle danske befolknings. Patienter, der er kandidater til tisotumab vedotin, har progredieret gennem tidligere behandlingslinjer, og de kumulative effekter af sygdomsprogression og tidligere behandlinger må forventes at medføre kropsvægte, der er sammenlignelige med eller lavere end dem, der er observeret i førstelinjestudiet med pembrolizumab - ikke højere.

Den studiebaserede vægt på 63,6 kg fra innovaTV 301 er derfor både klinisk velbegrundet og metodologisk i tråd med den tilgang, Medicinrådet tidligere har accepteret i samme indikation.

Tilsidesættelse af observerede data for samlet overlevelse

Genmab har bekymringer vedrørende beslutningen om primært at basere den modellerede overlevelse på parametrisk ekstrapolation frem for de observerede Kaplan-Meier-data fra innovaTV 301.

Den samlede overlevelse i innovaTV 301 er statistisk signifikant med moden opfølgning, hvilket giver et robust evidensgrundlag i de første 12-15 måneder til direkte anvendelse i modellen. Genmab anerkender, at parametrisk ekstrapolation spiller en vigtig rolle i sundhedsøkonomisk modellering, særligt når observerede data er umodne, eller når parametriske modeller giver en god tilpasning til studiedata. Ingen af disse betingelser er imidlertid opfyldt for de første 12 måneder i dette tilfælde.

Medicinrådets tilgang afviger fra egen praksis i flere vurderinger inden for avanceret onkologi. For eksempel blev der i den sundhedsøkonomiske vurdering af dostarlimab til dMMR/MSI-H endometriecancer eksplicit

drøftet og accepteret at anvende observerede overlevelsesdata frem til måned 12, da ekstrapoleringerne dermed stemmer bedre overens med de kliniske data. Det samme princip bør gælde her[1].

De valgte parametriske distributioner passer ikke tilstrækkeligt til studiedata for de første 12 måneder og introducerer en systematisk skævhed i omkostningseffektivitetsresultaterne: de undervurderer den samlede overlevelse i tisotumab vedotin-armen og overvurderer samtidig overlevelsen i kemoterapi-armen sammenlignet med de observerede data.

Genmab har derfor anvendt observerede Kaplan-Meier-data for de første 12 måneders opfølgning, hvor den parametriske tilpasning er dårlig, og har reserveret parametrisk ekstrapolering til perioden efter måned 12, hvor data er mindre modne, og ekstrapolation er nødvendig. Genmab vurderer, at denne tilgang er metodologisk solid, i tråd med Medicinrådets egen praksis og bedre afspejler den kliniske evidens fra innovaTV 301.

Uopfyldt behandlingsbehov

Medicinrådets vurderingsrapport beskriver de relevante behandlingsmuligheder for denne indikation som topotecan-monoterapi eller bedste understøttende behandling - begge forbundet med beskedne resultater og uden dokumenteret gevinst i samlet overlevelse fra et randomiseret kontrolleret studie. Dette understreger det betydelige uopfyldte behandlingsbehov, der fortsat eksisterer ved anden- og tredjelinjebehandling af r/m CC.

Vi minder samtidig om, at kræft i livmoderhalsen oftest diagnosticeres hos yngre kvinder i alderen 30-45 år, og at overlevelsen ved anden- og tredjelinjebehandling af r/m CC med nuværende standardbehandling er beskeden.

Tisotumab vedotin er det eneste lægemiddel i denne indikation med en prospektivt dokumenteret, statistisk signifikant gevinst i samlet overlevelse fra et fase III studie. Det repræsenterer en væsentlig klinisk værdi for en patientpopulation med meget begrænsede tilbageværende behandlingsmuligheder.

Genmab bemærker desuden, at den relevante patientpopulation står overfor en særlig alvorlig prognose med meget begrænsede resterende behandlingsmuligheder, og at denne kontekst er relevant for Rådets samlede vurdering i henhold til alvorlighedsprincippet.

Genmab opfordrer Medicinrådet til at genoverveje antagelsen om kropsvægt og til at sikre, at den modellerede overlevelse baseres på den observerede kliniske evidens fra innovaTV 301. Kvinder med tidligere behandlet recidiverende eller metastatisk cervixcancer har meget begrænsede behandlingsmuligheder på dette stadie af sygdommen. Det er afgørende, at vurderingen afspejler den bedst tilgængelige evidens for at understøtte adgang til en behandling, der kan give patienter en meningsfuld klinisk gevinst og mulighed for mere tid med deres familier.

Med venlig hilsen,

Frans Søltoft
Sundhedsøkonom, Global Market Access
Genmab A/S

[1] Den pågældende vurdering deler væsentlige karakteristika med den aktuelle sag: et tilsvarende sygdomsforløb i en avanceret onkologisk population, en sammenlignelig modenhed af opfølgningsdata og en modelstruktur, hvor valget mellem observerede og ekstrapolerede data har en stor indvirkning på omkostningseffektivitetsresultaterne.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

18.05.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.05.2026
Leverandør	Genmab
Lægemiddel	Tivdak (tisotumab vedotin)
Ansøgt indikation	Behandling af voksne patienter med recidiverende eller metastatisk cervixcancer med sygdomsprogression, som får eller har fået systemisk behandling
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Tivdak (tisotumab vedotin):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Tivdak	40 mg (1 stk.)	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Tivdak, indkøbes lægemidlet til AIP.

[redacted]

Aftaleforhold

Prisen er betinget af en anbefaling og Amgros vil i så fald indgå en aftale på Tivdak [redacted]. Leverandøren har mulighed for at sætte prisen ned i aftaleperioden.

Konkurrencesituationen

For patienter, der progredierer på eller efter systemisk behandling i førstelinje er behandlingsmulighederne begrænsede. Blandt patienter, der fortsat er egnede til systemisk behandling, er enkeltstof kemoterapi en mulighed. I Danmark anvendes topotecan til behandling i anden linje. Tivdak er den eneste antistof-konjugat (ADC), der er godkendt til denne indikation.

Tabel 2 viser lægemiddeludgifter for et behandlingsforløb for Tivdak og topotecan. Bemærk at behandlingsvarigheden er forskellig for de to behandlinger. Jf. Tabel 8 i *Medicinrådets vurdering af tisotumab vedotin til behandling af recidiverende eller metastatisk livmoderhalskræft med sygdomsprogression under eller efter systemisk behandling* er den gennemsnitlige behandlingsvarighed på Tivdak 5 måneder (svarende til ca. 21 uger), mens den er 4,2 måneder (svarende til ca. 18 uger) for topotecan.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Tivdak	40 mg (1 stk.)	2 mg/kg* hver 3. uge, i.v. Behandlingsvarighed: 5 måneder	[redacted]	[redacted]
Topotecan "Accord"	1 mg/ml (4 ml)	1,25 mg/m^2** på dag 1-5, hver 3. uge, i.v. Behandlingsvarighed: 4,2 måneder	515,70	7.977

*Kropsvægt er 70 kg, jf. Medicinrådets vurdering af tisotumab vedotin til behandling af recidiverende eller metastatisk livmoderhalskræft med sygdomsprogression under eller efter systemisk behandling
**Overfladeareal 1,65 m^2, jf. Medicinrådets vurdering af tisotumab vedotin til behandling af recidiverende eller metastatisk livmoderhalskræft med sygdomsprogression under eller efter systemisk behandling

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke ansøgt	
England	Under vurdering	Link til status
Sverige	Under vurdering	Link til status

Opsummering

Prisen og aftalen for Tivdak afhænger af Medicinrådets anbefaling og gælder ved anbefaling i perioden [redacted] hvor Tivdak er eneste godkendte ADC-alternativ til kemoterapi i indikationen.

Application for the assessment of tisotumab vedotin for adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
Name	**Frans Søltoft**
Title	Director, Global Market Access & Pricing
Phone number	+45 3144 9035
E-mail	[redacted]
Name	**Jesper Kofoed Damm**
Title	Associate Director, Medical Affairs (EU)
Phone number	+45 3144 9065
E-mail	[redacted]

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Abbreviations

Overview of abbreviations	
ADC	Antibody-drug conjugate
AE	Adverse event
AIC	Akaike's Information Criterion
BIC	Bayesian Information Criterion
CC	Cervical cancer
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DGCG	The Danish Gynaecologic Cancer Group
DOR	Duration of Response
ESMO	European Society for Medical Oncology
EQ-5D-5L	EuroQol-5 Dimension-5 Level
FAS	Full Analysis Set
FIGO	Federation of Gynecology and Obstetrics
HPV	High-risk human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental Cost-Effectiveness Ratio
IDMC	Independent data monitoring committee

Overview of abbreviations	
IPD	Individual patient-level data
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Microtubule disrupting agent monomethyl auristatin E
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PF	Progression-free
PPS	Post-progression survival
PR	Partial response
PRO	Patient reported outcome
QALY	Quality-Adjusted Life Year
r/mCC	Recurrent or metastatic cervical cancer
SCC	Squamous cell carcinoma
SD	Stable disease
SLR	Systematic literature review
TEAE	Treatment emergent adverse events
TF	Tissue-factor
TTP	Time to progression
TTR	Time to response

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Tivdak®
Generic name	Tisotumab vedotin
Therapeutic indication as defined by EMA	Treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy (1).
Marketing authorization holder in Denmark	Genmab A/S Carl Jacobsens Vej 30 2500 Valby Denmark
ATC code	L01FX23
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	28th March 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	N/A
Other therapeutic indications approved by EMA	N/A
Other indications that have been evaluated by the DMC (yes/no)	N/A
Joint Nordic assessment (JNHB)	Not suitable for JNHB assessment, due to differences in treatment of recurrent or metastatic cervical cancer after progression between Nordic countries.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	40 mg powder for solution (for infusion)

2. Summary table

Summary	
Indication relevant for the assessment	Treatment of adult patients with recurrent or metastatic cervical cancer (r/mCC) with disease progression on or after systemic therapy.
Dosage regiment and administration	The recommended dose of tisotumab vedotin (TV) is 2 mg/kg every three weeks, until disease progression or toxicity (up to maximum of 200 mg for patients of 100kg or more). Prior to the first infusion and as clinically indicated, an eye care professional should conduct an ophthalmic exam, including visual acuity and slit lamp exam (1).
Choice of comparator	Among patients eligible for treatment, single-agent chemotherapy remains the standard treatment option in the second- and third-line treatment setting.
Prognosis with current treatment (comparator)	Existing evidence from several sources demonstrates poor survival benefits (median OS of ~9 months; median progression-free survival [PFS] ~3 months) with single-agent chemotherapies (2-13). Evidence supporting the efficacy and use of most of these single-agent chemotherapies used in previously treated r/mCC is based on uncontrolled studies with relatively small sample sizes, and often in r/mCC patient populations that no longer reflect current treatment practices (2-13).
Type of evidence for the clinical evaluation	Head-to-head study. The innovaTV 301 trial (NCT04697628) entailed a phase 3, open-label trial of tisotumab vedotin as second- or third-line therapy in patients with r/mCC. Patients were randomised (1:1) to either tisotumab vedotin (2 mg/kg Q3W), or investigator's choice (IC) of chemotherapy (either topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed).
Most important efficacy endpoints (Difference/gain compared to comparator)	**Primary endpoints:** Median overall survival was 11.5 months in the TV arm and 9.5 months in the chemotherapy arm (HR: 0.70 [95% CI: 0.54–0.89], p-value: 0.004) (14) **Key secondary endpoints:** • Median progression-free survival was 4.2 months in the TV arm and 2.9 months in the chemotherapy arm (HR: 0.67 [95% CI: 0.54–0.82], p-value: <0.001) (14) • Objective response rate was 17.8% in the TV arm and 5.2% in the chemotherapy arm (OR: 4.0 [95% CI: 2.1-7.6], p-value: <0.001) (14). • Disease control rate was 75.9% in the TV arm and 58.2% in the chemotherapy arm (14).

Summary	
Most important serious adverse events for the intervention and comparator	In both arms, the most common treatment-emergent serious adverse event was urinary tract infection with 4.4% in the TV arm and 7.1% in the chemotherapy arm. Ocular events of any grade were observed in 52.8% of patients in the TV arm and 0.0% in the chemotherapy arm, while peripheral neuropathy occurred in 5.6% 0.0%, respectively.
Impact on health-related quality of life	In innovaTV 301, health-related quality of life (HRQoL) was assessed with the EuroQol-5 dimension (EQ-5D, consisting of EQ-5D-5 level [5L] descriptive system and EQ visual analogy scale [VAS]). The EQ-5D VAS scores in both arms were stable from baseline to Cycle 5. The EQ-5D-5L index scores in both arms were stable from baseline to Cycle 8. Health economic model: A gain of [redacted] QALY was achieved over a lifetime horizon.
Type of economic analysis that is submitted	Cost-utility analysis, based on a semi-Markov model.
Data sources used to model the clinical effects	InnovaTV 301 was a head-to-head trial of TV versus chemotherapies in patients with previously treated r/mCC
Data sources used to model the health-related quality of life	HRQoL collected via EQ-5D-5L in innovaTV 301
Life years gained	0.22 years
QALYs gained	[redacted] QALY
Incremental costs	[redacted] DKK
ICER (DKK/QALY)	[redacted] DKK/QALY
Uncertainty associated with the ICER estimate	The trial-derived utilities impact the QALY gain and therefore the ICER estimate. The ICER is also sensitive to prices of chemotherapies and extrapolations of survival outcomes in both arms.
Number of eligible patients in Denmark	Annual incidence of CC in Denmark is approximately 325-350 patients per year. Around 40 patients per year present with previously treated r/mCC. Of these patients, it is expected 20 patients will be fit enough and thus eligible for second-line treatment. Incidence: 20 patients per year. Prevalence: Not reported, due to high mortality.
Budget impact (in year 5)	2,443,440 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

Cervical cancer (CC) is the fourth most common cancer in women worldwide and has the fourth highest mortality rate among cancers in women (15). It disproportionately affects younger women in the most productive years of their lives.

CC is defined as a disease in which abnormal cells in the lining of the cervix, the lowermost part of the uterus that connects to the vagina, grow and divide in an uncontrolled manner. It is also called cancer of the uterine cervix. The cervix is covered by two kinds of cells: squamous and glandular. Squamous cells are found in the outer layer of the cervix (ectocervix). Glandular cells are found in the cervical canal (endocervix). The point where these two cells meet is called the squamocolumnar junction or transformation zone, which is generally where CC begins (16, 17).

3.1.2 Symptoms

CC is often asymptomatic. However, early CC may have symptoms including:

- Vaginal bleeding between periods, after menopause, after sex
- Pain during sex
- Pain in the pelvis
- Menstrual bleeding that is heavier or lasts longer than usual
- Unusual vaginal discharge

Advanced CC may also be accompanied by extreme tiredness, leg swelling or pain, low back or abdominal pain, cough or problems urinating (17, 18).

3.1.3 Prognostic factors

Cervical cancer is a rare type of cancer resulting from a persistent infection of the lower genital tract by one of about 15 high-risk human papillomavirus (HPV) types (19). 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 (15, 17, 20).

There are three main subtypes of cervical cancer:

- Squamous cell carcinoma (SCC) accounts for 70% to 90% of CC cases (17, 21-25). 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 (26) 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 (27, 28).

3.1.4 Disease staging

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 standardized classification system used to stage gynaecological cancers (Table 1) (19).

Table 1 International Federation of Gynecology and Obstetrics Staging for Cervical Cancer

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

[a]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC.
Source: Bhatla, Aoki (19)

3.1.5 Progression to recurrent or metastatic disease

Recurrent or metastatic CC (r/mCC) refers to a subgroup of CC patients who are either diagnosed with metastatic disease (stage IV, Table 1) or had originally been diagnosed with early-stage CC (stage I-III, Table 1) and experienced disease recurrence following initial therapy. CC can recur in the cervix or return with spread to distant organs.

CC can spread via local invasion, the regional lymphatics, or the bloodstream (17). R/mCC generally refers to CC that is either diagnosed at stage IVB or has recurred with distant metastasis and is no longer amenable 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 (17). Clinical outcomes of patients newly diagnosed with mCC depend on tumour biology, extent, and localization of metastasis. For recurrent patients, the location of recurrence affects clinical outcomes.

For patients with early-stage CC, 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 (19). Risk factors for disease recurrence include lymph node (29) or parametria involvement, as well as tumour volume (Table 2) (19, 30).

Table 2. Risk Factors for Cervical Cancer Recurrence

Risk factors
• 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, Aoki (19)

3.1.6 Prognosis

R/mCC is incurable, and treatment is often palliative with goals of slowing tumour growth, extending life, delaying metastatic progression, and maintaining or improving quality of life (19, 31). Existing evidence demonstrates poor survival benefits (median OS of ≤9 months; median PFS ≤5 months) with single-agent chemotherapies (2-13).

As stated in the treatment recommendations published by the Danish Gynaecologic Cancer Group (DGCG) (32), there is currently no recommended standard-of-care (SoC) option for second-line treatment following progression on platinum-based chemotherapy in Denmark. Additionally, the literature offers no validated estimates of prognosis for this particular clinical context.

3.1.7 Health-related quality of life

As a disease that disproportionately impacts younger women during productive years (35 to 45 years of age) (33), CC can have a negative impact on society and families, including economic and personal wellbeing (34-37) (38). Morbidity and early death among r/mCC patients contribute to substantial societal burden in terms of productivity loss (39-41).

Women with CC report significantly worse health-related quality-of-life (HRQoL) compared with individuals without CC (42, 43). Data from the US Medical Expenditure Panel Survey (MEPS) showed that patients with CC reported significantly more frequent limitations in physical activities, social interactions, and cognitive functions (43). Significantly lower Short Form-12 health survey (SF-12) and health utility scores, and higher depression severity were observed in women with CC compared to those without CC.

3.2 Patient population

In Denmark, approximately 300 women are diagnosed with CC each year across all disease stages. Most of these patients have early-stage disease, with only a minority ultimately developing r/mCC (Table 3). Over the past five years, annual incidence ranged from 267 to 326 cases, with prevalence remaining around 9,000 women (Table 3) (44). These estimates align well with the understanding of Danish CC-treating clinicians consulted by Genmab, who estimated around 350 incident cases yearly.

Table 3 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	297	267	329	325	326
Prevalence in Denmark	8,980	8,933	8,915	8,936	NA
Global prevalence	NA	NA	NA	NA	NA

Source: Nordcan (44)

Based on the annual report from the Danish Gynaecological Cancer Database (DGCD) (45), 279 incident cases of cervical cancer were registered in Denmark between 1 July 2023 and 30 June 2024. Across all registered cases, 17.2% were reported as stage IIIC (lymph-node metastatic disease).

There is no Danish data available describing the proportion of patients who subsequently develop recurrent disease. However, internal estimates from Genmab suggest that roughly 40 new r/mCC patients are diagnosed each year, based on guidance from Danish CC-treating clinicians. This is in line with what was expected in the assessment of pembrolizumab in combination with chemotherapy for first-line r/m CC, where 30 incident patients were estimated (46). Of these patients, it is expected 20 would be eligible for a second-line (2L) treatment such as TV.

Table 4 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years					
Patients with r/mCC	40	40	40	40	40
Eligible for 2L treatment	20	20	20	20	20

3.3 Current treatment options

The Danish Gynaecologic Cancer Group (DGCG) has outlined the clinical guidelines for oncologic treatment of non-curable persistent, recurrent, or metastatic cervical cancer. Treatment strategies are uniform across persistent, recurrent, and metastatic disease and are applicable to the predominant histological subtypes, including squamous cell carcinoma and adenocarcinoma (32, 47).

For first-line treatment of r/mCC, pembrolizumab and chemotherapy (cisplatin + paclitaxel) with or without bevacizumab is recommended as treatment in adult patients whose tumours express programmed Death-Ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1 (32, 47). Other treatment options are cisplatin and paclitaxel with or without bevacizumab for patients not eligible for a PD-L1 due to undesired toxicity, previous exposure to a PD-L1 treatment or were PD-L1 negative (CPS < 1) (32).

The Danish treatment recommendations for r/mCC in patients whose disease progresses during or after systemic therapy provide little guidance (32). For r/mCC patients with disease progression on or after systemic therapy (corresponding to second-line or later), therapeutic options remain limited. Among patients eligible for treatment (i.e., those not considered candidates for palliative care), the SoC in the second- and third-line setting is single-agent chemotherapy. As confirmed by Danish clinicians consulted by Genmab and existing literature (48), none of the existing single-agent chemotherapies is considered superior to the others. The observation that single-agent chemotherapy demonstrates comparable efficacy aligns with international treatment recommendations from the European Society for Medical Oncology (ESMO) (49). According to the ESMO guidelines (49), several single-agent chemotherapies, including vinorelbine, topotecan, gemcitabine and paclitaxel, have been evaluated in patients whose disease progresses after first line therapy. The ESMO guidelines note that response rates are generally low, and the

duration of response is short. As a result, no recommendation has been made regarding the most effective option for second-line treatment. TV would be introduced as an alternative treatment option in this line of therapy (refer to

Figure 1, below).

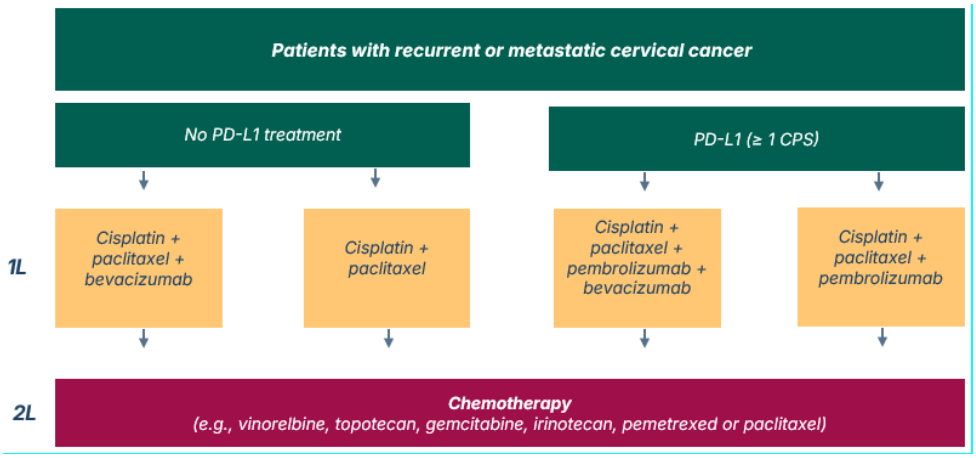


Figure 1 Current treatment algorithm

Abbreviations: 1L- first-line; 2L, second-line; CPS, Combined Positive Score; PD-L1, Programmed Death-Ligand 1.
Adapted from: DCGC (32), previous DMC assessment (46), and ESMO guidelines (49)

3.4 The intervention

Tivdak (tisotumab vedotin) is indicated for the treatment adult patients with r/mCC with disease progression on or after systemic therapy.

Previously, TV was studied in a phase II study innovaTV 204 which yielded promising results. The European Commission approval was granted 28th March 2025 and is based on the results from the phase III trial - innovaTV 301.

TV is an antibody-drug conjugate (ADC) composed of a human tissue factor (TF)- specific human monoclonal immunoglobulin G1 antibody (tisotumab) chemically conjugated via a protease-cleavable valine-citrulline linker to the microtubule disrupting agent monomethyl auristatin E (MMAE) (50). TV leverages elevated TF expression levels on tumour cells to initiate several mechanisms for cell-killing, including MMAE-mediated direct and bystander cytotoxicity, ICD, ADCC, ADCP, and inhibition of TF: activated factor VII -dependent downstream signalling (50).

Table 5 Overview of intervention - tisotumab vedotin

Overview of intervention	
Indication relevant for the assessment	Treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

Overview of intervention	
ATMP	No.
Method of administration	Intravenous infusion (IV)
Dosing	The recommended dose of tisotumab vedotin is 2 mg/kg every three weeks, until disease progression or toxicity (up to maximum of 200 mg for patients of 100 kg or more) (1).
Dosing in the health economic model (including relative dose intensity)	2.0 mg/kg Q3W, with an RDI of 89.31%.
Should the medicine be administered with other medicines?	No. Tisotumab vedotin is a monotherapy.
Treatment duration / criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Prior to the first infusion and as clinically indicated, an eye care professional should conduct an ophthalmic exam, including visual acuity and slit lamp exam (1). Patients should be instructed to use topical preservative-free corticosteroid eye drops, such as dexamethasone 0.1% (or an equivalent preparation as prescribed), by administering one drop in each eye three times daily, starting one day before each infusion and continuing for three days after each infusion (1). Additionally, patients should be instructed to use topical preservative-free ocular vasoconstrictor drops, such as brimonidine tartrate 0.2% (or an equivalent preparation as prescribed), by administering one drop in each eye immediately prior to each infusion (1).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No.
Package size(s)	40 mg powder for solution (for infusion)

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

Based on the innovaTV 301 trial (14), TV would be an alternative to treatment with single-agent chemotherapy if recommended in Denmark as the second- or third-line treatment of patients with r/mCC. As the current treatment recommendations offer limited guidance it is not clear how TV will alter subsequent treatment strategies. However, single-agent chemotherapies are expected to be offered to patients in later lines if TV becomes available in second-line.

3.5 Choice of comparator(s)

Since there is no specific preference for any one of the available chemotherapies in Denmark (please refer to Section 3.3), the treatments included in the chemotherapy basket in innovaTV 301 (i.e., topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) are expected to be clinically equivalent to the standard-of-care (SoC) in Danish clinical practice. The base-case analysis relies on the comparison between TV and the expected SoC in Denmark (i.e., any of the chemotherapies).

The included chemotherapies in the innovaTV 301 trial are described in the tables below, though are considered in one basket when presenting the clinical results and modelling the effectiveness in the health economic model.

Table 6 Description of comparator - topotecan

Overview of comparator	
Generic name	Topotecan
ATC code	L01CE01
Mechanism of action	Topotecan inhibits topoisomerase-I by stabilising the covalent complex of enzyme and strand-cleaved DNA which is an intermediate of the catalytic mechanism. The cellular sequela of inhibition of topoisomerase-I by topotecan is the induction of protein-associated DNA single-strand breaks.
Method of administration	Intravenous infusion (IV)*
Dosing	1 or 1.25 mg/m2 IV on Days 1 to 5, every 21 days
Dosing in the health economic model (including relative dose intensity)	1.125 mg/m^{2**} IV on Days 1 to 5, every 21 days; mean dose intensity 97.3%
Should the medicine be administered with other medicines?	No.

Overview of comparator	
Treatment duration/ criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	• 1 mg/ml x 1 ml • 4 mg/ml x 4 ml

Abbreviations: mg, milligrams; m^2, squared meter; IV, intravenous; ml, intravenous.
Note: *Topotecan must be reconstituted and further diluted before use.
Package sizes are sourced from Medicinpriser.dk to align with the expected local practice
Source: innovaTV 301 clinical study protocol (51); EMA (52); Medicinpriser.dk (53)

Table 7 Description of comparator - vinorelbine

Overview of comparator	
Generic name	Vinorelbine
ATC code	L01CA04
Mechanism of action	Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. Spiralisation of the tubulin is induced to a lesser degree than with vincristine. Vinorelbine blocks mitosis in phase G2-M, causing cell death in interphase or at the following mitosis.
Method of administration	Intravenous infusion (IV)
Dosing	30 mg/m2 IV on Days 1 and 8, every 21 days
Dosing in the health economic model (including relative dose intensity)	30 mg/m2 IV on Days 1 and 8, every 21 days; mean dose intensity: 81.4%
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	• 10 mg/ml x 1 ml • 10 mg/ml x 5 ml

Abbreviations: mg, milligrams; m^2, squared meter; IV, intravenous; ml, millilitre.
Package sizes are based on those specified in the health economic model and sourced from Medicinpriser.dk to align with the expected local practice
Source: EMC (54); Medicinpriser.dk (53)

Table 8 Description of gemcitabine

Overview of comparator	
Generic name	Gemcitabine
ATC code	L01BC05
Mechanism of action	Gemcitabine is a potent and specific deoxycytidine analog. After uptake into malignant cells, gemcitabine is phosphorylated by deoxycytidine kinase to form gemcitabine monophosphate, which is then converted to the active compounds, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). These active metabolites are nucleosides that mediate antitumour effects. dFdCTP competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA, thereby competitively inhibiting DNA chain elongation. Incorporation of dFdCTP into the DNA chain ultimately leads to chain termination, DNA fragmentation, and apoptotic cell death of malignant cells.
Method of administration	Intravenous infusion (IV)
Dosing	1000 mg/m2 IV on Days 1 and 8, every 21 days
Dosing in the health economic model (including relative dose intensity)	1000 mg/m2 IV on Days 1 and 8, every 21 days; mean dose intensity: 82.6%
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	• 10 mg/ml x 120 ml • 10 mg/ml x 140 ml • 10 mg/ml x 160 ml • 10 mg/ml x 180 ml • 10 mg/ml x 200 ml • 10 mg/ml x 220 ml

Abbreviations: mg, milligrams; m^2, squared meter; IV, intravenous; ml, millilitre.
Note: Package sizes are based on those specified in the health economic model and sourced from Medicinpriser.dk to align with the expected local practice
Source: EMC (55); Medicinpriser.dk (53)

Table 9 Description of irinotecan

Overview of comparator	
Generic name	Irinotecan
ATC code	L01CE02
Mechanism of action	Irinotecan is a prodrug that is converted in the body to its active metabolite, SN-38. This active form binds to the topoisomerase I–DNA complex and prevents the re-ligation of single-strand breaks created during normal DNA unwinding. As a result, DNA damage accumulates, and when the replication fork encounters these breaks, they are converted into double-strand breaks, leading to cell death, particularly in rapidly dividing cancer cells.
Method of administration	Intravenous infusion (IV)
Dosing	100 or 125 mg/m2 IV weekly for 28 days, every 42 days
Dosing in the health economic model (including relative dose intensity)	112.5 mg/m2 IV weekly for 28 days, every 42 days; mean dose intensity: 68.6%*
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	• 20 mg/ml × 5 ml • 20 mg/ml × 15 ml • 20 mg/ml × 25 ml

Abbreviations: mg, milligrams; m^2, squared meter; IV, intravenous; ml, millilitre.
Note: Package sizes are based on those specified in the health economic model and sourced from Medicinpriser.dk to align with the expected local practice. * Average of 100 and 125 taken as average dose
Source: EMC (56); Medicinpriser.dk (53)

Table 10 Description of pemetrexed

Overview of comparator	
Generic name	Pemetrexed
ATC code	L01BA04

Overview of comparator	
Mechanism of action	Pemetrexed, is a cytotoxic medicine (a medicine that kills cells that are dividing, such as cancer cells). In the body, pemetrexed is converted into an active form that blocks the activity of the enzymes that are involved in producing 'nucleotides' (the building blocks of DNA and RNA). As a result, the active form of pemetrexed slows down the formation of DNA and RNA and prevents the cells from dividing and multiplying. The conversion of pemetrexed into its active form occurs more readily in cancer cells than in normal cells, leading to higher levels of the active form of the medicine and a longer duration of action in cancer cells. This results in the division of cancer cells being reduced, while normal cells are only slightly affected.
Method of administration	Intravenous infusion (IV)
Dosing	500 mg/m2 on Day 1, every 21 days
Dosing in the health economic model (including relative dose intensity)	500 mg/m2 on Day 1, every 21 days; mean dose intensity: 94.2%
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	• 25 mg/ml x 4 ml • 25 mg/ml x 20 ml

Abbreviations: mg, milligrams; m^2, squared meter; IV, intravenous; ml, millilitre.
Note: Package sizes are based on those specified in the health economic model and sourced from Medicinpriser.dk to align with the expected local practice
Source: EMA (57); Medicinpriser.dk (53)

3.6 Cost-effectiveness of the comparator(s)

The DMC has not recommended or completed assessment of a treatment for r/mCC in the second-line setting yet. As chemotherapy is generally accessible and represents the sole treatment option for patients with r/mCC in the second-line setting (an assessment confirmed by Danish clinicians consulted by Genmab) chemotherapy is assumed to be cost-effective and is therefore considered the appropriate comparator in the health economic model. In this context, an additional analysis appears redundant.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

OS, PFS, and clinical response (measured by objective response rate [ORR], disease control rate [DCR], time to response [TTR], and duration of response [DOR]) are relevant outcomes in this application. The efficacy outcomes are defined in Table 11 (refer to Appendix B for details).

Table 11 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS)	24 July 2023 (10.8 months)	OS is defined as the time from randomization to date of death due to any cause or censoring date, whichever occurred first	Kaplan-Meier (KM) estimates were used for analysis.
Progression-free survival (PFS)	24 July 2023 (10.8 months)	PFS is defined as the time from randomization to first documentation of PD or death due to any cause, or censoring date whichever occurred first.	RECIST v1.1 as assessed by investigator. KM estimates were used for analysis.
Objective response rate (ORR)	24 July 2023 (10.8 months)	Proportion of participants with a confirmed complete response (CR)** or partial response (PR)*** per RECIST v.1.1.	RECIST v1.1 as assessed by the investigator.
Disease control rate (DCR)	24 July 2023 (10.8 months)	Proportion of participants with a confirmed complete response (CR)**, partial response (PR)*** or stable disease (SD) **** per RECIST v.1.1.	RECIST v1.1 as assessed by the investigator.
Time-to-response (TTR)	24 July 2023 (10.8 months)	TTR is defined as the time from the randomization date to the date of the first confirmed objective response (CR** or PR*** that was subsequently confirmed)	Assessed by the investigator. Descriptive statistics.
Duration of response (DOR)	24 July 2023	DOR was defined as the time from the date of the first confirmed objective response (CR** or PR***	RECIST v1.1 as assessed by the investigator. KM estimates were used for analysis.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	(10.8 months)	that was subsequently confirmed) to the date of the first documented PD per RECIST v1.1 or death from any cause, whichever occurred first.	

* Time point for data collection used in analysis (follow up time for time-to-event measures)
** CR was defined as disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm. ***PR was defined as at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. PD: at least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.**** The minimum criteria for stable disease (SD) duration are defined as ≥ 5 weeks after the date of randomization.

Validity of outcomes

OS is considered as a key clinical endpoint in oncology trials and has long been considered the gold standard for demonstrating clinical benefit. However, reliance on OS has limitations, as it can be influenced by subsequent therapies and it might take long to gain mature data for effective therapies. PFS is another widely utilized endpoint in oncology trials. It measures the duration during which patients remain alive without disease progression (58). Unlike OS, PFS is not impacted by the effects of subsequent treatments, making it a valuable complement to OS (59).

4. Health economic analysis

As demonstrated in the innovaTV 301 trial, TV provided clinical benefit over investigator's choice (IC) of chemotherapy. As there is no preference for any single-agent chemotherapy in 2L r/mCC in clinical guidelines or amongst treating clinicians in Denmark, IC of chemotherapy is considered the SoC against which TV compares. To assess the added clinical benefit and expected treatment costs, a cost-utility analysis (CUA) was conducted.

4.1 Model structure

A semi-Markov model was developed to estimate survival and progression outcomes for TV and SoC patients using data from the innovaTV 301 trial (DCO January 2024). This model structure allows mortality risk to depend explicitly on disease state and time since progression, thereby providing a clinically plausible representation of post-progression outcomes – specifically, implementing a common post-progression mortality rate. Partitioned survival models estimate PFS and OS separately without structural constraints, while the PD health state is calculated as the area between OS and PFS. Given the absence of evidence demonstrating a stable or predictable relationship between PFS and OS in previously treated r/mCC, relying on a partitioned survival modelling structure that enforces such a relationship may be less appropriate. A semi-Markov modelling approach has also been accepted previously by the Danish Medicines

Council (DMC) in its assessment of pembrolizumab + chemotherapy ± bevacizumab in r/mCC, where the DMC noted that the available evidence did not support a clear correlation between PFS and OS (46). This supported the view that no clinical rationale existed to prefer a partitioned survival model over a state-transition model in that disease setting.

The model is comprised of three mutually exclusive health states: progression-free (PF), progressed Disease (PD), and death. All patients entered the model in the PF health state. In each weekly model cycle, the following transitions were possible:

- 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

All transition probabilities were estimated using individual patient-level data (IPD) from the innovaTV 301 trial for TTP, time from PF to death, and PPS.

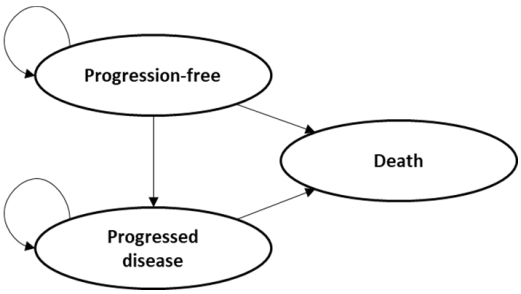


Figure 2 Three-state semi-Markov model for previously treated r/mCC

4.2 Model features

Features of the health economic model are described on a high-level in Table 12. Model features were implemented in line with the DMC methods guide (60), to comply with the assessment criteria in the Danish setting.

Table 12 Features of the economic model

Model features	Description	Justification
Patient population	Adult r/mCC patients with disease progression on or after systemic therapy	In line with EMA label (1).
Perspective	Limited societal perspective	According to DMC methods guide (60)

Model features	Description	Justification
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines(60). Based on mean age at diagnosis in innovaTV 301 trial.
Cycle length	One week	To align with treatment cycles
Half-cycle correction	Yes	Yes. According to DMC methods guide (60)
Discount rate	3.5 % for costs and effects	The DMC applies a discount rate of 3.5 % for all years. According to DMC methods guide (60)
Intervention	Tisotumab vedotin (2 mg/kg Q3W)	Intervention of interest
Comparator(s)	Chemotherapy, existing of proportions observed in innovaTV 301.	Aligned with innovaTV 301 and validated by Danish clinicians providing guidance to Genmab
Outcomes	OS, PFS, HRQoL, and safety	These outcomes capture the disease progression, HRQoL, and safety of both treatment alternatives in r/mCC.

Abbreviations: r/mCC, recurrent or metastatic cervical cancer; EMA, European Medicines Agency; DMC, Danish Medicine Council; OS, overall survival; PFS, progression-free survival; HRQoL, health-related quality-of-life; Q3W, every three weeks.

5. Overview of literature

No systematic literature reviews (SLR) were conducted, as the innovaTV 301 trial comprised the relevant head-to-head comparison against a mix of possible chemotherapies for patients with previously treated r/mCC. Clinical outcomes and HRQoL outcomes informing the health economic analysis were informed by the trial.

5.1 Literature used for the clinical assessment

This application is based on a head-to-head study with a comparison of TV versus the chemotherapy group in innovaTV 301 (i.e., topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) that is expected to be clinically equivalent to the 2L chemotherapy options in Denmark. Table 13 presents an overview of the innovaTV 301 (DCO 2023) along with additional relevant supporting materials.

Table 13 Relevant literature included in the assessment of efficacy and safety

Reference	Trial name*	NCT identifier	Dates of study	Used in comparison of*
Vergote I, González-Martín A, Fujiwara K, Kalbacher E, Bagaméri A, Ghamande S, et al. Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer. N Engl J Med. 2024;391(1):44-55.(14)	innovaTV 301	NCT04697628	Start: 22/02/2021 Completion: 24/07/2023 Data cut-off: 24/07/2023 Future data cut expected in 2026	TV vs. SoC for adult patients with r/mCC) with disease progression on or after systemic therapy.
InnovaTV 301 Clinical study report [Data on file]. 2023.	innovaTV 301	NCT04697628	Start: 22/02/2021 Completion: 24/07/2023 Data cut-off: 24/07/2023 Not prespecified data cut: January 2024 Future data cut expected in 2026	TV vs. SoC for adult patients with r/mCC) with disease progression on or after systemic therapy.

Abbreviations: r/mCC, recurrent or metastatic cervical cancer; SoC, standard of care; TV, Tisotumab Vedotin

5.2 Literature used for the assessment of health-related quality of life

The HRQoL of patients in this health economic analysis was informed by the collected EuroQol-5 Dimension-5 Level (EQ-5D-5L) in innovaTV 301. No literature review was conducted to identify HRQoL information from literature.

Table 14 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economic model

No SLR was conducted to identify literature used for inputs to the health economic model. All clinical and HRQoL parameters and transition were derived directly from innovaTV 301 (DCO Jan 2024). Cost parameters were sourced according to DMCs costing guidelines (61).

Table 15 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of TV compared to chemotherapy for previously treated r/mCC

6.1.1 Relevant studies

This application builds on the innovaTV 301 head-to-head trial (NCT04697628). InnovaTV 301, is a phase 3, randomised, open-label study comparing TV to chemotherapy in subjects with 2L or third line (3L) recurrent or metastatic cervical cancer (r/mCC). Eligible subjects were randomised 1:1 to either TV 2.0 mg/kg Q3W or 1 out of 5 chemotherapy choices (topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed). No crossover between the 2 treatment arms was permitted. Additionally, the efficacy and safety of TV were explored in the innovaTV 204 phase II trial of TV (62), with findings broadly consistent with those observed in innovaTV 301. Response and disease control rates reported from that study showed a higher effectiveness of TV, with an ORR of 24% and a DCR of 72%. A median OS of 12.1 months and a median PFS of 4.2 months were reported. However, given the single-arm, phase II design of innovaTV 204, these data were not incorporated into the present comparative assessment of TV versus SoC.

The innovaTV 301 analysis was a prespecified interim analysis of OS conducted by an independent data monitoring committee (IDMC) based on a DCO of 24 July 2023, at which time 263 OS events had occurred. At this interim analysis, the IDMC determined that the prespecified efficacy boundary for OS had been crossed. In accordance with the study protocol and the IDMC recommendation, this interim analysis was therefore declared final for the OS endpoint and represents the primary and sole decision-relevant DCO for OS in the innovaTV 301 study. The results of this prespecified final analysis were subsequently published in July 2024 in the *New England Journal of Medicine* (14).

Following this, a subsequent, non-prespecified DCO with a DCO of 16 January 2024 was generated and made available to the European Medicines Agency (EMA) as part of the regulatory review package. This later data cut was not requested by the EMA, was not prespecified in the study design, and did not form the basis of the regulatory approval of TV. Because the prespecified efficacy boundary for OS had already been crossed at the interim analysis (DCO 24 July 2023), the OS analysis was formally concluded at that time. Clinical results from the 2023 DCO are presented in this dossier. An overview of the innovaTV 301 study is presented in Table 12. Further details are provided in Appendix A.

As mentioned in Section 3.3, there is no defined comparator in Denmark besides treatment with single-agent chemotherapy. Hence, the effectiveness of chemotherapy agents used in innovaTV 301 (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) are expected to be clinically equivalent to the chemotherapies offered in Denmark.

Table 16 Overview of study design for studies included in the comparison

innovaTV 301, NCT04697628	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Vergote I, González-Martín A, Fujiwara K, Kalbacher E, Bagaméri A, Ghamande S, et al. Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer. N Engl J Med. 2024;391(1):44-55.(14)	Randomized phase III / open-label / active comparator-control	The study was initiated February 2021, and the primary completion was in July 2023. The median survival follow-up time for this data-cut is 10.8 months. The study is still on-going, and a final analysis is planned when all OS events have occurred; this is expected in 2026	Adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy	Tisotumab vedotin: 2.0 mg/kg every 3 weeks (Q3W)	Investigator's choice of one chemotherapy treatments: Topotecan: 1 or 1.25 mg/m2 intravenous (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	Primary outcome: • Overall survival (OS) [Median follow-up 10.8 months] Secondary outcomes: • Progression Free Survival (PFS) as Assessed by Investigator [Median follow-up 10.8 months] • Confirmed Objective Response Rate (ORR) as Assessed by Investigator [From randomization to the clinical cutoff date. Maximum follow up was 25 months] • Time-to-Response (TTR) as Assessed by the Investigator [From randomization to the clinical cutoff date. Maximum follow up was 25 months] • Duration of Response (DOR) by Investigator Assessment [From randomization to the clinical cutoff date. Maximum follow up was 25 months] • Number of Participants with Treatment Emergent Adverse Events (TEAEs) [From start of treatment up to 30 days after last dose of study treatment (up to 25 months)]

innovaTV 301, NCT04697628	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
					Pemetrexed: 500 mg/m2 IV on Day 1, every 21 days	• EuroQOL Five Dimensions Five Level (EQ-5D-5L) Index Score [From start of treatment until end of follow-up. Data cutoff July 2023] • EQ-5D Visual Analog Scale (VAS) Scores [From start of treatment until end of follow-up. Data cutoff July 2023] • European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Total Score [From start of treatment until end of follow-up. Data cutoff July 2023]] • EORTC Quality of Life Questionnaire Cervical Cancer Module (QLQ-CX24) Total Scores [From start of treatment until end of follow-up. Data cutoff July 2023]] All follow-up periods were predefined.

6.1.2 Comparability of studies

Not relevant, as comparison based on head-to-head study innovaTV 301.

6.1.2.1 Comparability of patients across studies

A summary of demographics and baseline characteristics of the study population is presented in Table 17. The median age was 50 years (range 26 to 80 years). Overall, 83.4% of subjects in the TV arm and 83.5% of subjects in the chemotherapy arm were <65 years of age. The racial and ethnic diversity of subjects in this study reflects the global footprint of the study: 35.6% vs 36.1% of subjects were Asian and 48.2% vs 49.0% of subjects were white in the TV and chemotherapy arms, respectively.

Demographic and baseline characteristics were well balanced between the TV and chemotherapy arms. A total of 451 subjects (89.8%) had metastatic disease at baseline, while the rest had pelvic recurrent disease (51 subjects, 10.2%). Best response to last systemic regimen was reported as CR in 44 subjects (8.8%), PR in 115 subjects (22.9%), SD in 85 subjects (16.9%), PD in 169 subjects (33.7%) and unknown in 83 subjects (16.5%)). The distribution of histology subtypes in the study was representative of the natural distribution of subtypes in a 2L and later population of subjects with r/mCC (National Cancer Institute 2020 (63)) and included squamous cell carcinoma (63.1%), adenocarcinoma (31.9%), and adenosquamous carcinoma (5.0%). Overall, this distribution appears to be consistent with the broader literature described in Section 3.1.3.

Prior treatment patterns were highly comparable between the two study arms, with no meaningful differences observed. An overview of prior treatments is summarised in Appendix K.

Table 17 Baseline characteristics of patients in innovaTV 301 (DCO 2023)

	Tisotumab vedotin (N253)	Chemotherapy[a] (N=249)	All patients (N=502)
Median age (range)	51 (26-80)	50 (27-78)	50 (26-80)
Age Category, n (%)			
<65 years	211 (83.4)	208 (83.5)	419 (83.5)
≥65 years	42 (16.6)	41 (16.5)	83 (16.5)
Geographic 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)

	Tisotumab vedotin (N253)	Chemotherapy[a] (N=249)	All patients (N=502)
Other	46 (18.2)	43 (17.3)	89 (17.7)
Race, n (%)			
White	122 (48.2)	122 (49.0)	244 (48.6)
Asian	90 (35.6)	90 (36.1)	180 (35.9)
American Indian or Alaska Native	7 (2.8)	7 (2.8)	14 (2.8)
Black or African American	4 (1.6)	6 (2.4)	10 (2.0)
Other	2 (0.8)	1 (0.4)	3 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)
Not Reportable	19 (7.5)	17 (6.8)	36 (7.2)
Unknow	8 (3.2)	6 (2.4)	14 (2.8)
Ethnicity, n (%)			
Not of Hispanic or Latino/a, or Spanish Origin	176 (69.6)	177 (71.1)	353 (70.3)
Hispanic or Latino/a, or of Spanish Origin	52 (20.6)	50 (20.1)	102 (20.3)
Not Reportable	19 (7.5)	17 (6.8)	36 (7.2)
Unknown	6 (2.4)	5 (2.0)	11 (2.2)
Histology type			
Squamous cell carcinoma	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)
Baseline ECOG performance-status score[b] – no. (%)			

	Tisotumab vedotin (N253)	Chemotherapy[a] (N=249)	All patients (N=502)
0	137 (54.2)	136 (54.6)	273 (54.4)
1	116 (45.8)	113 (45.4)	229 (45.6)
Disease status at study entry, n (%)			
Recurrent	27 (10.7)	24 (9.6)	51 (10.2)
Metastatic	226 (89.3)	225 (90.4)	451 (89.8)
Prior bevacizumab administration[b], n (%)			
Yes	164 (64.8)	157 (63.1)	321 (63.9)
No	89 (35.2)	181 (36.9)	181 (36.1)
Prior anti-PD-[L]1 administration[b,c], n (%)			
Yes	71 (28.1)	67 (26.9)	138 (27.5)
No	182 (71.9)	182 (73.1)	364 (72.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1; SD, standard deviation
[a]The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
[b]Baseline disease characteristics are based on the EDC records.
[c]Note that accrual of subjects previously treated with anti-PD-[L]1 began after Protocol Amendment #3 to account for the shift in the treatment paradigm.
Source: InnovaTV 301 Clinical study report (data on file) (51); Vergote et al. (14)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

As discussed in Section 3.2, r/mCC patients are rare in Denmark, and the characteristics of the patients are not well studied in the existing literature. It is therefore assumed that the innovaTV 301 trial is the best-available information to reflect the Danish patients' characteristics.

Table 18 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (innovaTV 301 trial global population (51))	Value used in health economic model (innovaTV 301 trial global population (51))
Age, years	51.44	51.44
Patient weight, kg	63.31	63.31

BSA, m²	1.65	1.65

Abbreviations: BSA, body surface area; kg, kilograms

6.1.4 Efficacy – results per innovaTV 301

In the following sections, a summary of key efficacy findings obtained from the innovaTV 301 study included in the comparative analysis is provided. The innovaTV 301 data presented in this assessment is based on the primary analysis (cut-off date 24 July 2023). Detailed information about the results of all outcomes included in the comparative analysis alongside the method for each analysis are provided in Appendix B. For HRs, graphical checks of the proportional hazard assumption are also provided in Appendix B.

Patient disposition

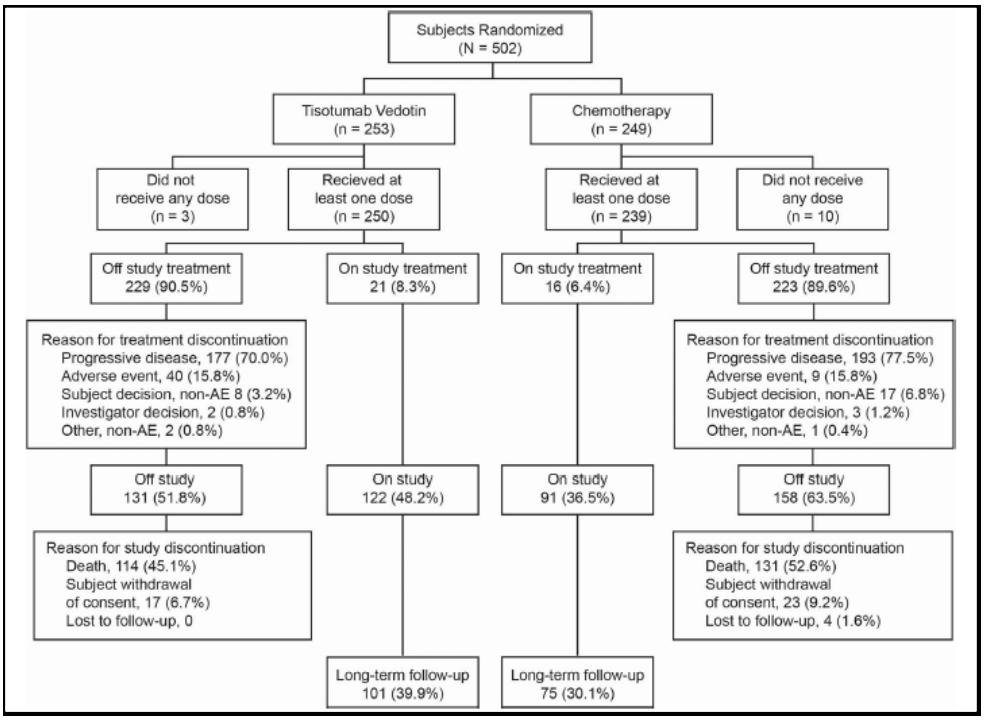
Of the 502 randomized subjects, 253 subjects were randomized to receive TV, and 249 subjects were randomized to receive chemotherapy (see Figure 3). In the TV arm, 250 subjects (98.8%) received at least 1 dose of TV, and 239 subjects (96.0%) received at least 1 dose of treatment in the chemotherapy arm. Subjects in the chemotherapy arm received topotecan (19 subjects, 7.9%), vinorelbine (17 subjects, 7.1%), gemcitabine (109 subjects, 45.6%), irinotecan (14 subjects, 5.9%), or pemetrexed (80 subjects, 33.5%).

Three subjects did not receive any dose of TV treatment, all due to sudden decline in health or death prior to C1D1. Ten subjects who were randomized to the chemotherapy arm did not receive treatment. Of these 10, 5 subjects withdrew consent prior to C1D1 because they did not wish to receive chemotherapy, 2 subjects were withdrawn prior to C1D1 in order to receive radiotherapy instead of investigator's choice chemotherapy, and 3 subjects did not receive drug due to sudden decline in health or death prior to C1D1.

At the data cut-off for the primary efficacy analysis (24 July 2023), 176 subjects (35.1%) remained in long-term follow up: 101/253 subjects (39.9%) in the TV arm and 75/249 subjects (30.1%) in the chemotherapy arm. Reasons for treatment discontinuation included:

- Progressed disease: 177 subjects (70.0%) in the TV arm vs 193 subjects (77.5%) in the chemotherapy arm
- Adverse events: 40 subjects (15.8%) in the TV arm vs 9 subjects (3.6%) in the chemotherapy arm
- Subject decision: 8 subjects (3.2%) in the TV arm vs 17 subjects (6.8%) in the chemotherapy arm.

Of the subjects who were off the study, 245 had died per the EOS CRF (114 [45.1%] in the TV arm vs 131 subjects [52.6%] in the chemotherapy arm), 40 had withdrawn consent (17 [6.7%] in the TV arm and 23 [9.2%] in the chemotherapy arm),and 4 subjects (1.6%) in the chemotherapy arm were lost to follow-up.



Abbreviations: AE, adverse event.
Deaths come from the End of Study CRF and may not include subjects whose death was documented on the Survival Status CRF.
Source: InnovaTV 301 Clinical study report (data on file) (51)

Figure 3 Patient distribution in innovaTV 301

InnovaTV 301 was initiated in 2018, at a time when anti-PD-L1 therapy had not yet become part of the therapeutic landscape. However, the treatment landscape evolved substantially over the course of the trial.

To reflect the changing treatment landscape, an amendment of the of the protocol was implemented on April 6, 2022. This amendment mandated previous treatment with an anti–PD-1 or anti–PD-L1 agent in patients who were eligible for and had access to these treatments after the approval of pembrolizumab in combination with chemotherapy for first-line treatment of recurrent cervical cancer. Patients should have received one or two previous systemic therapies for recurrent or metastatic cervical cancer, not including chemotherapy in an adjuvant, maintenance, or neoadjuvant context or in combination with radiation therapy.

Datasets analysed

The primary and secondary endpoints included in this application used the ITT analysis set. The ITT analysis set comprises all 502 randomized subject, 489 subjects were included in the safety analysis set, and 434 subjects were included in the patient reported outcome (PRO) analysis set (Table 19).

The primary efficacy endpoint is OS assessed by stratified log-rank test. The secondary efficacy endpoints include PFS and confirmed ORR based on RECIST v1.1 as assessed per investigator assessment.

Overall survival and progression-free survival end points were estimated with the use of the Kaplan–Meier method, with 95% confidence intervals presented with the medians and hazard ratios (HR), according to treatment group. A stratified Cox model was used to estimate hazard ratios and 95% confidence intervals. The proportional-hazards assumption for treatment groups was assessed using a plot of the log of the negative log of the Kaplan–Meier estimate of the survival function against the log of time by treatment group, as well as a plot of Schoenfeld residuals over time.

The 95% confidence intervals reported with the hazard ratios have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Overall survival was calculated by censoring survival time at the last date patients were known to be alive for those who had not died at the time of the analysis.

Table 19 Summary of analysis sets

Analysis set	Description
ITT Analysis Set	ITT set includes all randomised subjects. Subjects are included in the treatment group assigned at randomization regardless of any actual treatment received.
Safety Analysis Set	Safety set includes all randomized subjects who received at least 1 dose of study treatment (TV or chemotherapy*).
PRO Full Analysis Set	The PRO FAS set includes all randomized subjects who received any amount of study treatment and have completed baseline and at least 1 post-baseline PRO assessment.

Abbreviations: ITT, intention to treat; PRO, patient reported outcome; TV, tisotumab vedotin
*The included chemotherapies were topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

Extent of exposure

In innovatv301, patients on TV received treatment for a longer time than those on chemotherapy. Median duration of exposure to TV was 3.65 months (range 0.4 to 18.9). A median of 5.0 doses was received (range 1 to 26). Median duration of exposure to chemotherapy was 2.76 months (range 0.1 to 20.9) with a median of 4.0 cycles (range 1 to 30). Treatment administration is summarized in Table 20.

Table 20 Summary of treatment administration (Safety analysis set, DCO 2023)

	Tisotumab Vedotin (N=250)	Chemotherapy [a] (N=239)
Number of subjects receiving at least one dose of treatment, n (%)	250 (100)	239 (100)
Duration of exposure (months) [b]		
n	250	239

Mean (STD)	[redacted]	[redacted]
Median	3.65	2.76
Min, max	0.4, 18.9	0.1, 20.9
Number of cycles received per subject [b]		
n	250	239
Mean (STD)	[redacted]	[redacted]
Median	5.0	4.0
Min, max	1, 26	1, 30

Abbreviations: STD, standard deviation
[a] The included chemotherapies were topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
[b] Duration of exposure (months) = (end date of treatment - first dose date + 1) / 30.4375. End date of treatment defined as min (last dose date, start of subsequent cancer-related therapy, end of treatment date, date of death, analysis cut-off date), where last dose date is last infusion date + 20 for tisotumab vedotin, pemetrexed and irinotecan, last infusion date + 16 for topotecan, and last infusion date + 13 for vinorelbine and gemcitabine
[c] Cycle with any amount of study drug received
Source: InnovaTV 301 Clinical study report (data on file) (51); DCO 24 July 2023

6.1.4.1 Overall survival [DCO: 24 July 2023]

The pre-specified interim OS analysis for innovaTV 301 was conducted by an independent data monitoring committee (IDMC) based on a data cutoff date of 24 July 2023, at which time 263 OS events had been observed. The IDMC determined that OS crossed the pre-specified efficacy boundary at this interim analysis; as such, this analysis is considered the final OS analysis.

At the time of the primary OS analysis, with a median OS follow-up time of 10.8 months (95% CI: 10.3, 11.6), 123 subjects (48.6%) in the TV arm and 140 subjects (56.2%) in the chemotherapy arm had died (see Table 21).

OS was significantly prolonged in the TV arm versus the chemotherapy arm, with a 30% reduction in the risk of death (stratified HR = 0.70 [95% CI: 0.54, 0.89]; p = 0.0038). The median OS was 11.5 months (95% CI: 9.8, 14.9) for subjects in the TV arm vs 9.5 months (95% CI: 7.9, 10.7) for subjects in the chemotherapy arm.

A Kaplan-Meier plot of OS is presented in Figure 4.

Table 21 Summary of overall survival (ITT analysis set, DCO 2023)

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)

Number of deaths, n (%)	123 (48.6)	140 (56.2)
Stratified hazard ratio[b, c] (95% CI)	0.70 (0.54, 0.89)	
Stratified log-rank p-value[c,d]	0.0038	
Median OS (months) (95% CI)[e]	11.5 (9.8, 14.9)	9.5 (7.9, 10.7)
Q1, Q3	6.7, 21.3	4.6, 16.3
Min, Max[f]	0.4, 25.0	0.0+, 21.9+
Median duration of follow-up (months) (95% CI)	10.8 (10.2, 12.1)	10.8 (10.2, 12.1)
Estimated OS rate[e] at		
6 months (95% CI)[e]	81.4 (75.9, 85.7)	66.9 (60.5, 72.5)
12 months (95% CI)[e]	48.7 (41.0, 55.8)	35.3 (28.0, 42.7)
18 months (95% CI)[e]	33.1 (24.2, 42.2)	23.5 (15.8, 32.2)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; Max, maximum; Min, minimum; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

[a]The included chemotherapies were 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 randomization.

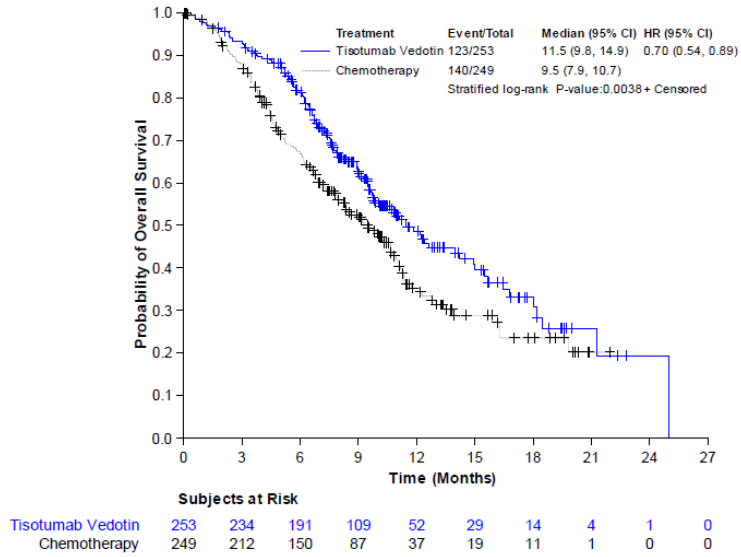
[d]Two-sided p-value calculated from stratified log-rank test.

[e]Median is estimated using Kaplan-Meier method and 95% CI is calculated using the complimentary log-log transformation method (Collett 1994 (64)).

[f]'+' means the observed time is from a censored subject.

The threshold for statistical significance is 0.0226 (2-sided).

Source: InnovaTV 301 Clinical study report (data on file) (51); Vergote et al. (14)



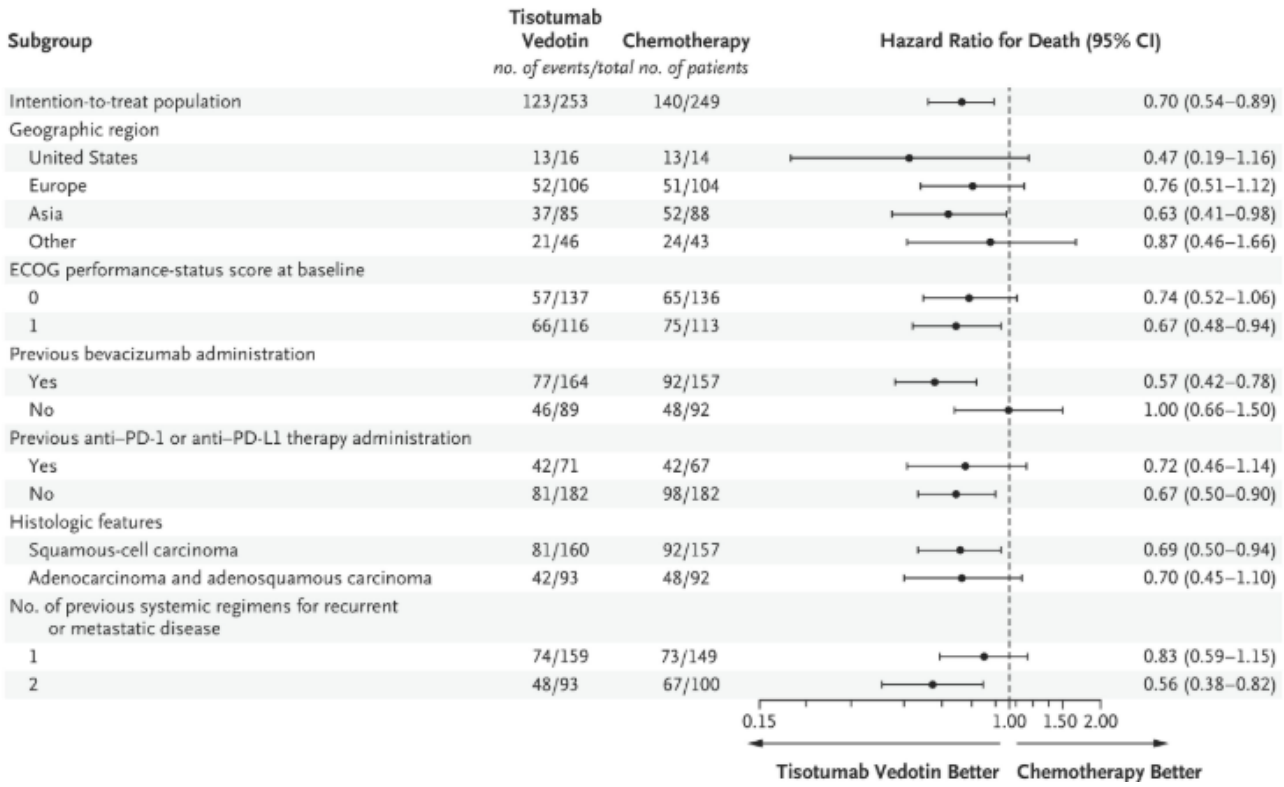
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.
HR is computed from the stratified Cox proportional hazards model using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.
Two-sided p-value based on stratified log-rank test.
Source: InnovaTV 301 Clinical study report (data on file) (51); Vergote et al. (14)

Figure 4 Kaplan-Meier plot of overall survival (ITT analysis set, DCO 2023)

The hazards of death in TV and chemotherapy were analysed visually in the KM plot (Figure 4), the log-cumulative hazard plot, and Schoenfeld residual plots (see Appendix B, Figure 24; Figure 25). From the KM plot, the OS of both arms seem relatively proportional. Notably, the OS of TV and chemotherapy converge around month 21, where numbers at risk are very low (below five, see Figure 4 above) and the uncertainty in the estimates is very high. Visually inspection of the log-cumulative hazard plot shows noise in the first weeks with very few observations, but the hazards are deemed to be proportional over time where noise becomes less, and more observations are present (see Appendix B; Figure 24). This conclusion is confirmed by the Schoenfeld residuals plot of OS, where the residuals seem to be randomly distributed around zero over time, indicating no change in the relative hazard (see Appendix B; Figure 25).

Subgroup

In InnovaTV 301, prespecified subgroup analyses were exploratory in nature and were conducted for the primary endpoint (OS) and key secondary endpoint of PFS. A forest plot of HRs of OS by subgroup is presented in Figure 5. OS benefit for the TV arm was observed regardless of prior PD-(L)1 therapy, histology (squamous carcinoma vs adenocarcinoma/adenosquamous carcinoma), or number of prior recurrent/metastatic systemic regimens.



Abbreviations: CI, confidence interval; CT, chemotherapy; 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; TV=tisotumab vedotin. **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-PD-1 or anti-PD-L1 administration: yes vs no) at randomization. Subgroup is defined based on eCRF records. If the subgroup is defined by a randomization stratification factor, Cox model is stratified for the randomization stratification factors other than the one that defines the subgroup.
Source: Vergote et al.(14)

Figure 5 Forest plot of overall survival (ITT analysis set, DCO 2023)

6.1.4.2 Progression-free survival [DCO: 24 July 2023]

A total of 198 subjects (78.3%) in the TV arm and 194 subjects (77.9%) in the chemotherapy arm had disease progression per investigator assessment or had died (Table 22). PFS was superior for the TV arm vs the chemotherapy arm with a 33% reduction in the risk of disease progression or death (stratified HR=0.67 [95% CI: 0.54, 0.82], p <0.0001) (Table 22). The median PFS as assessed by investigator was 4.2 months (95% CI: 4.0, 4.4) in the TV arm compared to 2.9 months (95% CI: 2.6, 3.1) in the chemotherapy arm. A Kaplan-Meier plot of PFS per investigator assessment is displayed in Figure 6.

The majority of subjects in the TV arm were censored due to no documented disease progression and were still on study (61.8%). In the chemotherapy arm, the most common reasons for censoring subjects were no documented disease progression and still on study (36.4%) and new anti-cancer treatment started before PD or death was observed (32.7%). Reasons for censoring are summarized in Appendix L, Table 76.

Table 22 Summary of PFS per investigator assessment (ITT analysis set, DCO 2023)

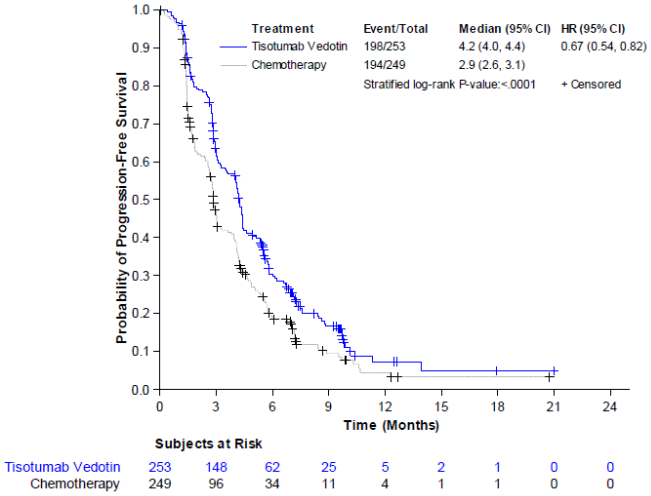
	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Subjects with PFS event, n (%)	198 (78.3)	194 (77.9)
Stratified hazard ratio[b, c] (95% CI)	0.67 (0.54, 0.82)	
Stratified log-rank p-value[c,d]	<0.0001	
Median PFS (months) (95% CI)[e]	4.2 (4.0, 4.4)	2.9 (2.6, 3.1)
Q1, Q3	2.7, 7.1	1.4, 5.4
Min, Max[f]	0.0+, 21.0+	0.0+, 20.8+
Estimated PFS rate[e] at		
3 months (95% CI)[e]	62.7 (56.2, 68.4)	45.8 (39.1, 52.2)
6 months (95% CI)[e]	30.4 (24.5, 36.5)	18.9 (13.8, 24.7)
9 months (95% CI)[e]	16.6 (11.7, 22.3)	9.4 (5.5, 14.5)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; Max, maximum; Min, minimum; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival.

[a]The 5 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 randomization.
[d]Two-sided p-value calculated from stratified log-rank test.
[e]Median is estimated using Kaplan-Meier method and 95% CI is calculated using the complimentary log-log transformation method (Collett 1994).
[f]'+' means the observed time is from a censored subject.
PFS hypothesis testing will be conducted only when the OS result crosses efficacy boundary. The threshold for statistical significance is 0.0453 (2-sided).
Source: InnovaTV 301 Clinical study report (data on file) (51); Vergote et al. (14)



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; PFS, progression-free survival. **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-PD-1 or anti-PD-L1 administration: yes vs no) at randomization. Two-sided p-value based on stratified log-rank test.
Source: InnovaTV 301 Clinical study report (data on file) (51); Vergote et al. (14)

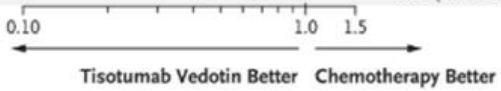
Figure 6 Kaplan-Meier Plot of PFS per investigator assessment (ITT analysis set)

The hazards of progression or death in TV and chemotherapy were also analysed visually in the KM plot (Figure 6), the log-cumulative hazard plot, and Schoenfeld residual plots (see Appendix B, Figure 26; Figure 27). From the KM plot, the PFS of both arms seem relatively proportional (see Figure 6, above). When visually assessing the log-cumulative hazard plot show, the hazards are deemed to be proportional over time. This conclusion is confirmed by the Schoenfeld residuals plot of OS, where the residuals (see Appendix B, Figure 26) seem to be randomly distributed around zero over time, indicating no change in the relative hazard (see Appendix B, Figure 27).

Subgroup

As previously noted, prespecified exploratory subgroup analyses were performed for the PFS endpoint in InnovaTV 301. A forest plot of HR for PFS by subgroup is presented in Figure 7. Generally, the subgroup analysis demonstrated a PFS benefit consistent with the overall population (i.e., ITT population). PFS benefit was similar in subjects in the TV arm regardless of prior anti-PD-(L)1 exposure, prior bevacizumab, ECOG status, and other factors.

Subgroup	Tisotumab Vedotin	Chemotherapy	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
Intention-to-treat population	198/253	194/249	0.67 (0.54–0.82)
Geographic region			
United States	13/16	8/14	0.37 (0.12–1.10)
Europe	86/106	81/104	0.71 (0.51–0.97)
Asia	69/85	73/88	0.60 (0.43–0.85)
Other	30/46	32/43	0.76 (0.44–1.30)
ECOG performance-status score at baseline			
0	104/137	106/136	0.70 (0.53–0.92)
1	94/116	88/113	0.62 (0.46–0.84)
Previous bevacizumab administration			
Yes	130/164	122/157	0.59 (0.46–0.76)
No	68/89	72/92	0.83 (0.59–1.16)
Previous anti–PD-1 or anti–PD-L1 therapy administration			
Yes	53/71	50/67	0.66 (0.44–0.99)
No	145/182	144/182	0.67 (0.53–0.85)
Histologic features			
Squamous-cell carcinoma	124/160	122/157	0.71 (0.55–0.93)
Adenocarcinoma and adenosquamous carcinoma	74/93	72/92	0.63 (0.44–0.89)
No. of previous systemic regimens for recurrent or metastatic disease			
1	123/159	119/149	0.68 (0.52–0.88)
2	74/93	75/100	0.66 (0.47–0.92)



Abbreviations: CI, confidence interval; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TV, tisotumab vedotin. **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-PD-1 or anti-PD-L1 administration: yes vs no) at randomization. Subgroup is defined based on eCRF records. If the subgroup is defined by a randomization stratification factor, Cox model is stratified for the randomization stratification factors other than the one that defines the subgroup.
Source: Vergote et al. (14)

Figure 7 Forest plot of PFS per investigator assessment (ITT analysis set

6.1.4.3 Clinical response [DCO: 24 July 2023]

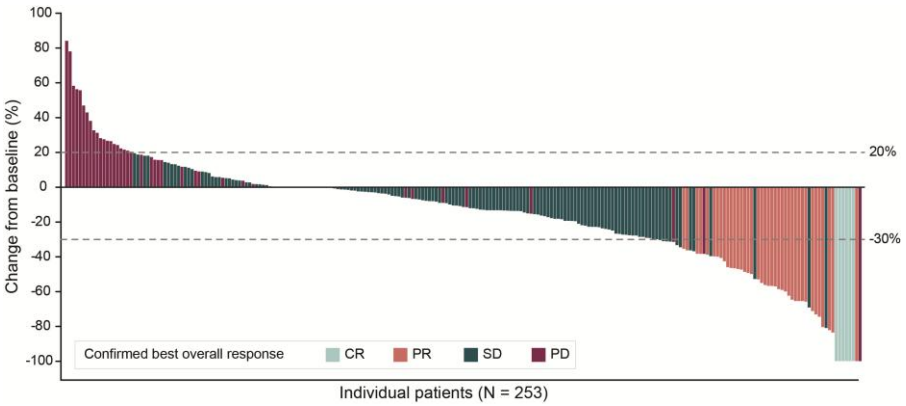
Treatment with TV resulted in a confirmed ORR as assessed by investigator which was significantly higher compared to that in the chemotherapy arm (17.8% vs 5.2%; OR, 4.0; 95% CI: 2.1, 7.6; P<0.0001) (Table 23). The confirmed overall response was CR in 6 subjects (2.4%) in the TV arm vs 0 subjects in the chemotherapy arm and PR in 39 subjects (15.4%) in the TV arm vs 13 subjects (5.2%) in the chemotherapy arm. Overall response of SD was reported in 147 subjects (58.1%) in the TV arm vs 132 subjects (53.0%) in the chemotherapy arm. Disease control rate (DCR), defined as the sum of CR, PR, and SD, was 75.9% in the TV arm vs 58.2% in the chemotherapy arm.

As shown in Figure 8, approximately 75% of patients in the TV arm experienced a clinical response measured by CR, PR, or SD. In contrast, Figure 9 depicts the corresponding changes in tumour burden observed in the chemotherapy arm, where a smaller proportion of patients (i.e., nearly 35%) achieved a clinical response.

Table 23 Clinical response per investigator assessment (ITT analysis set)

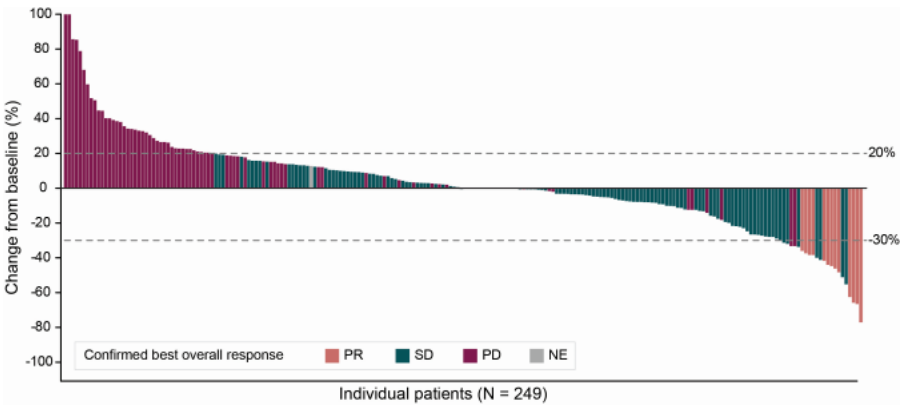
	Tisotumab Vedotin (N=253)	Chemotherapy [a] (N=249)
Clinical response components, n(%)		
Complete response (CR)	6 (2.4)	0
Partial response (PR)	39 (15.4)	13 (5.2)
Stable disease (SD)	147 (58.1)	132 (53.0)
Objective response rate (CR+PR)[b], n (%)	45 (17.8)	13 (5.2)
95% CI[c] for objective response rate	(13.3, 23.1)	(2.8, 8.8)
Stratified Odds Ratio (95% CI)[d]	4.0 (2.1, 7.6)	-
Stratified CMH p-value [d]	<0.0001	-
Disease control rate (CR+PR+SD), n (%)	192 (75.9)	145 (58.2)
95% CI[c] for disease control rate	(70.1, 81.0)	(51.8, 64.4)

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ECOG, Eastern Cooperative Oncology Group; ITT,intent-to-treat; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival.
[a] The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
[b] Objective response is confirmed CR or PR according to RECIST 1.1.
[c] Two-sided 95% exact CI, computed using the Clopper-Pearson method (Clopper 1934).
[d] Cochran-Mantel-Haenszel method controlling for 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 randomization.
ORR hypothesis testing will be conducted only when the OS result crossed efficacy boundary and PFS result also crossed efficacy boundary. The threshold for statistical significance is 0.05 (2-sided).
Source: InnovaTV 301 Clinical study report (data on file) (51); Vergote et al. (14)



Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; SD, stable disease
Source: Data on file (65)

Figure 8 Visual representation of clinical response from the innovaTV 301 trial, tisotumab vedotin



Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; SD, stable disease
Source: Data on file (65)

Figure 9 Visual representation of clinical response from the innovaTV 301 trial, chemotherapy

The median time to achieve an objective response per investigator assessment (i.e., TTR) was 1.58 months (range 1.2 to 4.5 months) for the TV arm vs 1.74 months (range 1.2 to 3.9 months) in the chemotherapy arm (Appendix B, Table 60), indicating antitumor activity within the first 2-3 cycles of treatment with TV.

Median DOR in the TV arm was 5.3 months (95% CI: 4.2, 8.3) as assessed by investigator. Median DOR in the chemotherapy arm was 5.7 months (95% CI: 2.8, -) (Appendix B, Table 60).

7. Comparative analyses of efficacy

Not applicable as comparison between TV and Danish clinical practice is possible with innovaTV 301.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

Table 24 present the results from the comparative analyses of TV vs. chemotherapy derived from the head-to-head trial: innovaTV 301 (NCT04697628).

Table 24 Results from the comparative analysis of tisotumab vedotin vs. investigators choice in innovaTV 301 (DCO 2023)

Outcome measure (median follow-up 10.8 months)	Tisotumab vedotin (N=253)	Chemotherapy* (N=249)	Result
OS	Median: 11.5 months (95% CI: 9.8-14.9)	Median: 9.5 months (95% CI: 7.9-10.7)	**HR: 0.70** (95% CI: 0.54–0.89) p-value: 0.004
PFS per investigator assessment by RECIST 1.1	Median: 4.2 months (95% CI: 4.0-4.4)	Median: 2.9 months (95% CI: 2.6-3.1)	**HR: 0.67** (95% CI: 0.54–0.82) p-value: <0.001
ORR per investigator assessment by RECIST 1.1 (%)	45/253 (17.8 [95% CI: 13.3-23.1])	13/249 (5.2 [95% CI: CI, 2.8-8.8])	Absolute risk: 12.6% Relative risk: **OR: 4.0** (95% CI: 2.1-7.6) p-value: <0.001
TTR per investigator assessment	Median: 1.6 months (95 % CI: 1.2-4.5)	Median: 1.7 months (95% CI: 1.2-3.9)	N/A

Outcome measure (median follow-up 10.8 months)	Tisotumab vedotin (N=253)	Chemotherapy* (N=249)	Result
DOR per investigator assessment by RECIST 1.1	Median: 5.3 months (95% CI: 4.2-8.3)	Median: 5.7 months (95% CI: 2.8-not reached)	N/A

Abbreviations: CI, confidence interval; DOR, duration of response; HR, hazard ratio; OR, odds ratio: ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTR, Time-to-Response
Note: *The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Source: InnovaTV 301 Clinical study report (data on file) (51); Vergote et al. (14)

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

There are two data cuts available from the InnovaTV 301 trial comprising the primary analysis and an ad-hoc follow-up analysis. The primary analysis was published in July 2024 in the New England Journal of Medicine by Vergote et al. (14). 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.

Transition probabilities were estimated using IPD from the innovaTV 301 trial (DCO: 16 January 2024, median follow-up [redacted] For transitions from PF (i.e., PF to PD and PF to 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 to Death), an exponential model was fitted to pooled PPS data from both arms, assuming a constant hazard. This pooled approach was used beyond month 12, while treatment-specific observed OS was applied during the first 12 months in both arms (details described Section 8.4).

8.1.1 Extrapolation of efficacy data

Transition probabilities starting from the PF state were estimated using the parametric multistate modelling approach described by Williams et al. (2017a & 2017b) (66, 67). 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, generalized gamma, and gamma

distributions. Within each weekly cycle of the model, the probability of each of these transitions were 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 (68). 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).

8.1.1.1 Extrapolation of transition from PF to PD

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 (AIC) and Bayesian information criterion (BIC) values
- Assessment of the underlying hazard functions over time and clinical plausibility of hazard assumptions

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

Table 25 Summary of assumptions associated with extrapolation of PF to PD

Method/approach	Description/assumption
Data input	innovaTV 301 (DCO Jan 2024)
Model	Seven parametric distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, generalized gamma, and gamma distributions
Assumption of proportional hazards between intervention and comparator	No proportional hazards assumed – separate survival modelling.
Function with best AIC fit	TV: Generalized gamma Chemotherapy: Generalized gamma
Function with best BIC fit	TV: Generalized gamma Chemotherapy: Generalized gamma
Function with best visual fit	No clear preference.

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	TV: Generalized gamma Chemotherapy: Generalized gamma
Validation of selected extrapolated curves (external evidence)	No external evidence available for TTP survival in r/mCC.
Function with the best fit according to external evidence	No external evidence available for TTP survival in r/mCC.
Selected parametric function in base case analysis	TV: Generalized gamma Chemotherapy: Generalized gamma
Adjustment of background mortality with data from Statistics Denmark	Yes, as per DMC guidelines (60)
Adjustment for treatment switching/cross-over	No, not applicable.
Assumptions of waning effect	No treatment waning included.
Assumptions of cure point	No.

Abbreviations: DCO, data cut-off; r/mCC, recurrent or metastatic cervical cancer; TV, tisotumab vedotin; DMC, Danish Medicine Council; TTP, time-to-progression.

The most appropriate parametric distribution for the transition of PF to PD – based on time-to-progression data from innovaTV 301 – was generalized gamma for both TV and chemotherapy arms. Choice of distribution, statistical fits, and smoothed hazards plots are included in Appendix D.1.

Figure 10 Observed time-to-progression and extrapolation of PF to PD (tisotumab vedotin arm)

Figure 11 Observed time-to-progression and extrapolation of PF to PD (chemotherapy arm)

8.1.1.2 Extrapolation of transition from PF to death

Transition probabilities starting from the PF state to death were estimated as described in 8.1.1.1.

Table 26 Summary of assumptions associated with extrapolation of PF to death

Method/approach	Description/assumption
Data input	innovaTV 301 (DCO Jan 2024)
Model	Seven parametric distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, generalized gamma, and gamma distributions
Assumption of proportional hazards between intervention and comparator	No proportional hazards assumed – separate survival modelling.
Function with best AIC fit	TV: Gompertz Chemotherapy: Log-normal
Function with best BIC fit	TV: Gompertz Chemotherapy: Exponential
Function with best visual fit	No clear preference.
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	No external evidence available for pre-progression survival in r/mCC.
Function with the best fit according to external evidence	No external evidence available for pre-progression survival in r/mCC.

Method/approach	Description/assumption
Selected parametric function in base case analysis	TV: Gompertz Chemotherapy: Log-normal
Adjustment of background mortality with data from Statistics Denmark	Yes, as per DMC guidelines (60)
Adjustment for treatment switching/cross-over	No, not applicable.
Assumptions of waning effect	No treatment waning included.
Assumptions of cure point	No.

Abbreviations: DCO, data cut-off; r/mCC, recurrent or metastatic cervical cancer; TV, tisotumab vedotin; DMC, Danish Medicine Council.

The pre-progression OS from innovaTV 301 (DCO January 2024) informed the extrapolation and derivation of transition probabilities of PF to D. The choice for the distributions is detailed in Appendix D.2. After six months onwards, the number at risk strongly declines both arms and becomes very low (below five) from month 12, as can be seen in Figure 6, highlighting the need for cautious interpretation.

Figure 12 Observed and extrapolated data of PF to D of tisotumab vedotin

Figure 13 Observed and extrapolated data of PF to D of chemotherapy

8.1.1.3 Extrapolation of transition from PD to death

After progression, patients discontinued TV or chemotherapy in the trial. Conservatively, no post-progression treatment benefits are assumed in patients treated with TV. After progression, patients in both the TV arm and the chemotherapy arm could be eligible for a common basket of subsequent treatments. Additionally, patients in innovaTV 301 were not stratified for any future subsequent treatments. These subsequent treatments are assumed to be a major determinant in any post-progression survival, which is additionally assumed to be independent of prior treatment. Therefore, the model assumes a common post-progression mortality rate across both arms. Thus, the most appropriate approach was to use pooled data for the post-progression survival from innovaTV 301, in order to derive the PD to D transition.

Table 27 Summary of assumptions associated with extrapolation of PD to death

Method/approach	Description/assumption
Data input	innovaTV 301 (DCO Jan 2024)
Model	Exponential – due to structural model restrictions
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Exponential
Adjustment of background mortality with data from Statistics Denmark	Yes, as per DMC guidelines (60)
Adjustment for treatment switching/cross-over	No, not applicable.
Assumptions of waning effect	No treatment waning included.
Assumptions of cure point	No.

Abbreviations: DCO, data cut-off; r/mCC, recurrent or metastatic cervical cancer; TV, tisotumab vedotin; DMC, Danish Medicine Council.

For transitions from PD (i.e., PD to 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 TV and chemotherapy 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 the only compatible option with the memoryless property of Markov models (69). In contrast, alternative parametric distributions would require tracking the time since progression for each patient, which is not compatible with Markov model structure. As displayed in Figure 14, the exponential distribution provided a very close visual fit to the observed data. An additional figure has been added in Appendix B that plots the post-progression survival for both arms separately, demonstrating a higher median post-progression survival for TV over chemotherapy (Figure 28Figure 28).

Figure 14 Observed post-progression survival and exponential distribution (both arms)

8.1.2 Calculation of transition probabilities

As described under 8.1.1, the transitions from the PF state were calculated as follows. Within each weekly cycle of the model, the probability of each of these transitions were 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 DSU TSD 21 (68). 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.

For transitions from the PD state, the exponential distribution was considered to model transition from PD to death based on pooled data from TV and chemotherapy 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 (69).

Table 28 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Progression-free survival	(remain)	$1-p_{PF-PD}-p_{PF-D}$	
	Progressed disease	p_{PF-PD} (poly-hazard model)	(68)

	Death	p_{PF-D} (poly-hazard model)	(68)
Progressed disease	(remain)	$1 - p_{PD-D}$	
	Death	P_{PD-D} (constant under exponential distribution)	(69)
Death	(remain)	-	-

Abbreviations:PF, progression-free; PD, progressed disease.

The distribution of patients in PF, PD and death over the time horizon in the analysis is displayed for TV in Figure 15, and for chemotherapy in Figure 16.

Figure 15 Stacked plot of Markov trace – tisotumab vedotin

Figure 16 Stacked plot of Markov trace – chemotherapy

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

The effects of subsequent therapies are assumed to be captured in the follow-up of OS and PFS in patients who have discontinued either TV or chemotherapy and are not included in the health economic model. By pooled the post-progression survival, no relative efficacy assumptions are made after progression and discontinuation.

8.4 Other assumptions regarding efficacy in the model

In the first 12 months of the time horizon, the health economic analysis used the observed OS data from innovaTV 301 (DCO: January 2024). The observed trial data in this period provides a more robust and credible basis for modelling survival than parametric estimates, as event maturity is high and censoring remains limited. The 12-month cutoff was selected because by that point, over 95% of patients had discontinued randomized treatment, marking a clinically meaningful transition from on-treatment to post-treatment disease management.

Beyond 12 months, censoring increases substantially and the observed data become less informative for long-term projections. Therefore, from this point forward, survival is extrapolated using parametric distributions that appropriately account for censoring and reflect the expected long-term hazard dynamics. The OS is beyond 12 months is derived through transitions in the semi-Markov model, ensuring structural consistency between PFS, PPS, and OS.

8.5 Overview of modelled average treatment length and time in model health state

An overview of time achieved OS and PFS in both treatments arms in the model is displayed side-by-side with the median estimate from innovaTV 301 (Table 29). Comparing the median survival estimates from the trial to the estimates from the model points to a substantial underestimation of PFS in TV, while the other estimates align very well.

Table 29 Estimates in the model

	Modelled average survival (CEM based on DCO 2024)	Modelled median survival (CEM based on DCO 2024)	Observed median survival from innovaTV 301 (DCO 2024)
OS			

	Modelled average survival (CEM based on DCO 2024)	Modelled median survival (CEM based on DCO 2024)	Observed median survival from innovaTV 301 (DCO 2024)
TV	14.6 months	11.5 months	11.7 months
Chemotherapy	11.8 months	8.8 months	9.1 months
PFS			
TV	6.7 months	3.9 months	4.3 months
Chemotherapy	4.5 months	2.8 months	2.9 months

Abbreviations: CEM, cost-effectiveness model; DCO, data cut-off; OS, overall survival; TV, tisotumab vedotion; PFS, progression-free survival.

Not only do the median survival outcomes modelled in the analysis align well with the innovaTV 301 trial, but they also match up to the findings of innovaTV 204 (62). In this trial, a median OS of 12.1 months was found and a median PFS of 4.2 months. This implies the model slightly underestimates the median survival when comparing to the phase II and III trials (14, 62).

In Table 30, the average months spent in PF, PD and on-treatment are displayed, as estimated by the health economic model.

Table 30 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length	Progression-free	Progressed disease
TV	4.92 months	6.71 months	7.90 months
Chemotherapy	4.06 months	4.46 months	7.35 months

Abbreviations: TV, tisotumab vedotin.

9. Safety

Safety data were derived by treatment arm using the safety analysis set from the innovaTV 301 trial (DCO: 24 July 2023). The safety analysis set for these two arms included 489 subjects that received any study treatment. This included 250 subjects that received TV and 239 that received chemotherapy (i.e., topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed). In this application, safety data (adverse events [AEs]) are presented as treatment-emergent adverse events (TEAEs). The median follow-up time for the safety data was 115 days (approximately 3.8 months).

Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) as recorded on case report form (CRF) and coded by Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

9.1 Safety data from the clinical documentation

TEAEs are newly occurring adverse events (i.e., not present at baseline) or adverse events that worsen after first dose of study treatment and up through 30 days after the last dose of study treatment. An overview of TEAEs is presented in Table 31.

The majority of subjects, 98.4% in the TV arm and 99.2% in the chemotherapy arm, experienced at least 1 TEAE. Grade 3 and higher TEAEs were reported in 130 subjects (52.0%) in the TV arm and 149 subjects (62.3%) in the chemotherapy arm. Treatment-emergent SAEs were reported in 82 subjects (32.8%) in the TV arm and 94 subjects (39.3%) in the chemotherapy arm. Treatment-related TEAEs were reported in 219 subjects (87.6%) in the TV arm and 204 subjects (85.4%) in the chemotherapy arm.

Table 31 Overview of safety events – safety analysis set (DCO: 24 July 2023)

	Tisotumab Vedotin (N = 250) (26)	Chemotherapy (N=239) (26)	Difference, % (95 % CI)
Number of adverse events, n	246 (98.4)	237 (99.2)	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	N/A	N/A	N/A
Number of serious adverse events*, n	82 (32.8)	94 (39.3)	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	N/A	N/A	N/A
Number of CTCAE grade ≥ 3 events, n	130 (52.0)	149 (62.3)	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	N/A	N/A	N/A
Number of adverse reactions, n	219 (87.6)	204 (85.4)	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	N/A	N/A	N/A

	Tisotumab Vedotin (N = 250) (26)	Chemotherapy (N=239) (26)	Difference, % (95 % CI)
Number and proportion of patients who had a dose reduction, n (%)**	74 (29.6)	59 (24.7)	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	40 (16.0)	9 (3.8)	N/A

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the [redacted]
** These numbers are based on TEAEs resulting in in dose reduction
§ CTCAE v. 5.0 must be used if available.
Data cutoff date: 24 July 2023, Dictionary: MedDRA v26.0
Source: InnovaTV 301 Clinical study report (data on file) (51)

Treatment-emergent SAEs were reported in 82 subjects (32.8%) in the TV arm and 94 subjects (39.3%) in the chemotherapy arm. The most common treatment-emergent SAE in both arms was urinary tract infection (4.0% and 7.1%, respectively) (Refer to Table 32). A list of all serious AEs observed in the innovaTV 301 trial is reported in Appendix E.

Table 32 Serious adverse events in >5% - safety analysis set (DCO: 24 July 2023)

Adverse events	Tisotumab Vedotin (N = 250)		Chemotherapy (N = 239)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Overall	82 (32.8)	N/A	94 (39.3)	N/A
Urinary tract infection	10 (4.0)	12	17 (7.1)	21

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or

incapacity, or results in a congenital anomaly or birth defect (see the [redacted]
Source: InnovaTV 301 Clinical study report (data on file) (51)

Grade 3-4 AEs reported in ≥5% of patients for at least one of the treatment arms are included, except for ocular event, for which any grade event is included as it is an AE of special interest (Table 33).

Table 33 Adverse events used in the health economic model

Adverse events	TV	Chemotherapy		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)				
Anaemia	8.4%	27.6%	innovaTV 301 (DCO 2023)	
Urinary tract infection	4.4%	7.1%	innovaTV 301 (DCO 2023)	
Neutropenia	3.6%	13.4%	innovaTV 301 (DCO 2023)	
Peripheral neuropathy event	5.6%	0.0%	innovaTV 301 (DCO 2023)	
Ocular event (any grade)	52.8%	0.0%	innovaTV 301 (DCO 2023)	AE of special interest
Ocular event (grade 3+)	4.0%	0%	innovaTV 301 (DCO 2023)	AE of special interest

Abbreviations: TV, tisotumab vedotin; DCO, data cut-off; AE, adverse event.

9.2 Safety data from external literature applied in the health economic model

No safety data from external literature was used in the health economic model.

Table 34 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

During innovaTV 301, HRQoL was investigated as a secondary outcome by EQ-5D-5L questionnaires and VAS, and oncology-specific questionnaires EORTC-QLQ-C30 (70) and cervical cancer-specific EORTC-QLQ-CX24 (71).

The generic EQ-5D-5L is preferred by the DMC because it facilitates comparison between different assessments. As only EQ-5D-5L is included in the model, this section will detail the collection and analysis of EQ-5D-5L and EQ-5D VAS scores. The median follow-up time for EQ-5D-5L assessments was 163 days (approximately 5.4 months).

Table 35 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	innovaTV 301	Used to inform health state utility values.

Abbreviations: EQ-5D-5L, EuroQol-5 Dimension-5 Level.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of HRQOL that can be used in a wide range of health conditions and treatments (72, 73). The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the participant's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the participant's own judgment. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

Responses to the 5 items are then converted to a weighted health state index (utility score) based on values derived from general population samples (72). This health utility score is between 0 and 1, where 0 is death and 1 is perfect health. In addition to the utility score, this questionnaire also records the respondent's self-rated health status on a vertical graduated (0 to 100) VAS. The health utility score, VAS and dimension scores will be summarized by treatment arm using descriptive statistics at baseline, and at each scheduled visit for actual values and changes from baseline.

10.1.2 Data collection

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 TV and chemotherapy were pooled for analysis. The Danish-specific EQ-5D-5L value set was then used to derive utility values for use in the model (74).

Completeness was calculated on a visit level as how many subjects filled in the questionnaire (at least one item answered) divided by the total number of subjects in the FAS population (n=434), regardless of subject drop-outs. For a particular scale, if at least half of the items in a scale have been answered for a timepoint, then the score will be calculated using the average of all items that were completed; otherwise, the scale score was set to missing. For single-item measures, if the item was missing, the scale score was set to missing (75).

No imputation was performed for missing evaluations and thus a subject who did not have an evaluation on a scheduled visit would be excluded from the analysis for that visit.

The assessment rate and scores of EORTC QLQ-C30 (Global Health status) are reported in Table 70 to Table 72).

Table 36 Pattern of missing data and completion – tisotumab vedotin (DCO 2023)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	231	[redacted]	[redacted]	[redacted]
Cycle 2	231	[redacted]	[redacted]	[redacted]
Cycle 3	231	[redacted]	[redacted]	[redacted]
Cycle 4	231	[redacted]	[redacted]	[redacted]
Cycle 5	231	[redacted]	[redacted]	[redacted]
Cycle 6	231	[redacted]	[redacted]	[redacted]
Cycle 7	231	[redacted]	[redacted]	[redacted]
Cycle 8	231	[redacted]	[redacted]	[redacted]
Cycle 9	231	[redacted]	[redacted]	[redacted]
Cycle 10	231	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 11	231	[redacted]	[redacted]	[redacted]
Cycle 12	231	[redacted]	[redacted]	[redacted]
Cycle 13	231	[redacted]	[redacted]	[redacted]
Cycle 14	231	[redacted]	[redacted]	[redacted]
Cycle 15	231	[redacted]	[redacted]	[redacted]
Cycle 16	231	[redacted]	[redacted]	[redacted]
Cycle 17	231	[redacted]	[redacted]	[redacted]
Cycle 18	231	[redacted]	[redacted]	[redacted]
Cycle 19	231	[redacted]	[redacted]	[redacted]
Cycle 20	231	[redacted]	[redacted]	[redacted]
Cycle 21	231	[redacted]	[redacted]	[redacted]
Cycle 22	231	[redacted]	[redacted]	[redacted]
Cycle 23	231	[redacted]	[redacted]	[redacted]
Cycle 24	231	[redacted]	[redacted]	[redacted]
Cycle 25	231	[redacted]	[redacted]	[redacted]
Cycle 26	231	[redacted]	[redacted]	[redacted]
Cycle 27	231	[redacted]	[redacted]	[redacted]
Cycle 28	231	[redacted]	[redacted]	[redacted]
Cycle 29	231	[redacted]	[redacted]	[redacted]
Cycle 30	231	[redacted]	[redacted]	[redacted]
End of treatment	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 12 Week	231	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Long-Term Follow-Up 24 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 36 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 48 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 60 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 72 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 84 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 96 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 108 Week	231	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 120 Week	231	[redacted]	[redacted]	[redacted]

Table 37 Pattern of missing data and completion – chemotherapy (DCO 2023)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of	Number of patients "at risk" at time point X	Number of patients who completed (% of patients

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
		patients at randomization)		expected to complete)
Baseline	203	[redacted]	[redacted]	[redacted]
Cycle 2	203	[redacted]	[redacted]	[redacted]
Cycle 3	203	[redacted]	[redacted]	[redacted]
Cycle 4	203	[redacted]	[redacted]	[redacted]
Cycle 5	203	[redacted]	[redacted]	[redacted]
Cycle 6	203	[redacted]	[redacted]	[redacted]
Cycle 7	203	[redacted]	[redacted]	[redacted]
Cycle 8	203	[redacted]	[redacted]	[redacted]
Cycle 9	203	[redacted]	[redacted]	[redacted]
Cycle 10	203	[redacted]	[redacted]	[redacted]
Cycle 11	203	[redacted]	[redacted]	[redacted]
Cycle 12	203	[redacted]	[redacted]	[redacted]
Cycle 13	203	[redacted]	[redacted]	[redacted]
Cycle 14	203	[redacted]	[redacted]	[redacted]
Cycle 15	203	[redacted]	[redacted]	[redacted]
Cycle 16	203	[redacted]	[redacted]	[redacted]
Cycle 17	203	[redacted]	[redacted]	[redacted]
Cycle 18	203	[redacted]	[redacted]	[redacted]
Cycle 19	203	[redacted]	[redacted]	[redacted]
Cycle 20	203	[redacted]	[redacted]	[redacted]
Cycle 21	203	[redacted]	[redacted]	[redacted]
Cycle 22	203	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 23	203	[redacted]	[redacted]	[redacted]
Cycle 24	203	[redacted]	[redacted]	[redacted]
Cycle 25	203	[redacted]	[redacted]	[redacted]
Cycle 26	203	[redacted]	[redacted]	[redacted]
Cycle 27	203	[redacted]	[redacted]	[redacted]
Cycle 28	203	[redacted]	[redacted]	[redacted]
Cycle 29	203	[redacted]	[redacted]	[redacted]
Cycle 30	203	[redacted]	[redacted]	[redacted]
End of treatment	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 12 Week	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 24 Week	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 36 Week	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 48 Week	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 60 Week	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 72 Week	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 84 Week	203	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Long-Term Follow-Up 96 Week	203	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 108 Week	203	N/A	N/A	N/A
Long-Term Follow-Up 120 Week	203	N/A	N/A	N/A

10.1.3 HRQoL results

Both the results of the EQ-VAS and EQ-5D-5L in the innovaTV301 trial (DCO 2023) are reported in this section. EQ-VAS scores were stable in both arms until cycle 5 (Figure 17 and Table 38) whereas EQ-5D-5L Index scores (weighted with the Danish tariff (74)) were sustained slightly longer before declining (Table 39 and Figure 18).

Figure 17 EQ-VAS Score change from baseline for TV and chemotherapy in innovaTV 301 (DCO 2023)

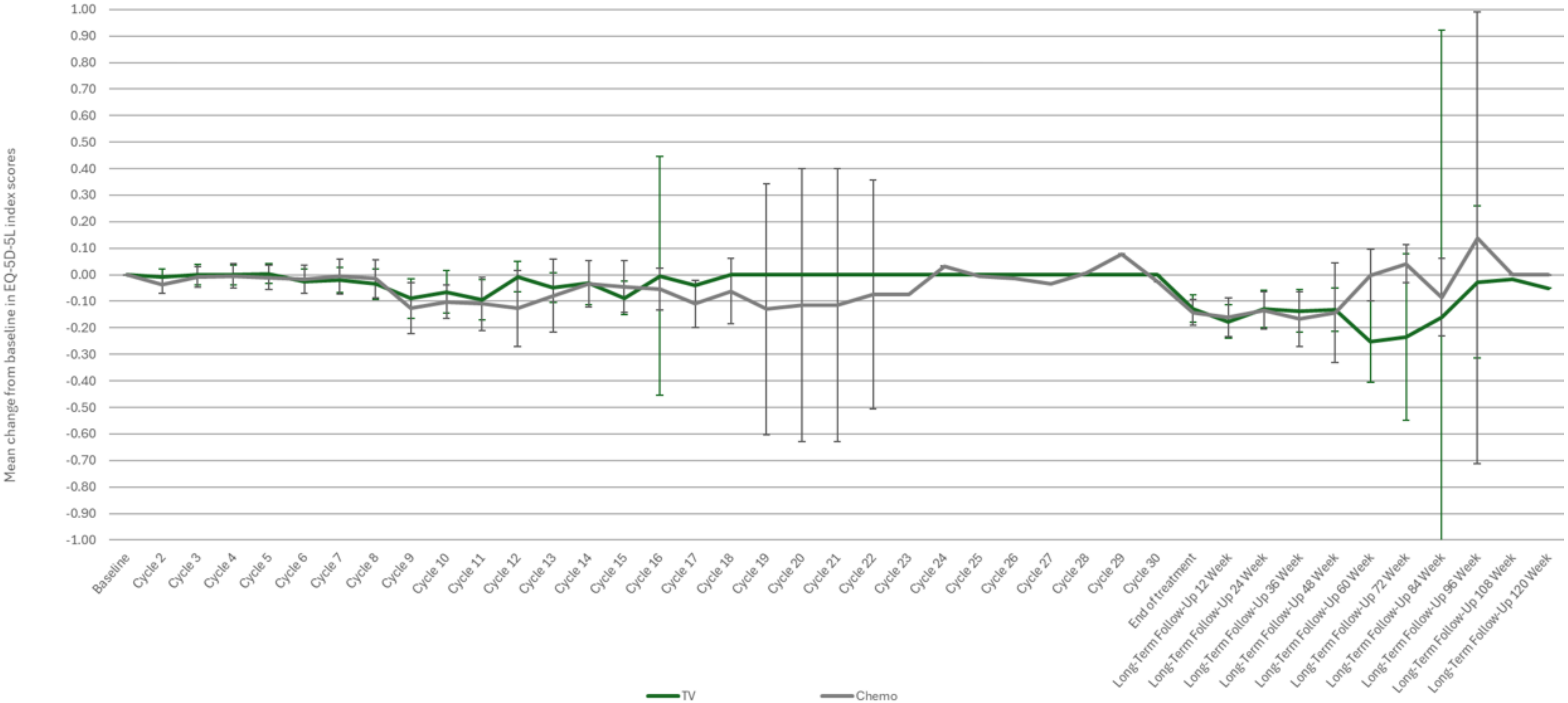
Table 38 HRQoL EQ VAS summary statistics (DCO 2023)

	TV		Chemotherapy		TV vs. chemotherapy
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	231	[redacted]	203	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	TV	Chemotherapy	TV vs. chemotherapy
Cycle 15	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]	N/A
Cycle 19	[redacted]	[redacted]	N/A
Cycle 20	[redacted]	[redacted]	N/A
Cycle 21	[redacted]	[redacted]	N/A
Cycle 22	[redacted]	[redacted]	N/A
Cycle 23	[redacted]	[redacted]	N/A
Cycle 24	[redacted]	[redacted]	N/A
Cycle 25	[redacted]	[redacted]	N/A
Cycle 26	[redacted]	[redacted]	N/A
Cycle 27	[redacted]	[redacted]	N/A
Cycle 28	[redacted]	[redacted]	N/A
Cycle 29	[redacted]	[redacted]	N/A
Cycle 30	[redacted]	[redacted]	N/A
End of treatment	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 12 Week	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 24 Week	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 36 Week	[redacted]	[redacted]	[redacted]

	TV	Chemotherapy	TV vs. chemotherapy
Long-Term Follow-Up 48 Week	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 60 Week	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 72 Week	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 84 Week	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 96 Week	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 108 Week	[redacted]	[redacted]	N/A
Long-Term Follow-Up 120 Week	[redacted]	[redacted]	N/A

Abbreviations: N/A, not available. Note: P-values lower than 0.05 are noted with an *



TV	231	203	174	161	132	112	79	63	41	30	25	19	14	11	8	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	157	85	80	51	34	22	9	2	2	1	1
Chemo	203	159	121	100	82	62	48	40	29	27	19	13	11	8	5	5	4	4	3	2	2	2	1	1	1	1	1	1	1	1	128	77	50	37	18	13	8	6	2	0	0

Figure 18 EQ-5D-5L DK index change from baseline for TV and chemotherapy in innovaTV 301 (DCO 2023) with table included completed assessments

Table 39 HRQoL EQ-5D-5L summary statistics (DCO 2023)

	TV		Chemotherapy		TV vs. chemotherapy
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	231	[redacted]	203	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	TV		Chemotherapy	TV vs. chemotherapy
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	N/A
Cycle 18	N/A	N/A	[redacted]	N/A
Cycle 19	N/A	N/A	[redacted]	N/A
Cycle 20	N/A	N/A	[redacted]	N/A
Cycle 21	N/A	N/A	[redacted]	N/A
Cycle 22	N/A	N/A	[redacted]	N/A
Cycle 23	N/A	N/A	[redacted]	N/A
Cycle 24	N/A	N/A	[redacted]	N/A
Cycle 25	N/A	N/A	[redacted]	N/A
Cycle 26	N/A	N/A	[redacted]	N/A
Cycle 27	N/A	N/A	[redacted]	N/A
Cycle 28	N/A	N/A	[redacted]	N/A
Cycle 29	N/A	N/A	[redacted]	N/A
Cycle 30	N/A	N/A	[redacted]	N/A

	TV		Chemotherapy	TV vs. chemotherapy	
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 12 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 24 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 36 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 48 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 60 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 72 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 84 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 96 Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-Term Follow-Up 108 Week	[redacted]	[redacted]	N/A	N/A	N/A
Long-Term Follow-Up 120 Week	[redacted]	[redacted]	N/A	N/A	N/A

Abbreviations: N/A, not available. Note: P-values lower than 0.05 are noted with an *

10.2 Health state utility values (HSUVs) used in the health economic model

The HRQoL in the health economic analysis incorporated utilities of health states (pre-progression and post-progression, using the Danish utility tariff), age-related utility adjustment, and disutilities due to AEs. Due to a data request for a UK submission, updated EQ-5D-5L scores were generated from the DCO 2024.

10.2.1 HSUV calculation

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. The utilities were estimated for pre-progression and post-progression states, separately:

- **EQ-5D measures for the pre-progression health state:** any EQ-5D assessments corresponding to patients in the pre-progression (i.e., PF) state were used. This included all data collected from baseline 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 (76).
- **EQ-5D measures for the post-progression health state:** any EQ-5D assessments corresponding to patients in the post-progression (i.e., PD) state were used. This included all data collected on or after the first documented progression event, based on PFS definition per innovaTV 301 trial protocol (76). For patients who were censored for, EQ-5D assessments occurring after the censor date were excluded for the analyses.

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 generalized 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 TV. Therefore, the resulting utility estimates reflect the average values for this population, stratified by health states. In the model, health-state utility values were further adjusted by age.

The base-case utilities of pre-progression and post-progression states based on GEE model were [redacted] and [redacted] respectively.

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 DK-

specific population norms, as described by the DMC in specific guidance (77). 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 aging on background health status over time.

10.2.1.1 Mapping

No mapping was required as HRQoL was assessed by EQ-5D-5L, which can be used directly with the Danish tariff.

10.2.2 Disutility calculation

Disutilities associated with AEs were not estimated from the HRQoL data collected in innovaTV 301 but were incorporated in the health economic analysis from secondary literature. These disutilities are described in 10.3.4.

10.2.3 HSUV results

For the GEE model, utility values were estimated with a robust variance estimator to account for correlation within patients' repeated assessments. Utility values by health states were estimated in one model with health state (progression-free vs. progressed disease) as the independent variable, and utilities from all included patients were used.

For the mixed effects model, utility values were estimated considering both the between-patient variation and the within patient variation (progression-free vs. progressed disease). That is, random intercept and random slope were both included in the regression.

Table 40 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs – descriptive				
Progression-free	[redacted]	EQ-5D-5L	Denmark	Estimate is based on mean of both trial arms.
Progressed disease	[redacted]	EQ-5D-5L	Denmark	Estimate is based on mean of both trial arms.
HSUV – GEE model				
Progression-free	[redacted]	EQ-5D-5L	Denmark	Estimate is based on mean of both trial arms.

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Progressed disease	[redacted]	EQ-5D-5L	Denmark	Estimate is based on mean of both trial arms.

Abbreviations: HSUV, health-state utility value; EQ-5D-5L, EuroQol-5 Dimension-5 Level; GEE, generalized estimating equation. Danish value set from Jensen et al. (2021) (74)

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Health-state utility values were informed by the EQ-5D-5L collected in innovaTV 301, therefore no supportive SLR was conducted to further identify evidence on the HRQoL of previously treated r/mCC patients. However, AE-related disutilities were not available from the innovaTV 301 trial, so these were identified from literature.

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

The disutilities assumed for AEs, excluding ocular events, are derived from other literature sources and are presented in Table 42. For some disutilities, the duration was available from innovaTV 301.

Table 41 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 42 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Disutilities due to adverse events				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Anaemia	-0.073 2.13 weeks	N/A	N/A	Liu 2023 (78) for disutility, Shah 2022 (79) for duration
Urinary tract infection	-0.019 0.57 weeks	N/A	N/A	Bermingham 2012 (80) for disutility, Shah 2022 (79) for duration
Neutropenia	-0.050 1.89 weeks	N/A	N/A	Liu 2023 (78) for disutility, Shah 2022 (79) for duration
Peripheral neuropathy event	-0.121 [redacted] weeks	N/A	N/A	Niño-de-Guzmán 2023 for disutility(81), innovaTV 301 trial (DCO 2023) (82) for duration
Ocular event (any grade)	-0.040 [redacted] weeks	N/A	N/A	Brown 2003 (83) for disutility, innovaTV 301 trial DCO 2023 (82) for duration

Abbreviations: DCO, data cut-off.

11. Resource use and associated costs

11.1 Medicines – tisotumab vedotin and chemotherapy

Drug acquisition costs were calculated as a function of unit drug costs, dosing, relative dose intensity (RDI), and duration of treatment (DoT). Drug wastage (i.e., no vial sharing) was assumed in the base-case model. If multiple packs were available of a drug, the pack with the lowest cost per mg was selected. TV was assumed to have a pharmacy purchase price (AIP) of 13,600 DKK per pack. Topotecan had an AIP of 500 DKK, vinorelbine 1,500 DKK, gemcitabine 385 DKK, irinotecan 350 DKK, and pemetrexed 110.50 DKK per pack (53). The drug acquisition costs for chemotherapy were estimated as the weighted average of these single-agent chemotherapies, assuming the distribution from the trial. RDIs for TV, topotecan and gemcitabine were informed by innovaTV 301 trial (76, 82).

The duration of treatment for TV and chemotherapy was estimated from IPD from innovaTV 301 (DCO January 2024) and was fitted to the seven parametric models also assessed for the efficacy extrapolations. The log-logistic was deemed the most appropriate in both arms due to best statistical fit. Details on the choice for this distribution and information on the other distributions are given in Appendix D.3.

Figure 19 Observed and extrapolated duration of treatment of tisotumab vedotin and chemotherapy

Table 43 Medicines used in the model

Medicine	Dose (innovaTV 301 trial protocol (76))	Relative dose intensity (innovaTV 301 trial (DCO Jul 2023) (51))	Frequency	Vial sharing
Tisotumab vedotin	2 mg/kg	[redacted]	Q3W	No
Topotecan	1 or 1.25 mg/m^2	[redacted]	Q3W x 5 days	No
Vinorelbine	30 mg/m^2	[redacted]	Q3W x 2 days	No
Gemcitabine	1000 mg/m^2	[redacted]	Q3W x 2 days	No
Irinotecan	100 or 125 mg/m^2	[redacted]	Q6W x 4 days	No
Pemetrexed	500 mg/m^2	[redacted]	Q3W	No

Abbreviations: DCO, data cut-off; mg, milligram; m^2, square-metres, Q3W, every three weeks; Q6W, every six weeks; QW, every week.

11.2 Medicines– co-administration

In line with the innovaTV 301 trial protocol, the model includes pre-medication costs for patients to be treated with TV (76). Two topical pre-medications dexamethasone (0.1%)

and brimonidine tartrate (0.2%) were included with AIPs of 114.50 DKK and 69.95 DKK per pack, respectively (53).

Table 44 Pre-medication for tisotumab vedotin

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Dexamethasone 0.1%	1 drop (0.05 mL) in each eye	100%	Q3D days 1-4 of three-week cycle	No
Brimonidine tartrate 0.2%	3 drops (0.15 mL) in each eye	100%	Day 1 Q3W	No

Dosing in accordance with innovaTV 301 trial protocol (76). Abbreviations: mL, intravenous; Q3D, every three days; Q3W, every three weeks.

11.3 Administration costs

The following administration costs are included in the health economic model. Intravenous infusion is necessary for TV and chemotherapy options (1, 76). No costs were assumed for oral or topical administrations.

Table 45 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Intravenous infusion	Q3W for TV, topotecan, vinorelbine, gemcitabine, pemetrexed. Q6W for irinotecan.	1,467	Diagnose DC539 Livmoderhalskræft, Procedure BWAA62 Medicingivning ved intravenøs infusion	DRG 2026 (84)
Topical administration	QD3 on day 1-4, G3W as pre-medication for TV	None	-	-

Dosing in accordance with innovaTV 301 trial protocol. Abbreviations: Q3W, every three weeks; TV, tisotumab vedotion; DRG, diagnose-related groups.

11.4 Disease management costs

The disease management of r/mCC is not well-defined in literature, let alone the Danish context. The healthcare resource use (HCRU) of patients with previously treated r/mCC was informed by information from Cancer UK (85). Danish costs were obtained and associated with the units of healthcare included in the model, to capture the economic impact of r/mCC, following guidance from the Danish costing manual (61).

Table 46 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Oncologist visit	See Table 47	809.28	1. konsultation	Læger.dk, Gynaekologi takstkort 2025 (86)
Complete blood count	See Table 47	223.99	Prøvetagning: Blod Analyse: P-kreatinin, P-glucosem, C-reaktivt protein, B-hæmoglobin	Laeger.dk, laboraterieundersøgelser takstkort 2025 (87)
Chemistry panel	See Table 47	223.99	Assumed the same as complete blood count	
Colposcopy	See Table 47	501.65	Kikkertundersøgelse af livmoderhalsen (Kolposkopi) + senere konsultation	Læger.dk, Gynaekologi takstkort 2025 (86)
PET-CT scans	See Table 47	2,861.00	30PR07 CT-scanning, ukompliceret Procedure: UXCD15 CT-skanning af nedre abdomen, inkl. bækken	DRG 2026 (84)
Chest X-ray	See Table 47	1,843.00	30PR18 Røntgenundersøgelse (alm), ukompliceret Procedure: UXRC00 øtgenundersøgelse af thorax.	DRG 2026 (84)
MRI	See Table 47	2,264.00	30PR03 MR-scanning, ukompliceret Procedure: UXMD15 MR-skanning af nedre abdomen, inkl. bækken	DRG 2026 (84)
Ocular assessment	See Table 47	477.52	Først konsultation	Læger.dk, øjenspecialet takstkort 2025 (88)
Eye examination	See Table 47	243.98	Senere konsultation	Læger.dk, øjenspecialet takstkort 2025 (88)

Abbreviations: PET-CT, positron emission tomography – computed tomography; MRI, magnetic resonance imaging. Note: DRG codes under diagnosis DC539 Livmodershalskræft.

Table 47 Frequency of healthcare resources for disease management

	Year 1 and 2	Year 3-5	Year 6+	Source
Pre-progression				
Oncologist visit	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
Complete blood count	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
Chemistry panel	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
Colposcopy	Every 6th month	Every 6th month	Every 6th month	Cancer UK (85)
PET-CT scans	Every 4th month	Every 12th month	Every 12th month	Cancer UK (85)
Chest X-ray	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
MRI	Every 4th month	Every 12th month	Every 12th month	Cancer UK (85)
Post-progression				
Oncologist visit	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
Complete blood count	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
Chemistry panel	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
Colposcopy	Every 6th month	Every 6th month	Every 6th month	Cancer UK (85)
PET-CT scans	Every 4th month	Every 12th month	Every 12th month	Cancer UK (85)
Chest X-ray	Every 2nd month	Every 4th month	Every 6th month	Cancer UK (85)
MRI	Every 4th month	Every 12th month	Every 12th month	Cancer UK (85)

11.5 Costs associated with management of adverse events

The costs associated with the management of adverse events were derived from the DRG codes related to the event, costed by Sundhedsdatastyrelsen. Ocular events are assumed to be captured in disease management cost, as ocular assessments are included for patients treated with TV. Disease management of ocular events was included in line with what has been previously implemented in an analysis by the DMC (89).

Table 48 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Anaemia	DRG code: 16MA98. Action diagnosis: (DD592) Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel. Underlying diagnosis: DC539 Livmodershalskræft (84).	2,195.00
Urinary tract infection	DRG code: 11MA98. Action diagnosis: (DN390) Urinvejsinfektion uden angivelse af lokalisation. Underlying diagnosis: DC539 Livmodershalskræft (84).	1,588.00
Neutropenia	DRG code: 16MA98. Action diagnosis: (DD709A) Neutropeni og agranulocytose forårsaget af lægemiddel. Underlying diagnosis: DC539 Livmodershalskræft (84).	2,195.00
Peripheral neuropathy event	DRG code: 01MA98. Action diagnosis: (DG598)Mononeuropati ved anden sygdom klassificeret andetsteds Underlying diagnosis: DC539 Livmodershalskræft (84).	2,061.00
Ocular event (any grade)	Included in disease management costs and eye drops	-

11.6 Subsequent treatment costs

The post-progression treatments that are available in the Danish clinical practice are the same choice of cytostatic treatments. The proportion of patients receiving any post-progression treatment [redacted] was derived from pooled TV and chemotherapy of innovaTV 301 (82). Cytotoxic chemotherapy and immunotherapy were the most common types of subsequent anticancer therapies among patients in both treatment arms. Gemcitabine was the most common subsequent chemotherapy.

An equal distribution between topotecan and gemcitabine was assumed to reflect the Danish clinical practice, and an equal split was assumed (Table 49).

Table 49 Distribution of subsequent treatments after TV or chemotherapy (DCO 2024)

	Tisotumab vedotin (n=253)	Chemotherapy (n=249)
Received post-progression treatment (%)	[redacted]	[redacted]
Patients with any subsequent systemic regimens, n/N (%)	**125 (49%)**	**106 (42.5%)**
Chemotherapy	[redacted]	[redacted]

Immunotherapy	[redacted]	[redacted]
Investigational agent	[redacted]	[redacted]
Chemo-Immunotherapy	[redacted]	[redacted]
Chemo-Bevacizumab	[redacted]	[redacted]
TIVDAK	[redacted]	[redacted]
TKI/Small Molecule	[redacted]	[redacted]
Other/Unknown	[redacted]	[redacted]
Distribution of post-progression treatment in model		
Topotecan	50%	50%
Gemcitabine	50%	50%
Costs of subsequent treatment		
Acquisition costs	6,220.30	6,220.30
Administration costs	20,621.86	20,621.86

Duration of treatment, RDI, wastage, dosing and dose schedules are assumed the same as pre-progression chemotherapy (see section 11.1, Table 50). The costs of drug acquisition and administration per chemotherapy are displayed in Table 51.

Table 50 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Topotecan	1 or 1.25 mg/m^2	[redacted]	Q3W x 5 days	No
Gemcitabine	1000 mg/m^2	[redacted]	Q3W x 2 days	No

Table 51 Costs of subsequent treatments

Post-progression treatment	Drug acquisition costs per week	Drug administration costs per week	Treatment duration (weeks)	Lump sum treatment costs	Lump sum administration costs

Topotecan	833.33	2,445.00	15.80	13,166.67	38,631.00
Gemcitabine	641.67	2,445.00	15.80	10,138.33	38,631.00

Mean duration of treatment is used to calculate lump sum cost. Mean duration of treatment is the treatment duration observed in the trial in the chemotherapy arm (as randomized treatment).

11.7 Patient costs

This cost-utility analysis was conducted from the limited societal perspective, meaning that both travel expenses and time spent by patients due to healthcare visits are costed and accounted for. For each healthcare visit, a number of hours used was assumed which is multiplied with 188 DKK to estimate patient time costs. Additionally, travel costs are calculated by multiplying 20 average km from hospital with DKK 3.79 per km of travel.

Table 52 Patient costs used in the model

Activity	Time spent
Average time per healthcare visit (incl. travel time)	3 hours
Anaemia	48 hours
Urinary tract infection	3 hours
Neutropenia	48 hours
Peripheral neuropathy event	48 hours
Ocular event (all grades)	3 hours

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Palliative care costs in both TV and chemotherapy arms were included in the health economic analysis to model the costs related to r/mCC as complete as possible (Table 53).

Table 53 Palliative care costs used in the model

Activity	Cost (DKK)	DRG code
Basic palliative care	24,910.00	DRG 2026: 13MA01 Gynækologiske infektioner, blødningsforstyrrelser eller andre gynæakologiske sygdomme eller mistake herom. Diagnose DC539 Livmodershalskræft, Procedure Basal palliativ indsats (lang insats, 12+ timer)

12. Results

12.1 Base case overview

An overview of the base case settings of the cost-effectiveness of TV in previously treated r/mCC in Denmark is given in Table 54.

Table 54 Base case overview

Feature	Description
Comparator	Chemotherapy as per innovaTV 301
Type of model	Semi-Markov model
Time horizon	30 years (lifetime)
Treatment line	Second-line, subsequent treatment included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in innovaTV 301. Danish population weights were used to estimate health-state utility values.
Costs included	Drug acquisition costs Health-care resource costs Costs of adverse events Patient time and travel costs
Dosage of medicine	Based on weight for TV, based on BSA for chemotherapy
Average time on treatment	TV: 4.92 months Chemotherapy: 4.06 months
Parametric function for PF to PD	TV: Generalized gamma Chemotherapy: Generalized gamma
Parametric function for PF to Death	TV: Gompertz Chemotherapy: Log-normal
Parametric function for PD to Death	Exponential
Inclusion of waste	Yes

Feature	Description
Average time in model health state	
Progression-free	TV: 6.71 months Chemotherapy: 4.46 months
Progressed-disease	TV: 7.90 months Chemotherapy: 7.35 months

12.1.1 Base case results

An overview of the base case settings of the discounted results of the cost-effectiveness of TV in previously treated r/mCC in Denmark is given in Table 55.

Table 55 Base case results, discounted estimates

	Tisotumab vedotin	Chemotherapy	Difference
Drug acquisition costs	317,193	7,125	310,068
Drug administration costs	25,736	32,459	-6,723
Adverse event costs	449	1,013	-564
Disease management costs	21,013	16,129	4,883
Subsequent treatment costs	4,564	4,583	-19
Patient time and transport costs	4,053	5,544	-1,491
Terminal care costs	24,278	24,469	-190
Total costs	**397,285**	**91,321**	**305,964**
Life years gained (Progression-free)	0.55	0.37	0.18
Life years gained (Progressed Disease)	0.64	0.60	0.04
Total life years	**1.19**	**0.97**	**0.22**
QALYs (Progression-free)	[redacted]	[redacted]	[redacted]

	Tisotumab vedotin	Chemotherapy	Difference
QALYs (Progressed Disease)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		**1,397,378 DKK**	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity analyses

To assess the robustness of this health economic analysis, multiple ways of testing the sensitivity to structural and parameter uncertainty were conducted.

12.2.1 Deterministic sensitivity analyses

The impact of the uncertainty of single parameters is assessed in a deterministic one-way sensitivity analysis (OWSA).

Table 56 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					[redacted]
Utility - PF	[redacted]	Lower bound	[redacted]	[redacted]	[redacted]
	[redacted]	Upper bound	[redacted]	[redacted]	[redacted]
Utility - PD	[redacted]	Lower bound	[redacted]	[redacted]	[redacted]
	[redacted]	Upper bound	[redacted]	[redacted]	[redacted]
Post-progression treatment administration costs -Chemotherapy	12,991.77	Lower bound	307,403	[redacted]	[redacted]
	15,878.83	Upper bound	304,525	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Post-progression administration treatment costs – TV	12,991.77	Lower bound	304,531	[redacted]	[redacted]
	15,878.83	Upper bound	307,397	[redacted]	[redacted]
Patient and travel time cost – AE – Chemotherapy one-off	3,072.96	Lower bound	306,668	[redacted]	[redacted]
	4,552,15	Upper bound	305,189	[redacted]	[redacted]
Pre-progression weekly disease management cost – Year 1 – TV	301.67	Lower bound	305,231	[redacted]	[redacted]
	368.71	Upper bound	306,697	[redacted]	[redacted]
Cost of IV infusion	1,320.30	Lower bound	306,636	[redacted]	[redacted]
	1,613.70	Upper bound	305,292	[redacted]	[redacted]
Pre-progression weekly disease management cost – Year 1 – Chemotherapy	301.67	Lower bound	306,528	[redacted]	[redacted]
	368.71	Upper bound	305,400	[redacted]	[redacted]
Post-progression treatment acquisition costs – Chemotherapy	4,137.02	Lower bound	306,422	[redacted]	[redacted]
	5,056.36	Upper bound	305,506	[redacted]	[redacted]
Post-progression treatment acquisition costs – TV	[redacted]	Lower bound	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	[redacted]	Upper bound	[redacted]	[redacted]	[redacted]

To visualise the impact of applying the upper and lower bounds of these parameters, the most impactful parameters in the OWSA are plotted in Figure 20.

Figure 20 Tornado diagram of one-way sensitivity analysis

To further assess the impact of structural model assumptions, multiple scenarios were run to identify the assumptions the analysis is most sensitive to. The top ten impactful scenarios are presented in Figure 21.

Figure 21 Visualisation of the impact of scenario analyses on the deterministic ICER

The most impactful settings of the model are related to the extrapolation of progression or death events, which is expected to have a substantial effect on the extrapolated effects. However, the model choices were the most appropriate based on statistical fit from the innovaTV 301 trial.

12.2.2 Probabilistic sensitivity analyses

To test overall parameter uncertainty, the model ran 1,000 iterations, varying all parameters with their respective distributions at every iteration. If no standard deviation was reported for a point estimate, a standard deviation of 10% of the point estimate was assumed. This resulted in 1,000 sets of probabilistic results, which are displayed in the cost-effectiveness plane (Figure 22). The mean probabilistic ICER was [redacted] DKK/QALY. All iterations found incremental benefits at incremental costs, placing them in the north-east quadrant of the cost-effectiveness plane. This number of iterations was deemed enough to estimate a stable probabilistic ICER, as is demonstrated in the convergence plot (Figure 23).

Figure 22 Cost-effectiveness plane with probabilistic outcomes

Most probabilistic results are in the north-east quadrant, indicating that under all modelled parameter uncertainty, TV very likely brings clinical value at additional costs. The convergence plot in Figure 23 displays the convergence of ICER estimates from 500 iterations onward, meaning 1,000 iterations is deemed sufficient to estimate a stable result.

Figure 23 Convergence plots on ICERs in probabilistic iterations

13. Budget impact analysis

Though the number of eligible patients is uncertain, the assumption in this submission is that around 20 patients will become eligible for TV every year. It is assumed market shares – given recommendation – will start at 20% and climb to 40%, which is expected to be the maximum uptake in 2L r/mCC based on Genmab's medical insights.

Number of patients (including assumptions of market share)

Table 57 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
TV	4	5	6	7	8
Chemotherapy	16	15	14	13	12
			Non-recommendation		
TV	0	0	0	0	0
Chemotherapy	20	20	20	20	20

Budget impact

Due to the low number of eligible patients in Denmark, the budget impact of introducing TV in 2L r/mCC is minimal, while introducing a life-extending treatment to these women.

Table 58 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	1,785,286	2,297,682	2,667,574	2,998,869	3,318,511
The medicine under consideration is NOT recommended	660,357	810,258	856,441	870,347	875,071
Budget impact of the recommendation	**1,124,929**	**1,487,424**	**1,811,133**	**2,128,522**	**2,443,440**

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 59 Main characteristic of studies included

Trial name: InnovaTV 301 trial	NCT number: NCT04697628
Objective	This open-label, randomized, global, phase 3 study is being done to find out whether tisotumab vedotin works better than chemotherapy to treat cervical cancer. People in this study have cervical cancer that has spread to other parts of the body (metastatic) or has come back after being treated (recurrent).
Publications – title, author, journal, year	Vergote I, González-Martín A, Fujiwara K, Kalbacher E, Bagaméri A, Ghamande S, Lee JY, Banerjee S, Maluf FC, Lorusso D, Yonemori K, Van Nieuwenhuysen E, Manso L, Woelber L, Westermann A, Covens A, Hasegawa K, Kim BG, Raimondo M, Bjurberg M, Cruz FM, Angelergues A, Cibula D, Barraclough L, Oaknin A, Gennigens C, Nicacio L, Teng MSL, Whalley E, Soumaoro I, Slomovitz BM; innovaTV 301/ENGOT-cx12/GOG-3057 Collaborators. Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer. N Engl J Med. 2024 Jul 4;391(1):44-55. doi: 10.1056/NEJMoa2313811. PMID: 38959480.
Study type and design	Phase 3, multinational, open-label, randomized trial, patients were assigned, in a 1:1 ratio, to receive either tisotumab vedotin intravenously at a dose of 2.0 mg per kilogram of body weight every 3 weeks or the investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) intravenously. Crossover between treatment groups was not allowed.
Sample size (n)	502 participants (ITT)
Main inclusion criteria	• Has recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology, and: • Has experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible), defined as either: o paclitaxel + cisplatin + bevacizumab + anti-PD-(L)1 agent, or o paclitaxel + carboplatin + bevacizumab + anti-PD-(L)1 agent, or o paclitaxel + topotecan/nogitecan + bevacizumab + anti-PD-(L)1 agent • Note: In cases where bevacizumab and/or anti-PD-(L)1 agent is not a standard of care therapy or the participant was ineligible for such treatment according to local standards, prior treatment with bevacizumab and/or anti-PD-(L)1 agent is not required. • Has received 1 or 2 prior systemic therapy regimens for recurrent and/or metastatic cervical cancer. Chemotherapy administered in

Trial name: InnovaTV 301 trial	NCT number: NCT04697628
	the adjuvant or neoadjuvant setting, or in combination with radiation therapy, should not be counted as a systemic therapy regimen. Single agent therapy with an anti-PD(L)1 agent for r/mCC cancer should be counted. • Measurable disease according to RECIST v1.1 as assessed by the investigator. • Has ECOG performance status of 0 or 1 prior to randomization. • Has life expectancy of at least 3 months.
Main exclusion criteria	• Has primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned as part of the inclusion criteria above. • Has clinically significant bleeding issues or risks. This includes known past or current coagulation defects leading to an increased risk of bleeding; diffuse alveolar haemorrhage from vasculitis; known bleeding 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. • Has 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. Cataracts alone is 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. • Any prior treatment with monomethyl auristatin E (MMAE)-containing drugs.
Intervention	250 participants with rCC/mCC were administered tisotumab vedotin 2.0 milligram per kilogram (mg/kg) as an intravenous (IV) infusion once every 3 weeks (Q3W). (ITT population = 253)
Comparator(s)	239 participants with rCC/mCC were treated with investigator's choice of chemotherapy which included either: Drug: topotecan • 1 or 1.25 mg/m2 intravenous (IV) on Days 1 to 5, every 21 days Drug: vinorelbine

Trial name: InnovaTV 301 trial	NCT number: NCT04697628
	• 30 mg/m2 IV on Days 1 and 8, every 21 days Drug: gemcitabine • 1000 mg/m2 IV on Days 1 and 8, every 21 days Drug: irinotecan • 100 or 125 mg/m2 IV weekly for 28 days, every 42 days Drug: pemetrexed • 500 mg/m2 IV on Day 1, every 21 days (ITT population = 249)
Follow-up time	Median follow-up of 10.8 months
Is the study used in the health economic model?	Yes. Model was updated with a latest available data (DCO: January 2024). No CSR or clinical report was made up of this data-cut however, though a minimal difference in median follow-up assures minimal difference.
Primary, secondary and exploratory endpoints	*Primary endpoint* • Overall survival *Secondary endpoint* • Progression Free Survival (PFS) based on RECIST v1.1 as assessed by investigator • Confirmed Objective Response Rate (ORR) based on RECIST v1.1 as assessed by investigator • Time-to-Response (TTR) as Assessed by the Investigator • Duration of Response (DOR) by Investigator Assessment • Number of Participants With Treatment Emergent Adverse Events (TEAEs) • EuroQOL Five Dimensions Five Level (EQ-5D-5L) Index Score • EQ-5D Visual Analog Scale (VAS) Scores • European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Total Score • EORTC Quality of Life Questionnaire Cervical Cancer Module (QLQ-CX24) Total Scores **Endpoints included in this application:** Except for HRQoL measured using the EORTC QLQ-C30 and QLQ-CX24, all other outcomes listed above were included in this application.
Method of analysis	The primary analysis of the efficacy endpoints was based on the intent-to-treat (ITT) analysis set, including all subjects who were randomized on or before the date of last-patient-in in the global study. Stratified

	primary analyses used stratification factors (ECOG, prior bevacizumab, and prior anti-PD-[L]1 therapy) with values as employed in the randomization. Demographics and baseline characteristics were also summarized on the ITT analysis set. The difference in OS between the tisotumab vedotin and chemotherapy arms was compared using the stratified log-rank test. The 2-sided p-value corresponding to the test of superiority of tisotumab vedotin over chemotherapy was presented. The estimated HR and its 95% confidence interval (CI) from the stratified Cox model were presented. The median OS was estimated using the Kaplan-Meier method and was presented along with estimated Kaplan-Meier curves and the corresponding 95% CI by treatment arm. PFS analysis was conducted using the same methods as described for the primary analyses on OS. In the primary analysis on PFS, subjects without evidence of radiographic disease progression or death were censored at the date of the last adequate tumour assessment (i.e., a radiologic scan with the overall disease response of complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]) prior to data cut-off date or the start of new anti-cancer therapy. Subjects with disease progression or death that occurred after 2 or more consecutively missed scans were censored at the last adequate tumour assessment prior to the missed scans. Subjects without post-baseline scan data were censored at the day of randomization. ORR was analysed using a Cochran-Mantel-Haenszel chi-squared test and 2-sided p-value for testing of superiority of tisotumab vedotin over chemotherapy was presented. The common odds ratio across strata was estimated and presented with its 95% CI. DOR and TTR were summarized descriptively by treatment group using the Kaplan-Meier approach. Descriptive analyses were used to evaluate patient-reported outcomes (PROs).
Subgroup analyses	As exploratory analyses, subgroup analyses were conducted for selected endpoints (i.e., primary and key secondary efficacy endpoints). Subgroups were defined using data recorded in the EDC. Subgroups included but were not limited to the following: • Age (<65, ≥65 years) • Region (US, Europe, Asian, Other) • Race (White, Non-White) • Ethnicity (Hispanic, Non-Hispanic) • ECOG performance status (PS) at baseline (0, 1) • Prior bevacizumab administration (yes, no) • Prior anti-PD-1/PD-L1 therapy administration (yes, no) • Histology (squamous cell carcinoma and adenosquamous carcinoma, adenocarcinoma) • Chemotherapy agent

Trial name: InnovaTV 301 trial	NCT number: NCT04697628
	• Number of prior recurrent/metastatic systemic regimens (1, 2) For the above subgroups, analyses of OS and PFS by treatment arm were conducted using log-rank tests and Cox proportional hazards model stratified by randomization stratification factors except for region. If the subgroup was a stratification factor, then the stratified models controlled for the rest of stratification factors. For subgroup variables with 2 levels, subgroup analysis may not have been performed on the variable if the total number of subjects in a subgroup was too small (e.g., <10% of the total sample size). For subgroup variables with more than 2 levels, pooling across levels was considered when the number of subjects within 1 level was too small.
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Results of the innovaTV 301 trial is presented in Table 60, below. All results are based on the latest efficacy data cut from 8th of August 2023. In Table 61 are the individual clinical response components (i.e. CR, PR, and SD) reported. Graphical checks of the proportional hazard assumption for OS and PFS in the ITT population are provided in Figure 24 to Figure 27.

Table 60 Results per study

Results of innovaTV 301 (NCT04697628)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS (follow-up 10.8 months).	Tisotumab Vedotin	253	11.5 (9.8-14.9) months	2.0 months	N/A	N/A	HR: 0.70	0.54–0.89	0.004	The median survival is based on the Kaplan-Meier estimator. 95% CI is calculated using the complimentary lo-log- transformation method (Collett, 1994)(64). The HR is based on a Cox proportional hazards model with adjustment for the variables (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) used for stratification	Vergote et al., 2024 (14)
	Chemotherapy*	249	9.5 (7.9–10.7) months								

										for randomization, and study arm. Two-sided p-value calculated from stratified log-rank test.	
Median PFS per investigator assessment by RECIST 1.1 (maximum up to 25 months)	Tisotumab Vedotin	253	4.2 (4.0-4.4) months	1.3 months	N/A	N/A	HR: 0.67	0.54–0.82	<0.001	The median progression-free survival is based on the Kaplan–Meier estimator. 95% CI is calculated using the complimentary lo-log-transformation method (Collett, 1994) (64). The HR is based on a Cox proportional hazards model with adjustment for the variables (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) used for stratification for randomization, and study arm. Two-sided p-value calculated from stratified log-rank test.	Vergote et al., 2024 (14)
	Chemotherapy*	249	2.9 (2.6-3.1) months								
Proportion of subjects achieving ORR per investigator assessment	Tisotumab Vedotin	253	45 (17.8 [13.3-23.1])	12.6%	N/A	N/A	OR: 4.0	2.1-7.6	<0.001	ORR is confirmed CR or PR according to RECIST 1.1.Two-sided 95% exact CI, computed using the Clopper-Pearson method (Clopper 1934) (90). The OR is based on the Cochran-	Vergote et al., 2024 (14)
	Chemotherapy*	249	13 (5.2 [CI, 2.8-8.8])								

by RECIST 1.1 (%) (maximum up to 25 months)										Mantel-Haenszel method controlling for 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 randomization.	
Proportion of subjects achieving DCR per investigator assessment by RECIST 1.1 (%) (maximum up to 25 months)	Tisotumab Vedotin	253	192 (75.92 [70.1, 81.0])	17.7%	N/A	N/A	N/A	N/A	N/A	DCR is confirmed CR, PR or SD according to RECIST 1.1.Two-sided 95% exact CI, computed using the Clopper-Pearson method (Clopper 1934) (90).	Clinical study report. innovaTV 301 (51)
	Chemotherapy*	249	145 (58.2 [51.8, 64.4])								
Median TTR per investigator assessment (maximum up to 25 months)	Tisotumab Vedotin	253	1.6 (1.2-4.5) months	0.16 months	N/A	N/A	N/A	N/A	N/A	Time from randomization to earliest occurrence of either CR or PR for subjects with confirmed response.	Clinical study report. innovaTV 301 (51)
	Chemotherapy*	249	1.7 (1.2-3.9 months)								
Median DOR per	Tisotumab Vedotin	253	5.3 (4.2-8.3) months	-0.4 months	N/A	N/A	N/A	N/A	N/A	The median DOR is based on the Kaplan-Meier estimator. 95% CI	Clinical study report.

investigator assessment by RECIST 1.1 (maximum up to 25 months)	Chemotherapy*	249	5.7 (2.8-not reached) months		is calculated using the complimentary log-log-transformation method (Collett, 1994)(64)	innovaTV 301 (51)

Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; OR, odds ratio: ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTR, Time-to-Response
*The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

Table 61 Results per study – CR and PR components

Results of innovaTV 301 (NCT04697628)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of subjects achieving CR, investigator assessment by RECIST 1.1 (%) (maximum up to 25 months)	Tisotumab Vedotin	253	6 (2.4)	2.4%	N/A	N/A	N/A	N/A	N/A	Observed	Clinical study report. innovaTV 301 (51)
	Chemotherapy*	249	0								

Proportion of subjects achieving PR, investigator assessment by RECIST 1.1 (%) (maximum up to 25 months)	Tisotumab Vedotin	253	39 (15.4)	10.2%	N/A	N/A	N/A	N/A	N/A	Observed	Clinical study report. innovaTV 301 (51)
	Chemotherapy*	249	13 (5.2)								
Proportion of subjects achieving SD, investigator assessment by RECIST 1.1 (%) (maximum up to 25 months)	Tisotumab Vedotin	253	147 (58.1)	5.1%	N/A					Observed	Clinical study report. innovaTV 301 (51)
	Chemotherapy*	249	132 (53.0)								

Abbreviations: CR, complete response; PR, partial response; SD, stable disease

Note: *The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

*The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Source: InnovaTV 301 Clinical study report (data on file) (51)

Figure 24 Log-negative-log of overall survival probability versus log(time) by treatment arm (ITT analysis set)

Source: InnovaTV 301 Clinical study report (data on file) (51)

Figure 25 Schoenfeld residuals plot of overall survival (ITT analysis set)

*The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Source: InnovaTV 301 Clinical study report (data on file) (51)

Figure 26 Log-negative-log of progression-free survival probability versus log(time) by treatment arm (ITT analysis set)

Source: InnovaTV 301 Clinical study report (data on file) (51)

Figure 27 Schoenfeld residuals plot of progression-free survival (ITT analysis set)

Figure 28 Post-progression survival curves for both arms in innovaTV (DCO 2024)

Appendix C. Comparative analysis of efficacy

No comparative analysis of efficacy was conducted.

Table 62 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

D.1 Extrapolation of PF to PD

D.1.1 Data input

Time-to-progression data from innovaTV 301 (DCO: January 2024).

D.1.2 Model

Independent 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, generalized gamma, and gamma distributions. Within each weekly cycle of the model, the probability of each of these transitions were 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 DSU TSD 21 (68). 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).

D.1.3 Proportional hazards

Extrapolations do not rely on proportional hazards assumption.

D.1.4 Evaluation of statistical fit (AIC and BIC)

The statistical fits of Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) are displayed in Table 63 and Table 64. For both treatment arms, generalized gamma provided the lowest AIC scores. For TV, this distribution also gave the best BIC scores, though for chemotherapy, the log-normal demonstrated the best statistical fit – though the differences were very minimal. The generalized gamma is therefore considered to have the best statistical fit in both arms.

Table 63 Statistical fits of parametric distribution to PF-PD transition (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
Generalized Gamma	1604.1	1614.7

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Table 64 Statistical fits of parametric distribution to PF-PD transition (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
Generalized Gamma	1394.6	1405.2

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

D.1.5 Evaluation of visual fit

Based on visual fit, generalized gamma was deemed to be a plausible distribution of the transition from PF to PD in both arms. No implausible survival tail was observed, and no over- or underestimation is visible during the overlapping period with observed data of time-to-progression.

D.1.6 Evaluation of hazard functions

The non-monotonic hazard shapes in the observed data point towards a distribution that can allow for these types of changes in hazard (Figure 29). The generalized gamma distribution again was deemed as a plausible distribution that can accommodate these hazard shapes.

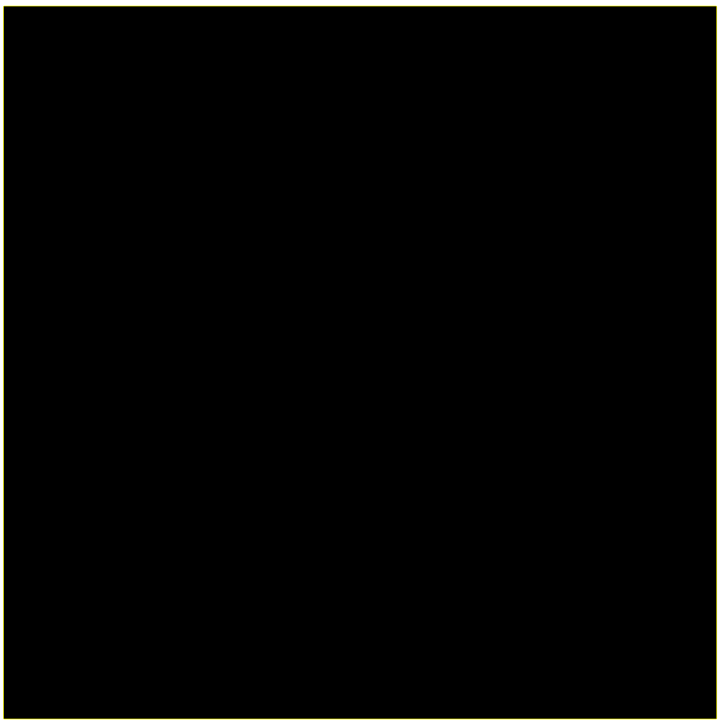

Figure 29 Smoothed hazard plot of time-to-progression of tisotumab vedotin and chemotherapy

D.1.7 Validation and discussion of extrapolated curves

No external evidence of PF to PD transition in r/mCC is available.

D.1.8 Adjustment of background mortality

Background mortality was adjusted for in the semi-Markov model traces.

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of PF to D

D.2.1 Data input

Pre-progression survival data from innovaTV 301 (DCO: January 2024).

D.2.2 Model

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, generalized gamma, and gamma distributions. Within each weekly cycle of the model, the probability of each of these transitions were 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 DSU TSD 21 (68). 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).

D.2.3 Proportional hazards

Extrapolations do not rely on proportional hazards assumption.

D.2.4 Evaluation of statistical fit (AIC and BIC)

The distributions with the best statistical fit, i.e. the lowest AIC and BIC scores, were the Gompertz distribution for TV (Table 65), and the lognormal distribution for chemotherapy on AIC, but exponential for BIC (Table 66) – though the estimates are very close and no substantial differences were observed.

Table 65 Statistical fits of parametric distribution to PF-D transition (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
Generalized Gamma	289.9	300.4

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Table 66 Statistical fits of parametric distribution to PF-D transition (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
Generalized Gamma	270.0	280.3

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

D.2.5 Evaluation of visual fit

No over- or underestimation is visible during the overlapping period with observed data of time-to-progression.

D.2.6 Evaluation of hazard functions

The hazards for chemotherapy and TV seem to be monotonically decreasing for both arms, though a kink is observed in the chemotherapy arm. The number at risk at that point is however assumed to be quite lower. This observation supports the choice for Gompertz distribution for TV and the lognormal distribution for chemotherapy.

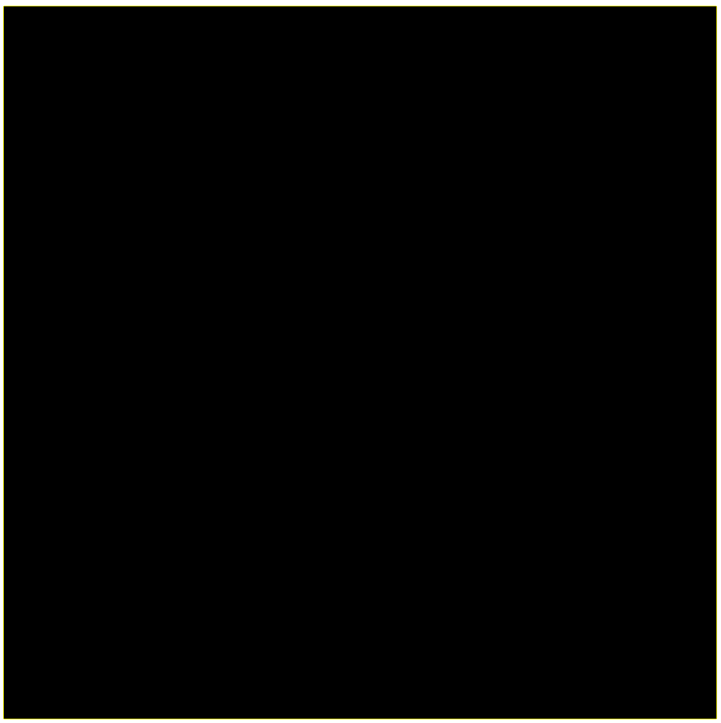

Figure 30 Smoothed hazard plot of pre-progression death of tisotumab vedotin and chemotherapy

D.2.7 Validation and discussion of extrapolated curves

No external evidence of PF to D transition in r/mCC is available.

D.2.8 Adjustment of background mortality

Background mortality was adjusted for in the semi-Markov model traces.

D.2.9 Adjustment for treatment switching/cross-over

N/A

D.2.10 Waning effect

N/A

D.2.11 Cure-point

N/A

D.3 Extrapolation of duration of treatment

D.3.1 Data input

Duration of treatment data from innovaTV 301 (DCO: January 2024).

D.3.2 Model

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, generalized gamma, and gamma distributions. Within each weekly cycle of the model, the probability of each of these transitions were calculated as a function of these two cause-specific hazards.

D.3.3 Proportional hazards

Extrapolations do not rely on proportional hazards assumption.

D.3.4 Evaluation of statistical fit (AIC and BIC)

The distributions with the best statistical fit, i.e. the lowest AIC and BIC scores, were the log-logistic distribution for TV and chemotherapy(Table 67 and Table 68).

Table 67 Statistical fits of parametric distribution of treatment duration (tisotumab vedotin)

Functional form	AIC	BIC
Exponential	1953.3	1956.8
Weibull	1908.2	1915.3
Log-Logistic	1882.1	1889.1
Lognormal	1884.5	1891.6
Gompertz	1945.2	1952.3
Gamma	1892.9	1900.0
Generalized Gamma	1884.8	1895.4

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Table 68 Statistical fits of parametric distribution of treatment duration (chemotherapy)

Functional form	AIC	BIC
Exponential	1767.3	1770.7
Weibull	1758.8	1765.7
Log-Logistic	1728.7	1735.6

Lognormal	1736.0	1742.9
Gompertz	1769.1	1776.1
Gamma	1749.6	1756.6
Generalized Gamma	1735.2	1745.7

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

D.3.5 Evaluation of visual fit

No implausible survival tail was observed for any of the distributions, and no over- or underestimation is visible during the overlapping period with observed data of time-to-progression.

Figure 31 Observed and extrapolated duration of treatment data of tisotumab vedotin

Figure 32 Observed and extrapolated duration of treatment data of chemotherapy

D.3.6 Evaluation of hazard functions

No smoothed hazards are available for duration of treatment survival.

D.3.7 Validation and discussion of extrapolated curves

N/A

D.3.8 Adjustment of background mortality

N/A

D.3.9 Adjustment for treatment switching/cross-over

N/A

D.3.10 Waning effect

N/A

D.3.11 Cure-point

N/A

Appendix E. Serious adverse events

All serious AEs are reported in Table 69. In this application, as stated, safety data (AEs) are presented as TEAEs.

Table 69 Serious adverse events

Preferred term	Tisotumab Vedotin (N = 250), n (%)	Chemotherapy (N = 239), n (%)
Overall	82 (32.8)	94 (39.3)
Urinary tract infection	10 (4.0)	17 (7.1)
Small intestinal obstruction	6 (2.4)	1 (0.4)
Abdominal pain	5 (2.0)	2 (0.8)
Sepsis	5 (2.0)	2 (0.8)
Pyrexia	4 (1.6)	4 (1.7)
Vaginal haemorrhage	4 (1.6)	3 (1.3)
Vomiting	4 (1.6)	2 (0.8)
Acute kidney injury	3 (1.2)	5 (2.1)

Constipation	3 (1.2)	0
Fatigue	3 (1.2)	4 (1.7)
Hyponatraemia	3 (1.2)	0
Pelvic pain	3 (1.2)	0
Anaemia	2 (0.8)	10 (4.2)
Hydronephrosis	2 (0.8)	7 (2.9)
Hypovolaemic shock	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]
Neutropenia	2 (0.8)	4 (1.7)
Non-cardiac chest pain	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pneumonia	2 (0.8)	3 (1.3)
Pyelonephritis acute	[redacted]	[redacted]
Stevens-Johnson syndrome	[redacted]	[redacted]
Urinary tract obstruction	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anal incontinence	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Bladder perforation	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Cholangitis	[redacted]	[redacted]

Conjunctivitis	[redacted]	[redacted]
Conjunctivitis bacterial	[redacted]	[redacted]
Cystitis radiation	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Disseminated intravascular coagulation	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Dyspnoea exertional	[redacted]	[redacted]
Enteritis	[redacted]	[redacted]
Enterocolitis infectious	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]
Erythema	[redacted]	[redacted]
Febrile neutropenia	1 (0.4)	8 (3.3)
Female genital tract fistula	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]
Gastrointestinal stoma complication	[redacted]	[redacted]
Gastrointestinal toxicity	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Haematochezia	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Ileus	[redacted]	[redacted]

Ileus paralytic	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Jaundice cholestatic	[redacted]	[redacted]
Large intestinal obstruction	[redacted]	[redacted]
Liver injury	[redacted]	[redacted]
Lymph node pain	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Malignant gastrointestinal obstruction	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Pancreatitis acute	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]
Proctitis	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Pyelonephritis	1 (0.4)	3 (1.3)
Pyuria	[redacted]	[redacted]
Rash macular	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Small intestinal perforation	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]
Stoma site discomfort	[redacted]	[redacted]
Urosepsis	[redacted]	[redacted]

Vertigo	[redacted]	[redacted]
Vulval abscess	[redacted]	[redacted]
Abdominal pain lower	[redacted]	[redacted]
Biliary obstruction	[redacted]	[redacted]
COVID-19	0	3 (1.3)
Cancer pain	[redacted]	[redacted]
Cardiac tamponade	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Device occlusion	[redacted]	[redacted]
Drug reaction with eosinophilia and systemic symptoms	[redacted]	[redacted]
Duodenal obstruction	[redacted]	[redacted]
Febrile bone marrow aplasia	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
Gastroesophageal reflux disease	[redacted]	[redacted]
Generalised oedema	[redacted]	[redacted]
Haematemesis	[redacted]	[redacted]
Hallucination	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Intermenstrual bleeding	[redacted]	[redacted]
Large intestine perforation	[redacted]	[redacted]

Lymphocyte count decreased	[redacted]	[redacted]
Nausea	0	3 (1.3)
Neutrophil count decreased	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Ovarian cyst torsion	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]
Pancytopenia	0	4 (1.7)
Pelvic infection	[redacted]	[redacted]
Pericardial effusion	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]
Rectal prolapse	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
Renal tubular disorder	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Rib fracture	[redacted]	[redacted]
Seizure	[redacted]	[redacted]
Shock haemorrhagic	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Truncus coeliacus thrombosis	[redacted]	[redacted]
Urinary tract infection bacterial	[redacted]	[redacted]

Urinary tract stoma complication	[redacted]	[redacted]
Urogenital fistula	[redacted]	[redacted]
Vesical fistula	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

Appendix F. Health-related quality of life

The pattern of missing data and completion for the EORTC-C30 instrument in the TV and chemotherapy arms is reported in Table 70 and Table 71, respectively. EORTC-C30 summary statistics is reported in Table 72.

The median follow-up time for EORTC-C30 assessments was 99 days (approximately 3.3 months.

Table 70 Pattern of missing data and completion – EORTC-C30 tisotumab vedotin (DCO 2023)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	231	[redacted]	[redacted]	[redacted]
Cycle 2	231	[redacted]	[redacted]	[redacted]
Cycle 3	231	[redacted]	[redacted]	[redacted]
Cycle 4	231	[redacted]	[redacted]	[redacted]
Cycle 5	231	[redacted]	[redacted]	[redacted]
Cycle 6	231	[redacted]	[redacted]	[redacted]
Cycle 7	231	[redacted]	[redacted]	[redacted]
Cycle 8	231	[redacted]	[redacted]	[redacted]
Cycle 9	231	[redacted]	[redacted]	[redacted]
Cycle 10	231	[redacted]	[redacted]	[redacted]
Cycle 11	231	[redacted]	[redacted]	[redacted]
Cycle 12	231	[redacted]	[redacted]	[redacted]
Cycle 13	231	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 14	231	[redacted]	[redacted]	[redacted]
Cycle 15	231	[redacted]	[redacted]	[redacted]
Cycle 16	231	[redacted]	[redacted]	[redacted]
Cycle 17	231	[redacted]	[redacted]	[redacted]
Cycle 18	231	[redacted]	[redacted]	[redacted]
Cycle 19	231	[redacted]	[redacted]	[redacted]
Cycle 20	231	[redacted]	[redacted]	[redacted]
Cycle 21	231	[redacted]	[redacted]	[redacted]
Cycle 22	231	[redacted]	[redacted]	[redacted]
Cycle 23	231	[redacted]	[redacted]	[redacted]
Cycle 24	231	[redacted]	[redacted]	[redacted]
Cycle 25	231	[redacted]	[redacted]	[redacted]
Cycle 26	231	[redacted]	[redacted]	[redacted]
Cycle 27	231	[redacted]	[redacted]	[redacted]
Cycle 28	231	[redacted]	[redacted]	[redacted]
Cycle 29	231	[redacted]	[redacted]	[redacted]
Cycle 30	231	[redacted]	[redacted]	[redacted]

Table 71 Pattern of missing data and completion – EORTC-C30 chemotherapy (DCO 2023)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of	Number of patients “at risk” at time point X	Number of patients who completed (% of patients

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
		patients at randomization)		expected to complete)
Baseline	203	[redacted]	[redacted]	[redacted]
Cycle 2	203	[redacted]	[redacted]	[redacted]
Cycle 3	203	[redacted]	[redacted]	[redacted]
Cycle 4	203	[redacted]	[redacted]	[redacted]
Cycle 5	203	[redacted]	[redacted]	[redacted]
Cycle 6	203	[redacted]	[redacted]	[redacted]
Cycle 7	203	[redacted]	[redacted]	[redacted]
Cycle 8	203	[redacted]	[redacted]	[redacted]
Cycle 9	203	[redacted]	[redacted]	[redacted]
Cycle 10	203	[redacted]	[redacted]	[redacted]
Cycle 11	203	[redacted]	[redacted]	[redacted]
Cycle 12	203	[redacted]	[redacted]	[redacted]
Cycle 13	203	[redacted]	[redacted]	[redacted]
Cycle 14	203	[redacted]	[redacted]	[redacted]
Cycle 15	203	[redacted]	[redacted]	[redacted]
Cycle 16	203	[redacted]	[redacted]	[redacted]
Cycle 17	203	[redacted]	[redacted]	[redacted]
Cycle 18	203	[redacted]	[redacted]	[redacted]
Cycle 19	203	[redacted]	[redacted]	[redacted]
Cycle 20	203	[redacted]	[redacted]	[redacted]
Cycle 21	203	[redacted]	[redacted]	[redacted]
Cycle 22	203	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 23	203	[redacted]	[redacted]	[redacted]
Cycle 24	203	[redacted]	[redacted]	[redacted]
Cycle 25	203	[redacted]	[redacted]	[redacted]
Cycle 26	203	[redacted]	[redacted]	[redacted]
Cycle 27	203	[redacted]	[redacted]	[redacted]
Cycle 28	203	[redacted]	[redacted]	[redacted]
Cycle 29	203	[redacted]	[redacted]	[redacted]
Cycle 30	203	[redacted]	[redacted]	[redacted]

Table 72 EORTC-C30 summary statistics (DCO 2023)

	TV		Chemotherapy		TV vs. chemotherapy
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]	Not reported.

	TV	Chemotherapy	TV vs. chemotherapy
Cycle 11	[redacted]	[redacted]	Not reported.
Cycle 12	[redacted]	[redacted]	Not reported.
Cycle 13	[redacted]	[redacted]	Not reported.
Cycle 14	[redacted]	[redacted]	Not reported.
Cycle 15	[redacted]	[redacted]	Not reported.
Cycle 16	[redacted]	[redacted]	Not reported.
Cycle 17	[redacted]	[redacted]	Not reported.
Cycle 18	[redacted]	[redacted]	Not reported.
Cycle 19	[redacted]	[redacted]	Not reported.
Cycle 20	[redacted]	[redacted]	Not reported.
Cycle 21	[redacted]	[redacted]	Not reported.
Cycle 22	[redacted]	[redacted]	Not reported.
Cycle 23	[redacted]	[redacted]	Not reported.
Cycle 24	[redacted]	[redacted]	Not reported.
Cycle 25	[redacted]	[redacted]	Not reported.
Cycle 26	[redacted]	[redacted]	Not reported.
Cycle 27	[redacted]	[redacted]	Not reported.
Cycle 28	[redacted]	[redacted]	Not reported.
Cycle 29	[redacted]	[redacted]	Not reported.
Cycle 30	[redacted]	[redacted]	Not reported.
End of treatment	[redacted]	[redacted]	Not reported.

Global Health Status from EORTC QLQ-C30

Appendix G. Probabilistic sensitivity analyses

An overview of the varied parameters in the probabilistic sensitivity analysis is displayed in Table 73.

Table 73 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Age (years)	51.44	50.42	52.47	Normal
Body surface area (m^2)	1.65	1.63	1.67	Normal
Body weight (kg)	63.31	61.88	64.74	Normal
Price of Tisotumab vedotin	13,600.00	11,065.50	16,391.94	Gamma
Price of Topotecan	500.00	406.82	602.64	Gamma
Price of Vinorelbine	1,500.00	1,220.46	1,807.93	Gamma
Price of Gemcitabine	385.00	313.25	464.04	Gamma
Price of Irinotecan	350.00	284.77	421.85	Gamma
Price of Pemetrexed	110.50	89.91	133.18	Gamma
PFS - Generalized Gamma - Independent model - Parameter A - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
PFS - Generalized Gamma - Independent model - Parameter B - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal

PFS - Generalized Gamma - Independent model - Parameter C - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
PFS - Generalized Gamma - Independent model - Parameter D - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
PFS - Generalized Gamma - Independent model - Parameter A - Chemotherapy - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
PFS - Generalized Gamma - Independent model - Parameter B - Chemotherapy - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
PFS - Generalized Gamma - Independent model - Parameter C - Chemotherapy - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
PFS - Generalized Gamma - Independent model - Parameter D - Chemotherapy - Overall population -	[redacted]	[redacted]	[redacted]	Multivariate Normal

innovaTV 301 trial - Markov				
OS - Gompertz - Independent model - Parameter A - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
OS - Gompertz - Independent model - Parameter B - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
OS - Gompertz - Independent model - Parameter C - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
OS - Gompertz - Independent model - Parameter D - Tisotumab vedotin - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
OS - Lognormal - Independent model - Parameter A - Chemotherapy - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
OS - Lognormal - Independent model - Parameter B - Chemotherapy - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal

OS - Lognormal - Independent model - Parameter C - Chemotherapy - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
OS - Lognormal - Independent model - Parameter D - Chemotherapy - Overall population - innovaTV 301 trial - Markov	[redacted]	[redacted]	[redacted]	Multivariate Normal
DoT - Generalized Gamma - Independent model - Parameter A - Tisotumab vedotin - Overall population - innovaTV 301 trial	[redacted]	[redacted]	[redacted]	Multivariate Normal
DoT - Generalized Gamma - Independent model - Parameter B - Tisotumab vedotin - Overall population - innovaTV 301 trial	[redacted]	[redacted]	[redacted]	Multivariate Normal
DoT - Generalized Gamma - Independent model - Parameter C - Tisotumab vedotin - Overall population - innovaTV 301 trial	[redacted]	[redacted]	[redacted]	Multivariate Normal
DoT - Log-Logistic - Independent model - Parameter A - Chemotherapy - Overall population - innovaTV 301 trial	[redacted]	[redacted]	[redacted]	Multivariate Normal
DoT - Log-Logistic - Independent model - Parameter B - Chemotherapy -	[redacted]	[redacted]	[redacted]	Multivariate Normal

Overall population - innovaTV 301 trial				
DoT - Log-Logistic - Independent model - Parameter C - Chemotherapy - Overall population - innovaTV 301 trial	[redacted]	[redacted]	[redacted]	Multivariate Normal
DoT - DoT (weeks) - Tisotumab vedotin	[redacted]	[redacted]	[redacted]	Normal
DoT - DoT (weeks) - Chemotherapy	[redacted]	[redacted]	[redacted]	Normal
Pre-progression disease management costs (weekly cost) - Year 1 - comparators	335.19	272.73	404.00	Gamma
Pre-progression disease management costs (weekly cost) - Year 2 - comparators	335.19	272.73	404.00	Gamma
Pre-progression disease management costs (weekly cost) - Year 3 - comparators	172.40	140.27	207.80	Gamma
Pre-progression disease management costs (weekly cost) - Year 4 - comparators	172.40	140.27	207.80	Gamma
Pre-progression disease management costs (weekly cost) - Year 5 - comparators	172.40	140.27	207.80	Gamma
Pre-progression disease management costs (weekly cost) - Year 6+ - comparators	142.70	116.10	171.99	Gamma
Pre-progression disease management costs (weekly cost) -	335.19	272.73	404.00	Gamma

Year 1 - Tisotumab vedotin				
Pre-progression disease management costs (weekly cost) - Year 2 - Tisotumab vedotin	335.19	272.73	404.00	Gamma
Pre-progression disease management costs (weekly cost) - Year 3 - Tisotumab vedotin	172.40	140.27	207.80	Gamma
Pre-progression disease management costs (weekly cost) - Year 4 - Tisotumab vedotin	172.40	140.27	207.80	Gamma
Pre-progression disease management costs (weekly cost) - Year 5 - Tisotumab vedotin	172.40	140.27	207.80	Gamma
Pre-progression disease management costs (weekly cost) - Year 6+ - Tisotumab vedotin	142.70	116.10	171.99	Gamma
Pre-progression disease management costs for ocular events at treatment initiation (one-off cost) - Tisotumab vedotin	477.52	388.53	575.55	Gamma
Pre-progression disease management costs for ocular events before each administration (weekly cost) - Tisotumab vedotin	43.36	35.28	52.26	Gamma
Post-progression disease management costs (weekly cost) -	335.19	272.73	404.00	Gamma

Year 1 - comparators and Tisotumab vedotin				
Post-progression disease management costs (weekly cost) - Year 2 - comparators and Tisotumab vedotin	335.19	272.73	404.00	Gamma
Post-progression disease management costs (weekly cost) - Year 3 - comparators and Tisotumab vedotin	172.40	140.27	207.80	Gamma
Post-progression disease management costs (weekly cost) - Year 4 - comparators and Tisotumab vedotin	172.40	140.27	207.80	Gamma
Post-progression disease management costs (weekly cost) - Year 5 - comparators and Tisotumab vedotin	172.40	140.27	207.80	Gamma
Post-progression disease management costs (weekly cost) - Year 6+ - comparators and Tisotumab vedotin	142.70	116.10	171.99	Gamma
Terminal care costs	24,910.00	20,267.77	30,023.76	Gamma
AE costs - Tisotumab vedotin	448.69	365.07	540.80	Gamma
AE costs - Chemotherapy	1,013.00	824.21	1,220.95	Gamma
Administration by component unit costs - Medicingivning ved intravenøs infusion	1,467.00	1,193.61	1,768.16	Gamma

Administration by component unit costs - Topical	0.00	0.00	0.00	Gamma
Administration by component unit costs - Oral	0.00	0.00	0.00	Gamma
Post-progression treatment acquisition costs - Tisotumab vedotin	6,220.30	5,061.08	7,497.26	Gamma
Post-progression treatment acquisition costs - Chemotherapy	6,220.30	5,061.08	7,497.26	Gamma
Post-progression treatment administration costs - Tisotumab vedotin	20,621.86	16,778.77	24,855.31	Gamma
Post-progression treatment administration costs - Chemotherapy	20,621.86	16,778.77	24,855.31	Gamma
Pre-progression treatment RDI - Tisotumab vedotin	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment RDI - Tisotumab vedotin - Dexamethasone 0.1%	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment RDI - Tisotumab vedotin - Brimonidine tartrate 0.2%	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment RDI - Chemotherapy - Topotecan	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment RDI -	[redacted]	[redacted]	[redacted]	Beta

Chemotherapy - Vinorelbine				
Pre-progression treatment RDI - Chemotherapy - Gemcitabine	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment RDI - Chemotherapy - Irinotecan	[redacted]	[redacted]	[redacted]	Beta
Pre-progression treatment RDI - Chemotherapy - Pemetrexed	[redacted]	[redacted]	[redacted]	Beta
Post-progression treatment RDI - Topotecan	[redacted]	[redacted]	[redacted]	Beta
Post-progression treatment RDI - Vinorelbine	[redacted]	[redacted]	[redacted]	Beta
Post-progression treatment RDI - Gemcitabine	[redacted]	[redacted]	[redacted]	Beta
Post-progression treatment RDI - Irinotecan	[redacted]	[redacted]	[redacted]	Beta
Post-progression treatment RDI - Pemetrexed	[redacted]	[redacted]	[redacted]	Beta
QALY decrement due to AE - Tisotumab vedotin	-0.0020021	0.00	0.00	Beta
QALY decrement due to AE - Chemotherapy	-0.0010830	0.00	0.00	Beta
Utility - pre-progression	[redacted]	[redacted]	[redacted]	Beta
Utility - post-progression	[redacted]	[redacted]	[redacted]	Beta

Patient travel and time costs - AE - Tisotumab vedotin-one-off	1,967.53	1,600.86	2,371.44	Gamma
Patient travel and time costs - AE - Chemotherapy - one-off	3,776.81	3,072.96	4,552.15	Gamma
Patient travel and time costs (weekly) - year 1	36.79	29.93	44.34	Gamma
Patient travel and time costs (weekly) - year 2	36.79	29.93	44.34	Gamma
Patient travel and time costs (weekly) - year 3	18.39	14.96	22.17	Gamma
Patient travel and time costs (weekly) - year 4	18.39	14.96	22.17	Gamma
Patient travel and time costs (weekly) - year 5	18.39	14.96	22.17	Gamma
Patient travel and time costs (weekly) - year 6+	12.26	9.98	14.78	Gamma

Appendix H. Literature searches for the clinical assessment

Not relevant. Head-to-head trial.

Appendix I. Literature searches for health-related quality of life

N/A

Appendix J. Literature searches for input to the health economic model

N/A.

Appendix K. Prior treatments in innovaTV 301

A summary of prior treatments is summarised in Table 74 and Table 75

Table 74 Summary of Prior Systemic and Radiation Therapies and Surgical Treatment (ITT analysis set)

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy [a] (N=249) n (%)
Subjects who received any prior systemic therapy or radiation for cervical cancer	253 (100)	249 (100)
Subjects who received any prior systemic therapy	253 (100)	249 (100)
Subjects who received any prior radiation therapy for cervical cancer	205 (81.0)	203 (81.5)
Subjects who received any prior radiation therapy for cervical cancer	118 (46.6)	116 (46.6)
Subjects who received external beam radiation therapy	198 (78.3)	190 (76.3)
Subjects who received brachytherapy	117 (46.2)	121 (48.6)
Subjects with bevacizumab in combination with chemotherapy doublet as 1L therapy [b]	155 (61.3)	147 (59.0)
Subjects who received any prior surgical treatment for cervical cancer	116 (45.8)	117 (47.0)

[a]The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
[b]Chemotherapy doublet includes: paclitaxel + cisplatin or paclitaxel + carboplatin or paclitaxel + topotecan.
Source: InnovaTV 301 Clinical study report – appendix 14 (51)

Table 75 Prior Systemic Regimen (ITT analysis set)

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy [a] (N=249) n (%)
Number of prior recurrent/metastatic systemic regimens		
1	159 (62.8)	149 (59.8)
2	93 (36.8)	100 (40.2)
Unknown	1 (0.4)	0

[a]The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Regimen can be a combination of individual drugs, for example, BEVACIZUMAB/CISPLATIN/TOPOTECAN.
Medications are sorted by descending order of frequency in total column.
Source: InnovaTV 301 Clinical study report – appendix 14 (data on file) (51)

Appendix L. Reasons for PFS censoring

Reasons for PFS censoring are summarised in Table 76.

Table 76 Reasons for PFS censoring per investigator assessment (ITT analysis set)

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy[a] (N=249) n (%)
Censored subjects	[redacted]	[redacted]
Reasons for censoring[b]		
New anti-cancer treatment (systemic, radiation, or surgery) started before PD or death observed	[redacted]	[redacted]
Death or progression right after two or more consecutively missed scheduled tumour assessments	[redacted]	[redacted]
No adequate post-baseline tumour assessments[c]	[redacted]	[redacted]
No documented disease progression, still on study	[redacted]	[redacted]
Off study without events	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]

[a]The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
[b]Denominator is number of censored subjects
[c]Censoring date will be date of randomisation when subject had no post-baseline tumor assessment and had ether no death or death after a prolonged duration (e.g., after the planned 2nd response assessment date)
The ordering of censoring is: 1. New anti-cancer treatment (systemic, radiation, or surgery) started before PD or death observed; 2. Death or PD right after two or more consecutively missed scheduled tumor assessments; 3. No adequate post-baseline tumor assessments; 4. No documented disease, still on study; 5. Off study without events
Source: InnovaTV 301 Clinical study report (data on file) (51)

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk