HTA Austria
Austrian Institute for
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GmbH

Tisotumab vedotin (TIVDAK®) for the treatment of adult patients with recurrent or metastatic cervical cancer

HTA-Appendix

Final Appendix

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Conflict of interest

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1 Introduction

1.1 Disease background

Table 1-1: FIGO staging of cancer of the cervix uteri (2018) [1]

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with a maximum depth of invasion ≤5 mm[a]
IA1	Measured stromal invasion ≤3 mm in depth
IA2	Measured stromal invasion >3 and ≤5 mm in depth
IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter[b]
IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
IB2	Invasive carcinoma >2 and ≤4 cm in greatest dimension
IB3	Invasive carcinoma >4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement is limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma ≤4 cm in greatest dimension
IIA2	Invasive carcinoma >4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma 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)[c], irrespective of tumour size and extent (with r and p notations)[d]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy-proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent pelvic organs
IVB	Spread to distant organs

Notes:

[a] Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumour size and extent, in all stages. Pathological findings supersede imaging and clinical findings.

[b] The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.

[c] Isolated tumour cells do not change the stage but their presence should be recorded.

[d] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r; if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

1.2 Standard of care in Austria

No content.

1.3 Medicinal product under evaluation

To reduce the risk of ocular adverse reactions, patients should adhere to the following recommendations for the application of:

- Topical preservative-free corticosteroid eye drops (e.g., dexamethasone 0.1%): 1 drop in each eye 3 times daily starting 1 day prior to each infusion and to continue as prescribed for 3 days after each infusion.
- Topical preservative-free ocular vasoconstrictor drops (e.g., brimonidine tartrate 0.2% 3 drops per eye or the equivalent as prescribed) immediately prior to each infusion.
- Cooling eye pads following the administration of eye drops, prior to the start of the infusion, during and for 30 minutes after the infusion.
- Topical preservative-free lubricating eye drops multiple times every day throughout treatment and for 30 days after the last dose of tisotumab vedotin [2].

2 Scope of assessment

2.1 Research question

No content.

2.2 Inclusion criteria

No content.

3 Methods

Guiding questions

Table 3-1: Health problem and current use

Element ID	Research question
A0001	For which health conditions, and for what purposes, is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table 3-2: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators, and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?
A0018	What are the other typical or common alternatives to the current technology?
A0022	Who manufactures the technology?

Table 3-3: Clinical effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect the progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?
D0029	What are the overall benefits and harms of the technology in health outcomes?

Table 3-4 Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to the dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Table 3-5: Economic aspects

Element ID	Research question
E0001	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
A0002	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated costs of the assessed technology and its comparator(s)?
G0007	What are the likely budget impacts of implementing the technologies being compared?
E0005	What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s) (outcome identification, measurement and valuation)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?
E0013	What methodological assumptions were made in relation to the technology and its comparator(s)?
E0012	To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?

Table 3-6: Organisational, ethical, and social aspects

Element ID	Research question
G0001:	How does the technology affect the current work processes?
G0002	What kind of involvement has to be mobilised for patients/participants and important others and/or caregivers?
G0101	What are the processes ensuring access to the new technology for patients/participants?
H0200	What are the experiences of living with the condition?
H0100	What expectations and wishes do patients have with regard to the technology, and what do they expect to gain from the technology?
H0006	How do patients perceive the technology under assessment?
H0002	What is the burden on caregivers?
H0202	How are treatment choices explained to patients?
F0010	What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?
F0011	What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.?
F0104	Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention?
F0005	Is the technology used for individuals who are especially vulnerable?
H0012	Are there factors that could prevent a group or person from gaining access to the technology?

3.1 Search strategy

3.1.1 Cochrane (06.02.2026)

Search name: Tisotumab vedotin	
Search date: 06.02.2026	
ID #	Search
1	('humax tf' OR 'humax-tf' OR 'tf 011' OR 'tf011' OR 'tisotumab'):ti,ab,kw (Word variations have been searched)
2	'humax tf adc' OR 'humax-tf-adc' OR 'tf 011 mmae' OR 'tf011mmae' OR 'tisotumab vedotin tftv' OR 'tisotumab vedotin-tftv' OR 'tivdak' OR 'tisotumab vedotin'
3	tisotumab
4	vendotin
5	tisotumab vedotin
6	tisotumab NEAR/1 vedotin
7	tisotumab NEXT vedotin
8	GCT1015*
9	humax NEXT tf
10	tf
11	humax*

12	#10 AND #11
13	tf011
14	humaxtfadc
15	igg1
16	1015
17	#15 AND #16
18	t41737f88a
19	tivdak
20	tivda*
21	{OR #3-#9} OR {OR #11-#14} OR [3-#20]
22	{OR #21, #1, #2}
23	cervix
24	cervi*
25	cervical
26	cervical*
27	[4-#26]
28	#22 AND #26
29	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
30	#28 NOT #29
Total hits: 23	

3.1.2 Embase (06.02.2026)

Search name: Tisotumab vedotin		
Search date: 06.02.2026		
ID #	Query	Results
48	#46 NOT #47	273
47	'clinical trial':dtype	552803
46	#40 AND #45	283
45	#41 OR #42 OR #43 OR #44	595759
44	'uterine cervix'	229802
43	cervical	462253
42	cervi*	595759
41	cervix	247339
40	#25 OR #26 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	825
39	humax?	4
38	tf NEAR/1 mmae	2
37	t4173*	4
36	igg110150111006	-
35	igg1 AND 1015 AND 011	1
34	humaxtf*	6
33	humax NEXT/1 tf	19
32	humax*	361
31	gct1015*	5
30	tivda*	56
29	tivdak	55
28	#26 AND #27	461
27	vedotin	13495
26	tisotuma*	473

25	'tisotumab'/exp OR 'tisotumab'	473
24	#22 NOT #23	273
23	'clinical trial':dtype	552803
22	#16 AND #21	283
21	#17 OR #18 OR #19 OR #20	595759
20	'uterine cervix'	229802
19	cervical	462253
18	cervi*	595759
17	cervix	247339
16	#1 OR #2 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	825
15	humax?	4
14	tf NEAR/1 mmae	2
13	t4173*	4
12	igg110150111006	-
11	igg1 AND 1015 AND 011	1
10	humaxtf*	6
Total hits: 273		

3.1.3 International HTA Database (06.02.2026)

Search name: Tisotumab vedotin	
Search date: 06.02.2026	
ID #	Search
6	(igg1 AND 105) OR (tf AND mmae) OR (tivdak*) OR (humax*) OR (tisotu*),"3","2026-02-12T11:14:57.000000Z"
5	igg1 AND 105,"0","2026-02-12T11:14:37.000000Z"
4	tf AND mmae,"1","2026-02-12T11:14:10.000000Z"
3	tivdak*,"0","2026-02-12T11:13:23.000000Z"
2	humax*,"1","2026-02-12T11:13:15.000000Z"
1	tisotu*,"1","2026-02-12T11:13:09.000000Z"
Total hits: 3	

3.1.4 Pubmed (06.02.2026)

Search name: Tisotumab vedotin		
Search date: 06.02.2026		
ID #	Search	Results
51	(((((((((tivdak) OR (TIVDAK)) OR (tivda*)) OR ((((011) OR ("tf mmae"[tiab:~2])) OR ("mmae 11"[tiab:~2])) OR (tf-011-mmae))) OR ((((igG1-1015*) OR ("igG1 1015"[tiab:~2])) OR (t41737f88a)) OR (t4173*))) OR (((((((tisotumab) OR ((tisotumab) AND (vedotin))) OR (tisotumab-vedotin)) OR (tisotuma*)) OR ("tisotumab tftv"[tiab:~2])) OR ("tisotumab vedotin"[tiab:~2])) OR ("tisotumab vedotin" [Supplementary Concept]))) OR (((((((((humax) OR (humax*)) OR ((humax*) AND (tf))) OR (humax* [Title/Abstrct:~2] tf)) OR (humax-tf)) OR (humax* [Title/Abstract:~2] adc)) OR (humax-tf-adc)) OR (humax-tf*)) OR (humaxtfadc))) OR ('humax tf' OR 'humax-tf' OR 'tf 011' OR 'tf011' OR 'tisotumab')) AND ((((cervi*) OR (cervix)) OR (cervical)) OR (cervica*))) NOT ((clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr))	79
50	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr)	238,866

49	(((((((tivdak) OR (TIVDAK)) OR (tivda*)) OR ((((011) OR ("tf mmae"[tiab:~2])) OR ("mmae 11"[tiab:~2])) OR (tf-011-mmae))) OR ((((igG1-1015*) OR ("igG1 1015"[tiab:~2])) OR (t41737f88a)) OR (t4173*))) OR (((((((tisotumab) OR ((tisotumab) AND (vedotin))) OR (tisotumab-vedotin)) OR (tisotuma*)) OR ("tisotumab tftv"[tiab:~2])) OR ("tisotumab vedotin"[tiab:~2])) OR ("tisotumab vedotin" [Supplementary Concept]))) OR ((((((((humax) OR (humax*)) OR ((humax*) AND (tf))) OR (humax* [Title/Abstrct:~2] tf)) OR (humax-tf)) OR (humax* [Title/Abstract:~2] adc)) OR (humax-tf-adc)) OR (humax-tf*)) OR (humaxtfadc))) OR ('humax tf' OR 'humax-tf' OR 'tf 011' OR 'tf011' OR 'tisotumab')) AND ((((cervi*) OR (cervix)) OR (cervical)) OR (cervica*))	88
48	(((cervi*) OR (cervix)) OR (cervical)) OR (cervica*)	839,762
47	cervica*	337,037
46	cervical	795,894
45	cervix	77,343
44	cervi*	387,55
43	(((((((tivdak) OR (TIVDAK)) OR (tivda*)) OR ((((011) OR ("tf mmae"[tiab:~2])) OR ("mmae 11"[tiab:~2])) OR (tf-011-mmae))) OR ((((igG1-1015*) OR ("igG1 1015"[tiab:~2])) OR (t41737f88a)) OR (t4173*))) OR (((((((tisotumab) OR ((tisotumab) AND (vedotin))) OR (tisotumab-vedotin)) OR (tisotuma*)) OR ("tisotumab tftv"[tiab:~2])) OR ("tisotumab vedotin"[tiab:~2])) OR ("tisotumab vedotin" [Supplementary Concept]))) OR ((((((((humax) OR (humax*)) OR ((humax*) AND (tf))) OR (humax* [Title/Abstrct:~2] tf)) OR (humax-tf)) OR (humax* [Title/Abstract:~2] adc)) OR (humax-tf-adc)) OR (humax-tf*)) OR (humaxtfadc))) OR ('humax tf' OR 'humax-tf' OR 'tf 011' OR 'tf011' OR 'tisotumab')	395
42	'humax tf' OR 'humax-tf' OR 'tf 011' OR 'tf011' OR 'tisotumab'	325
41	((((((tivdak) OR (TIVDAK)) OR (tivda*)) OR ((((011) OR ("tf mmae"[tiab:~2])) OR ("mmae 11"[tiab:~2])) OR (tf-011-mmae))) OR ((((igG1-1015*) OR ("igG1 1015"[tiab:~2])) OR (t41737f88a)) OR (t4173*))) OR (((((((tisotumab) OR ((tisotumab) AND (vedotin))) OR (tisotumab-vedotin)) OR (tisotuma*)) OR ("tisotumab tftv"[tiab:~2])) OR ("tisotumab vedotin"[tiab:~2])) OR ("tisotumab vedotin" [Supplementary Concept]))) OR ((((((((humax) OR (humax*)) OR ((humax*) AND (tf))) OR (humax* [Title/Abstrct:~2] tf)) OR (humax-tf)) OR (humax* [Title/Abstract:~2] adc)) OR (humax-tf-adc)) OR (humax-tf*)) OR (humaxtfadc))	180
40	((tivdak) OR (TIVDAK)) OR (tivda*)	114
39	tivda*	11
38	TIVDAK	113
37	tivdak	113
36	(((011) OR ("tf mmae"[tiab:~2])) OR ("mmae 11"[tiab:~2])) OR (tf-011-mmae)	7
35	tf-011-mmae	2
34	"mmae 11"[tiab:~2]	2
33	"tf mmae"[tiab:~2]	4
32	11	1
31	mmae	912
30	(((igG1-1015*) OR ("igG1 1015"[tiab:~2])) OR (t41737f88a)) OR (t4173*)	20
29	t4173*	19
28	t41737f88a	18
27	"igG1 1015"[tiab:~2]	1
26	igG1-1015*	1
25	((((((tisotumab) OR ((tisotumab) AND (vedotin))) OR (tisotumab-vedotin)) OR (tisotuma*)) OR ("tisotumab tftv"[tiab:~2])) OR ("tisotumab vedotin"[tiab:~2])) OR ("tisotumab vedotin" [Supplementary Concept])	108
24	"tisotumab vedotin" [Supplementary Concept]	18
23	(((((tisotumab) OR ((tisotumab) AND (vedotin))) OR (tisotumab-vedotin)) OR (tisotuma*)) OR ("tisotumab tftv"[tiab:~2])) OR ("tisotumab vedotin"[tiab:~2])	108
22	"tisotumab vedotin"[tiab:~2]	105
21	"tisotumab tftv"[tiab:~2]	9
20	tftv	13
19	tisotuma*	108

18	tisotumab-vedotin	106
17	(tisotumab) AND (vedotin)	106
16	vedotin	3,058
15	tisotumab	108
14	(((((((humax) OR (humax*)) OR ((humax*) AND (tf))) OR (humax* [Title/Abstrct:~2] tf)) OR (humax-tf)) OR (humax* [Title/Abstract:~2] adc)) OR (humax-tf-adc)) OR (humax-tf*)) OR (humaxtfadc)	63
13	humaxtfadc	2
12	humax-tf*	2
11	humax-tf-adc	2
10	humax* [Title/Abstract:~2] adc	6
9	adc	48,34
8	humax-tf	1
7	humaxtf	0
6	humaxtf - Schema: all	0
5	humax* [Title/Abstrct:~2] tf	3
4	(humax*) AND (tf)	3
3	tf	40,322
2	humax*	63
1	humax	60
Total hits: 79		

3.2 Study selection – PRISMA flow chart

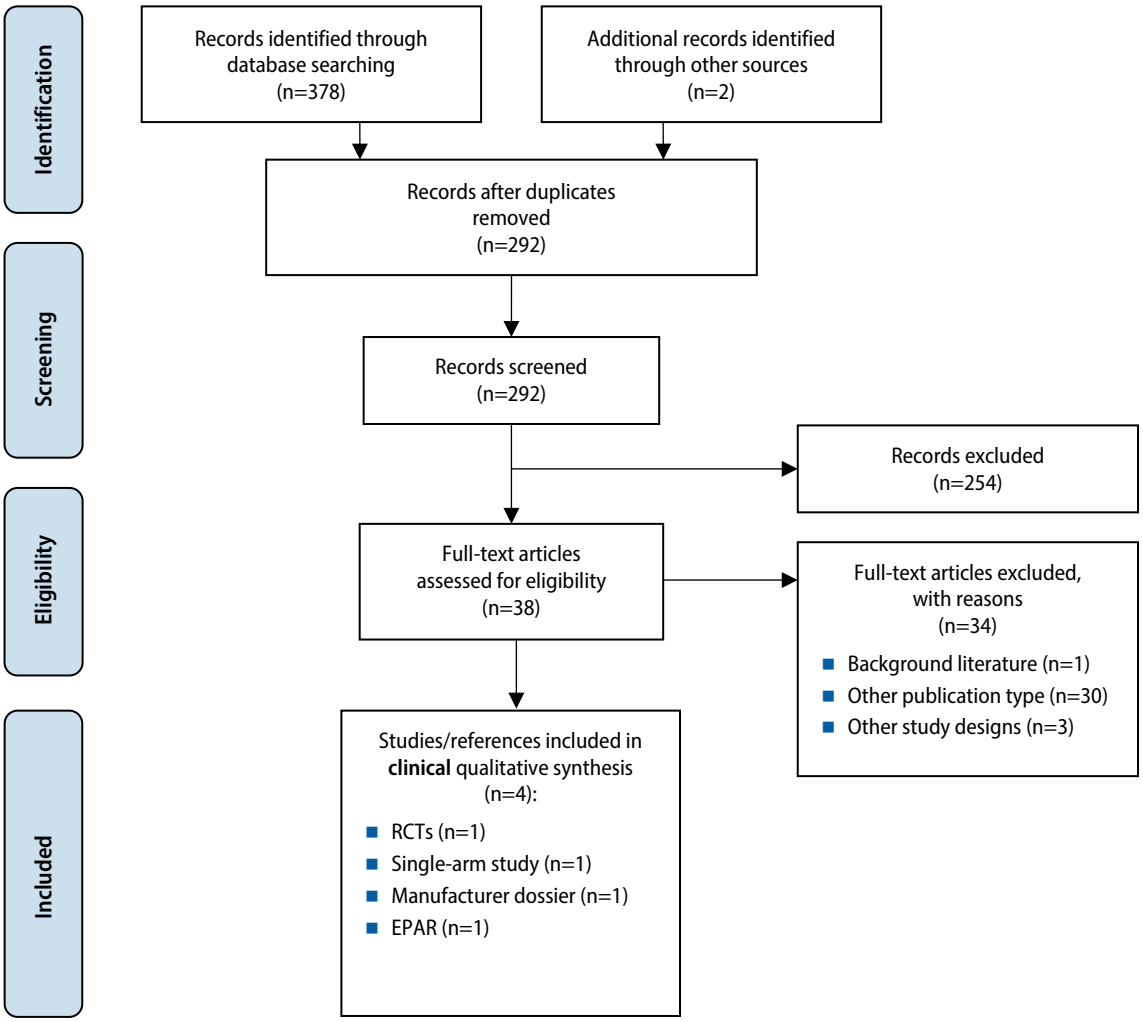

Figure 3-1: PRISMA flow diagram of the identification and selection of clinical evidence

Abbreviations: EPAR ... European Public Assessment Report, n ... number of references, RCT ...randomised controlled trial

4 Clinical effectiveness and safety

4.1 Characteristics of the included studies

Table 4-1: In- and exclusion criteria of the innovaTV 301 study [3]

Inclusion criteria	Exclusion criteria
■ Age ≥18 years, or considered an adult by local regulations, at the time of consent. ■ Signed informed consent form indicating that the patient understands the purpose of and procedures required for the study and is willing to participate in the study prior to any other study-related assessments or procedures. ■ Recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology, and: a. Disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible), defined as either: – paclitaxel+cisplatin+bevacizumab+ anti-PD-(L)1 agent, or – paclitaxel+carboplatin+bevacizumab+ anti-PD-(L)1 agent, or – paclitaxel+topotecan/nogitecan+bevacizumab+ anti-PD-(L)1 agent b. Has received 1 or 2 prior systemic therapy regimens for recurrent and/or metastatic cervical cancer. Chemotherapy administered in 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 should be counted. c. Is not a candidate for curative therapy, including but not limited to radiotherapy or exenterative surgery. ■ Measurable disease according to RECIST v1.1 as assessed by the investigator, defined as: a. A minimum of one non-nodal lesion ≥10 mm in the longest diameter from a nonirradiated area OR b. Lymph node lesion ≥15 mm in the shortest diameter from a non-irradiated area. ■ Must demonstrate acceptable screening laboratory values: ○ **Renal Function:** Calculated eGFR (MDRD formula) ≥50 mL/min/1.73m2 ○ **Liver Function:** - ALT ≤3× ULN (if liver tumour/metastases are present, then ≤5×ULN is allowed)	■ Primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned in inclusion criteria. ■ Clinically significant bleeding issues or risks: ○ Known past or current coagulation defects leading to an increased risk of bleeding ○ Diffuse alveolar hemorrhage from vasculitis ○ Known bleeding diathesis ○ Ongoing major bleeding ○ Trauma with increased risk of life-threatening bleeding ○ History of severe head trauma or intracranial surgery within 8 weeks of study entry. ■ Cardiovascular issues or risks: a. Clinically significant cardiac disease, including unstable angina or acute myocardial infarction, 6 months prior to screening b. Any medical history of congestive heart failure (grade III or IV as classified by the New York Heart Association) c. Any medical history of decreased cardiac ejection fraction of <45% d. A marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval >450 msec) e. A complete left bundle branch block (defined as a QRS interval ≥120 msec in left bundle branch block form) or an incomplete left bundle branch block ■ CNS: any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening is allowed). ■ Ophthalmological: Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis, ocular Stevens-Johnson syndrome or toxic epidermal necrolysis, mucus pemphigoid, and participants with penetrating ocular transplants are ineligible. Cataracts alone is not an exclusion criterion. ■ Other cancer: known past or current malignancy other than inclusion diagnosis. Exceptions are malignancies with a negligible risk of metastasis or death. ■ Brain metastases are allowed if the following criteria are met: definitive therapy (eg, surgery or stereotactic brain radiotherapy) has been completed >8 weeks before the first dose of study treatment; no evidence of clinical or radiologic progression of the brain metastases; participant has completed perioperative corticosteroid therapy or steroid taper.

Inclusion criteria	Exclusion criteria
- AST ≤3×ULN (if liver tumour/metastases are present, then ≤5×ULN is allowed) - Bilirubin ≤1.5×ULN (except in participants diagnosed with Gilbert's syndrome, direct bilirubin ≤2×ULN) ○ **Haematological Status** - C1 Hemoglobin ≥5.6 mmol/L (9.0 g/dL) - ANC ≥1500/ μ L (1.5x109/L) - Platelet count ≥100×109/L ○ **Coagulation Status (for participants NOT on anti-coagulation therapy)** - aPTT ≤1.5×ULN - INR ≤1.2 ○ **Coagulation Status (for participants on anti-coagulation therapy)** - aPTT ≤1.5×ULN - INR ≤2.5d ■ ECOG performance status of 0 or 1 prior to randomization. ■ Life expectancy of at least 3 months. ■ Negative serum pregnancy test for participants of reproductive potential. ■ Participants who are postmenopausal, permanently sterilised, or previously subjected to bilateral oophorectomy, bilateral salpingectomy and/or hysterectomy can be considered as not having reproductive potential. ■ Participants of reproductive potential must agree to use adequate contraception during and for 6 months after the last study treatment administration. ■ Participants must agree not to breastfeed or donate ova, starting at the time of informed consent and continuing through 6 months after receiving the last dose of study drug administration. ■ Where required by local health authorities, has negative serology for hepatitis B surface antigen/HBV DNA, or hepatitis C antibody (HCVAb) or RNA. Active hepatitis C is defined by a known positive HCVAb result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. ■ Willing and able to adhere to the prohibitions and restrictions specified in the protocol.	■ Surgery/procedures: major surgery within 4 weeks or minor surgery within 7 days prior to the first study treatment administration. Participants must have recovered adequately from the toxicity or complications from the intervention prior to starting study treatment. Participants who have planned major surgery during the treatment period must be excluded from the study. ■ Peripheral neuropathy ≥grade 2. ■ Prior anti-cancer therapy: a. Any prior treatment with MMAE-derived drugs. b. Radiotherapy within 21 days prior to the first administration of study treatment. Participants must have recovered from all clinically significant radiation-related toxicities. At least 42 days must have elapsed from the last administration of chemo-radiotherapy. c. Small molecules, chemotherapy, immunotherapy, or monoclonal antibodies within 28 days prior to the first administration of study treatment. d. Currently participating in or has participated in a study of an investigational agent or device and received active treatment within 28 days prior to the first dose of study treatment. ■ Other: a. Ongoing significant, uncontrolled medical condition. b. Clinically significant active viral, bacterial, or fungal infection requiring IV or oral treatment with antimicrobial therapy ending <7 days prior to first study treatment administration. c. Clinically relevant bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage. d. Participants with clinical symptoms or signs of gastrointestinal obstruction and who require parenteral hydration or nutrition at the time of the first dose of study treatment. ■ Has known seropositivity of HIV; known medical history of hepatitis B or C infection. ■ Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of tisotumab vedotin. ■ Participant is pregnant or intends to conceive children within 6 months of ending study treatment. ■ Participant is breastfeeding and cannot discontinue breastfeeding for the duration of the study and ≥6 months after the last study treatment administration. ■ Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments. ■ Known allergies, hypersensitivity, or intolerance to study treatment or its excipients. ■ Known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

Abbreviations: ALT …alanine aminotransferase, ANC …absolute neutrophil count, aPTT …activated partial thromboplastin time, AST …aspartate aminotransferase, CNS …central nervous system, ECOG …Eastern Cooperative Oncology Group, eGFR …estimated glomerular filtration rate, HBV …hepatitis B virus, HCVAb …hepatitis C antibody, HIV …human immunodeficiency virus, INR …International normalized ratio, MMAE …monomethyl auristatin E, n … number of randomized patients, PD-1 …programmed cell death 1, PD-L1 …programmed cell death-ligand 1, r/mCC … recurrent/metastatic cervical cancer, RECIST …Response Evaluation Criteria In Solid Tumors, ULN …upper limit of normal

Table 4-2: Study endpoints for the innovaTV 301 study [3]

Study reference/ID Outcome category	Endpoints as defined in the study protocol
InnovaTV-301	
Primary efficacy endpoint	■ Overall survival
Key secondary efficacy endpoints	■ Progression-free survival based on RECIST v1.1 as assessed by the investigator ■ Confirmed objective response rate based on RECIST v1.1 as assessed by the investigator
Exploratory efficacy endpoints	■ Tumour tissue factor expression (via immunohistochemistry or RNA) in relation to efficacy endpoints ■ Baseline characteristics and changes from baseline of biomarkers from peripheral blood and/or formalin-fixed paraffin-embedded tumour tissue in relation to efficacy endpoints ■ PK concentrations and anti-drug antibodies associated with tisotumab vedotin
Safety endpoints	■ Treatment-emergent adverse events (TEAEs) of all grades ■ TEAEs leading to dose interruption, dose reduction, dose delay or study treatment discontinuation ■ Serious adverse events ■ AEs of special interest

Abbreviations: RECIST ...Response Evaluation Criteria In Solid Tumors, PK ...pharmacokinetics, RNA ...ribonucleic acid, TEAE ...treatment-related adverse events

Table 4-3: Study protocol amendments in the innovaTV 301 study [5]

Version/ amendment	Date	Section # and name	Description of Change	Brief Rationale
innovaTV 301				
Original protocol	17 Sept 2020			
Amendment 1	23 Nov 2020	1.1 Synopsis, 1.2 Study Schema, 1.3 Schedule of Activities, 2.1.3 Control Arm, 4.3 Justification for Dose, 6 Study Intervention, 10.7.5 Recommended Dose Modifications for Pemetrexed	Pemetrexed added as an option for the investigator's choice chemotherapy arm	Increase treatment flexibility for investigators with participants in the comparator arm
		6.6.1.2 Dose Delay for Tisotumab Vedotin, 7.1.1 Summary of Safety Stopping Rules	Duration of tisotumab vedotin dose delay due to toxicity changed from 12 weeks to 6 weeks before treatment is discontinued	Enhancement of participant safety
		1.3, Schedule of Activities	Biomarker and PRO collection timepoints were made identical for both treatment arms	Correction
		5.3, Lifestyle Considerations	Added lifestyle recommendations to avoid contributing factors to the development of dry eye	Enhancement of participant safety
		Throughout protocol	Sponsor company name updated	Seattle Genetics has changed its name to "Seagen Inc"

Version/ amendment	Date	Section # and name	Description of Change	Brief Rationale
		1.1 Synopsis, 4.2 Scientific Rationale for Study Design	Description of IDMC edited to be consistent with wording used in Section 9.8.1	Consistency of language throughout the protocol
		1.1 Synopsis, 5 Study Population	Participant number description changed to the number randomised; Definition of "Enrolled" removed	Clarification
		8.2.6 Clinical Laboratory Assessments	Pregnancy test results are no longer excepted from reporting to the central laboratory	Consistency of the collection of results for all clinical laboratory testing
		10.7 Recommended Dose Modifications for Chemotherapy Arm	Source citations added for recommended dose modifications	Compliance with best practices for study protocols
Amendment 2	20 Aug 2021	Title page	Logo and study numbers for cooperative groups ENGOT and GOG added	In addition to reflecting the cooperative groups on the study
		Title page		New medical monitor assigned to the study
		1.3 Schedule of Activities	Randomisation window changed from within ≤3 days of C1D1 to within ≤7 days	Time window for randomisation extended to better accommodate premedication and dosing schedules for the investigator's choice of chemotherapy options
		1.3 Schedule of Activities	Steroid eye drops are to be administered on Day -1 of each cycle	Clarification
		1.3 Schedule of Activities	Row added for Patient Eye Drop Diary	Clarification
		1.3 Schedule of Activities	Predose sampling for biomarker collection is specified to be within 24 hours prior to dosing	Clarification
		1.3 Schedule of Activities	Plasma protein and plasma DNA/RNA biomarker collection updated to include Cycles 20 and 24	Additional assessments to extend the collection of biomarkers
		1.3 Schedule of Activities	Separated footnotes for the optional biopsy collected at the time of radiographic disease progression and the biopsy collected per standard of care while the participant is on study	Clarification
		1.3 Schedule of Activities	Premedication for chemotherapy at C1D1 was removed	Clarification
		2.3 Benefit/Risk Assessment	Existing information referenced for the benefits and risks of treatment with tisotumab vedotin. Additional statements added on known and potential risks	Provision of additional information in the Benefit/Risk Assessment section in response to feedback from the global regulatory authority

Version/ amendment	Date	Section # and name	Description of Change	Brief Rationale
		4.1 Overall Design, 9.2 Sample Size Determination	Verbiage added to denote that no crossover is allowed in the study	Clarification
		4.4.2 Study Termination	Verbiage added to define conditions for termination of the entire trial	Clarification as requested by the global health authority
		4.4.2 Study Termination	Verbiage added to clarify whether or not there is access to the drug once the study is completed	Clarification as requested by the global health authority
		5.1 Inclusion Criteria, 1.1 Synopsis	Inclusion criterion for minimum age modified	Changed to allow for regional differences in the age of consent
		5.1 Inclusion Criteria	Calculated eGFR (MDRD formula) threshold changed from >50 mL/min/1.73m2 to ≥50 mL/min/1.73m2	Clarification
		5.1 Inclusion Criteria	Haematological status assessment timing after transfusion changed from at least 2 weeks after transfusion to at least 1 week after transfusion	Timing of haematological status after transfusion with blood products and/or growth factor support was reduced to reduce barriers to enrollment
		5.1 Inclusion Criteria	Inclusion criterion 12 removed	This criterion is no longer included in late-stage Seagen protocols. Biopsy tissue procurement is still required as part of screening procedures
		6.6.2.2 Other AEs for Tisotumab Vedotin, Section 7.1.1 Summary of Safety Stopping Rules	Permanent discontinuation of tisotumab vedotin added as a dose modification rule for bleeding events and elevated liver parameters of grade 4 severity	Changes requested by the global health authority
		8.2.1 Tumor Imaging	Verbiage added to clarify that tumour images may be collected for a potential blinded independent central review	Clarification
		8.2.1.1 Baseline Imaging Assessments	Verbiage “if clinically suspected” added for whole-body bone scan imaging	Clarification
		8.3.6 Clinical Laboratory Assessments Table 9	HbA1C has been removed from the table of laboratory assessments	Correction
		8.7.3 Tumour Tissue Sample Collection	Verbiage ‘At screening’ added to clarify timing, and that biopsy collected as per standard of care was performed if the participant provides consent	Clarification
		9.5.6 Exploratory Analyses	Verbiage added to clarify that ADA concentration will not be summarised, only ADA incidence	Correction

Version/ amendment	Date	Section # and name	Description of Change	Brief Rationale
		9.6.2 Safety Laboratory Tests, Vital Signs, and ECG Parameters	Verbiage added to clarify that the 12-lead ECG will not be summarised	Correction
		9.6.1 AEs	Verbiage added to clarify which TEAE analyses will be summarised	Correction
Amendment 3	06 Apr 2022	Title Page	-	New medical monitor assigned to the study
		1.1. Synopsis, 4.1. Overall Design, 7.1. Discontinuation of Study Treatment, 8.2.1.2. Post baseline imaging assessments	Verbiage added throughout for continued imaging to be "until evidence of radiographic disease progression or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first".	Clarification
		1.3 Schedule of Activities	eGFR to be collected within 7 days of C1D1 instead of within 28 days in Tables 1 and 3	Correction
		1.3 Schedule of Activities	Laboratory assessments (Haematology, Biochemistry, and Coagulation factors) and Pregnancy test moved up in Tables 1 and 3	Clarification for better visibility
		1.3 Schedule of Activities	"After Cycle 1, pre-dose laboratory procedures can be conducted ≤72 hours prior to dosing", specified to be applicable to all laboratory assessments in Tables 1 and 3	Clarification
		1.3 Schedule of Activities	Radiology assessments to be performed at EOT, with the exception of previous tumour imaging obtained within 4 weeks	Clarification
		1.3 Schedule of Activities	Health-related quality of life assessments to be collected "< 7 days" of C1D1 instead of "≤ 7 days".	Correction
		1.3 Schedule of Activities	Eye drops administration specified to be 'prior to dosing'	Clarification
		1.3 Schedule of Activities	"Reference to Table 2 for detailed time points" for Anti-drug antibodies (immunogenicity) and Pharmacokinetic sampling rows in Tables 1 and 3 extended to apply to EOT visit	Clarification
		1.3 Schedule of Activities	Plasma protein biomarkers removed	Change due to program-wide recommendations
		1.3 Schedule of Activities	Footnote for HRQOL assessments corrected for the control arm in Table 3	Correction

Version/ amendment	Date	Section # and name	Description of Change	Brief Rationale
		1.3 Schedule of Activities	Ocular assessments and eye examination are not to be performed at unscheduled visits for the control arm, as updated in Table 3	Correction
		2.1.1. Unmet Need, 2.2.1. Overview of the Disease	Details of KEYNOTE-826 study and anti-PD-(L)1 therapy added	Updates to reflect the changing treatment landscape
		4.3. Justification for Dose, 6.1.2 Chemotherapy Control Arm, 10.7.1 Recommended Dose, Modifications for Topotecan, 10.7.2 Recommended Dose Modifications for Irinotecan	Clarified starting dose for topotecan and irinotecan	Change to provide more flexibility to physicians in the treatment of trial participants
		5.1 Inclusion Criteria and Synopsis	Prior anti-PD-(L)1 therapy added	Changes to reflect the updated treatment landscape
		5.2 Exclusion Criteria	Exclusion #6 language revised to focus on prognosis/survival	Clarification
		5.2 Exclusion Criteria	Exclusion #12 amended to include exceptions for latent or controlled HIV infection.	Clarification
		5.4 Screen Failures	Sponsor approval of rescreening removed	Change to remove barriers to enrolment that did not affect patient safety
		5.4 Screen Failures	Clarified that biopsy is no longer required for eligibility as per Amendment 2.	Clarification
		6.1.1. Tisotumab Vedotin Arm	Physical Description updated	Changes to match updates to the Pharmacy Manual
		6.3.1 Treatment Randomisation	Heading removed to simplify the section	Clarification
		6.5.1.1. Tisotumab Vedotin Arm Premedication for Tisotumab Vedotin	"as needed" removed for self-administration of lubricating eye drops	Clarification
		6.5.3. Prohibited Concomitant Therapy	Herbal medicines removed	Change to allow enrollment of participants in regions where herbal medicines are commonly used
		7.1.2.2. Survival Follow-up	Specified follow-up to start from the date of the EOT visit for participants who are taken off treatment before receiving any study drug	Clarification
		8.4.2. Adverse Event Reporting	Safety reporting period for all AEs amended to 30 days after the last study treatment	Clarification
		8.4.6. Pregnancy	Follow-up duration extended to up to 6 months of age for the child	Change to allow for longer follow-up in cases of pregnancy in accordance with regulatory agency feedback

Version/ amendment	Date	Section # and name	Description of Change	Brief Rationale
		8.7. Biomarkers	Clarified and simplified biomarker language according to the current standard biomarker group language	Clarification
		(8.7.2) Biomarker Assessments in Blood Samples	The circulating tissue factor assay was removed from the biomarker analysis, and the section was removed	The assay was deemed not informative
		8.7.2 Tumour Tissue Sample Collection	Verbiage added to clarify that the most recent archival tumour biopsy is to be submitted for the purposes of screening and not submitted in the case of a screen failure	Clarification

Abbreviations: ADA …anti-drug antibody, AE …adverse event, C1D1 …Cycle 1 Day 1, DNA …deoxyribonucleic acid, eGFR …estimated glomerular filtration rate, EOT …end-of-treatment, ENGOT …European Network of Gynaecological Oncological Trial groups HIV …human immunodeficiency virus, HRQOL …health-related quality of life, GOG …Gynecologic Oncology Group, IDMC …independent data monitoring committee, MDRD …Modification of Diet in Renal Disease, PRO …patient-reported outcome, PD-L1 …programmed cell death ligand 1, RNA …ribonucleic acid, TEAE …treatment-emergent adverse event

4.2 Study population

Table 4-4: Baseline demographics and disease characteristics of participants in the innovaTV 301 study [5]

Study reference/ID characteristics category	Study intervention	
innovaTV 301/ENGOT-cx12/GOG-3057	Intervention (n=253)	Control (n=249)
Age (years), median (range)	51 (26-80)	50 (27-78)
Baseline ECOG performance status score, n (%)		
0	137 (54.2)	136 (54.6)
1	116 (45.8)	113 (45.4)
Geographic region, n (%)		
United States	16 (6.3)	14 (5.6)
Europe	106 (41.9)	104 (41.8)
Asia	85 (33.6)	88 (35.3)
Other	46 (18.2)	43 (17.3)

Study reference/ID characteristics category	Study intervention	
No. of previous lines of systemic therapy for recurrent or metastatic disease, n (%)		
1	159 (62.8)	149 (59.8)
2	93 (36.8)	100 (40.2)
Unknown	1 (0.4)	0
Previous systemic therapy or radiation for cervical cancer	253 (100)	249 (100)
Previous receipt of bevacizumab	164 (64.8)	157 (63.1)
Previous receipt of anti–PD-1 or anti–PD-L1 agent	71 (28.1)	67 (26.9)
Race or ethnic group, n (%)		
White	122 (48.2)	122 (49.0)
Asian	90 (35.6)	90 (36.1)
American Indian or Alaska Native	7 (2.8)	7 (2.8)
Black	4 (1.6)	6 (2.4)
Other	2 (0.8)	1 (0.4)
Native Hawaiian or other Pacific Islander	1 (0.4)	0
Not reported	19 (7.5)	17 (6.8)
Unknown	8 (3.2)	6 (2.4)
Disease status at trial entry, n (%)		
Pelvic recurrent only	27 (10.7)	24 (9.6)
Extrapelvic metastatic	226 (89.3)	225 (90.4)
Histologic feature, n (%)		
Squamous-cell carcinoma	160 (63.2)	157 (63.1)
Adenocarcinoma	85 (33.6)	75 (30.1)
Adenosquamous carcinoma	8 (3.2)	17 (6.8)
Evaluable biopsy sample, n (%)	210 (83.0)	194 (77.9)
Positive membrane tissue factor expression - n/total n(%)	194/210 (92.4)	183/194 (94.3)

Abbreviations: ECOG ...Eastern Cooperative Oncology Group, n ... number of randomized patients, PD-1 ...programmed cell death 1, PD-L1 ...programmed cell death-ligand 1

4.3 Results on relative effectiveness and safety

4.3.1 ESMO-MCBS scorecard for tisotumab vedotin (InnovaTV-301)

Table 4-5: ESMO-MCBS scorecard for tisotumab vedotin (InnovaTV-301) [6]

ESMO-MCBS score	3
Indication Details	
Therapeutic class	Antibody-drug conjugate
Control Arm	Investigator's choice of chemotherapy consisting of topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed
FDA Therapeutic Indication	Tisotumab vedotin for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy
Tumour Type	Gynaecological malignancies
Tumour Sub-type	Cervical cancer
Tumour Stage	Recurrent or metastatic
Trial Name	innovaTV 301
NCT Number	NCT04697628
Trial Phase	Phase III
Approval Details	
FDA Approval	FDA approval April 2024
Primary Outcome(s)	
Primary Outcome(s)	OS (primary), PFS (secondary)
Evaluated Outcome	OS
Form(s)	Form 2a
Outcome Data	
PFS Control	2.9 months
PFS Gain	1.3 months
PFS HR	0.67 (95% CI, 0.54 - 0.82); two-sided p<0.001
OS Control	9.5 months
OS Gain	2 months
OS HR	0.70 (95% CI, 0.54 - 0.89); two-sided p = 0.004
Adjustments	
QoL Comment	Reviewed, but not qualified for an ESMO-MCBS credit
Score	
Preliminary non-curative Score	3
Non-curative score	3

ESMO-MCBS score	3
Pending data	OS pending data
Comment	While innovaTV 204 (Phase II) and innovaTV 301 (Phase III) are distinct clinical trials, innovaTV 301 was designed as a confirmatory Phase III study based on the outcomes and learnings from innovaTV 204.
Scorecard Details	
ESMO-MCBS version	ESMO-MCBS v2.0
Issue date	21.07.2025

Abbreviations: CI ...confidence interval, ESMO-MCBS ...European Society For Medical Oncology – Magnitude Of Clinical Benefit Scale, FDA ...U.S. Food and Drug Administration, HR ...hazard ratio, OS ...overall survival, p ...p-value, QoL ... quality of life

4.4 Certainty of the evidence

4.4.1 Risk of bias

Table 4-6: Risk of bias of the study for tisotumab vedotin (innovaTV 301) [4] (RCT at study outcome level: Cochrane RoB 2.0 [5, 7, 8])

Domain	Bias arising from randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall RoB	Comments
Study/ Outcome	low	low	some concerns[1]	low	some concerns[2]	some concerns	■ Exploratory analyses without multiplicity adjustment and not part of the hierarchical testing procedure ■ Open-label design (not considered to materially affect OS assessment)

[1] Missing outcome data mainly affecting patient-reported outcomes due to decreasing completion rates over time.

[2] InnovaTV 301 is currently ongoing.

Abbreviations: est. ...estimated, RCT ... randomised controlled trial, RoB ... risk of bias, OS ... overall survival

5 Price comparisons, treatment costs and budget impact

5.1 Pharmacoeconomic model(s)

5.1.1 Submitted pharmaco-economic model

No model has been submitted.

5.1.2 Economic evaluation based on pharmaco-economic models

Table 5-1: Economic evaluation of tisotumab vedotin

Author, year [reference]	Country	Intervention and comparator	Target population (base-case)	Economic evaluation	Model	Perspective and time horizon	Utility values	Severity modifier	Discount rate	Model assumptions and limitations
Briceño-Casado et al., 2026 [9]	Spain (ES)	Tisotumab vedotin (TV; intravenous 2.0 mg/kg body weight) vs Single-agent chemotherapy (ChT) at the clinician's choice, using the ratios from the control arm of the innovaTV-301 trial: gemcitabine 44%, pemetrexed 32%, topotecan 8%, vinorelbine 7%, and irinotecan 6%	Pts. diagnosed with inoperable or metastatic recurrent cervical cancer (r/mCC) after failure of first-line ChT with or without pembrolizumab, assuming that PD-L1-positive ChT currently receive first-line ChT combined with pembrolizumab	Cost-utility analysis (CUA). ICUR was calculated as the difference in costs divided by the difference in QALYs between TV and ChT of the physician's choice	Partitioned survival model (PSM) with three mutually exclusive health states: progression-free (PF; baseline), progression, and death (end state).	Spanish National Health System perspective 60-month time horizon (agreed with experts and considered sufficient for the vast majority of patients to reach the death state)	Extracted from the literature (references Thurgar et al. 2021 and Huo et al. 2024)	Not applied	Reported only for the sensitivity analysis (SA): 0-5%	Efficacy data extracted from the innovaTV-301 RCT. The price of TV (not yet marketed in Spain) was assumed to be equivalent to cemiplimab's price (€1,536.57 per administration), given the lack of evidence of additional clinical benefit. Costs of grade ≥3 AE from the clinical trial were included, allocated at the start of follow-up. Limitations: PSM limits possibilities for SA, particularly probabilistic SA Utility values not available from the innovaTV-301 trial Social costs not included

					The generalised F function was selected for OS and the exponential function for PFS, based on Akaike Information Criterion (AIC), visual comparison with trial curves, and independent clinical expert validation. Estimated hazard ratios (HRs) were 0.6928 for OS and 0.6708 for PFS					No comparison with cemiplimab due to the absence of a direct clinical comparison and unreliable PD-L1 <1% subgroup data Only AEs of grade ≥3
Huo et al., 2024 [10]	USA (authors based in China)	TV vs Investigator's choice of single-agent ChT (gemcitabine, vinorelbine, topotecan, pemetrexed, or irinotecan) Post-progression: (assumed): 50% docetaxel; 50% best supportive care. All pts received one-time end-of-life care.	Pts. with r/mCC receiving second- or third-line treatment, previously treated with ChT ± bevacizumab and/or PD-(L)1 inhibitors	CUA; ICUR	Three-state Markov cohort model (progression-free survival (PFS)→ progressive disease (PD) → death) Log-logistic selected for both PFS and OS in both arms based on AIC/BIC. Applied half-cycle correction	U.S. third-party public healthcare payer (Medicare reimbursement basis) Lifetime horizon	Extracted from literature (references Thurgar et al. 2021; Liu et al., 2022; Nagees et al., 2008) PFS: 0.817 PD: 0.779 Anaemia disutility: 0.073 Neutropenia : 0.090	Not applied	3% per annum for both costs and health outcomes (varied 0–5% in SA)	Efficacy data extracted from the innovaTV-301 RCT <u>Cost of TV (price):</u> 293,641USD ($6,730 per vial (self-calculated)) <u>Limitations:</u> Incomplete trial results Transition probabilities relied on reconstructed KM data Cost source: Medicare reimbursement, not applicable to other US providers Only AEs of grade ≥3 and with an incidence rate of ≥5%

Abbreviations: AEs …adverse events, AIC …Akaike Information Criterion, CUA …cost-utility analysis, ChT …chemotherapy, HR …hazard ratio, OS… overall survival, PD …progressive disease, PD-L1 …programmed cell death-ligand 1, PFS… progression-free survival, pts… patients, QALY …quality-adjusted life years, r/mCC… recurrent or metastatic cervical cancer

Table 5-2: Main results of the included economic evaluations of tisotumab vedotin

Author, year [reference]	Country	Incremental costs (base-case)	Incremental effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection
Briceño-Casado et al., 2026 [9]	ES	**€12,138**: €19,900 (TV) vs €7,762 (ChT)	**0.341 QALYs**: 1.229 (TV) vs 0.889 (ChT)	**€35,600/QALY gained**	ES has no formally adopted CE-threshold. Mention proposed values in the literature ranging from €21,000 to €60,000/QALY gained	Deterministic one-way sensitivity analysis (OWSA): Largest impact- HR of OS: ICUR ranged from €23,283 per QALY gained (HR 0.54, lower CI bound) to €95,626/QALY gained (HR 0.89, upper CI bound) 2nd: PFS utility for TV: ICUR ranged from €31,609 (utility 0.90) to €68,966 (utility 0.50) per QALY gained TV price: €31,476 (lower bound €1,306.08) to €39,924 (upper bound €1,767.05) per QALY gained	While the existence of a benefit carries low uncertainty (based on an RCT), its magnitude could vary significantly → a reason to consider an outcome-based pricing agreement. Authors argue that given the modest and uncertain clinical benefit (ESMO-MCBS score of 3, not reaching the 4–5 threshold for substantial benefit), the ICUR "should not be at the maximum limit of acceptability," and price negotiations should achieve a lower cost than the base case.
Huo et al., 2024 [10]	US	**$206,779**: $293,641 vs $86,862	**0.25 QALYs**: 1.15 vs 0.90	**$839,108/QALY gained**	$150,000/QALY gained	OWSA: Most influential factors: per-mg cost of TV, utility of PD, utility of PFS, and the discount rate PSA: 0% probability of TV being cost-effective at the $150,000/QALY threshold; all iterations in the higher cost-higher effect quadrant	Even when PFS and PD utility values were varied to their extremes in a sensitivity analysis, the conclusion did not change, reinforcing that the cost-effectiveness problem is primarily price-driven rather than driven by uncertainty in quality-of-life estimates. FDA's accelerated approval of TV represents an important therapeutic advance for r/mCC patients with limited later-line options, but argue that clinical benefit alone is insufficient. Needed price reduction- even at the lower bound of the sensitivity range ($134.61/mg), the ICER remained above threshold.

Abbreviations: ChT… chemotherapy, CI …confidence interval, ES… Spain, ESMO-MCBS …European Society For Medical Oncology – Magnitude Of Clinical Benefit Scale, FDA …U.S. Food and Drug Administration, HR… hazard ratio, ICUR … incremental cost-utility ratio, OWSA… one-way sensitivity analysis, PD …progressive disease, PFS …progression-free survival, PSA… probability sensitivity analysis, QALY… quality-adjusted life year, RCT… randomised controlled trial,

5.1.3 Quality assessment of the included economic evaluation based on pharmaco-economic models

Table 5-3: Check of reporting standards – the CHEERS checklist [11]

#	Domain	Briceño-Casado et al. (2026) [9]	Huo et al. (2024) [10]
TITLE			
1	Title	☑ Yes	☑ Yes
ABSTRACT			
2	Abstract	☑ Yes	☑ Yes
INTRODUCTION			
3	Background & objectives	☑ Yes	☑ Yes
METHODS			
4	Health economic analysis plan	✕ No[3]	✕ No[4]
5	Study population	⚠ Partial[5]	☑ Yes
6	Setting and location	☑ Yes	☑ Yes
7	Comparators	☑ Yes	☑ Yes
8	Perspective	☑ Yes	⚠ Partial[6]

[3] There is no mention of a pre-registered or pre-specified health economic analysis plan. No protocol registration (e.g., PROSPERO or OSF) is referenced. This is increasingly expected in independent HTA-oriented analyses to reduce the risk of post-hoc analytical decisions.

[4] No pre-specified or registered health economic analysis plan is mentioned. No protocol registration on any platform (e.g. PROSPERO, OSF, or a clinical trial registry) is referenced. This is particularly relevant given that the analysis was conducted on conference-reported trial data, where post hoc analytical flexibility in model design cannot be excluded.

[5] The target population is described clinically (r/mCC after first-line failure, PD-L1 context), but patient-level demographic details such as mean age, ECOG performance status, or socioeconomic characteristics are not reported. These are only implicitly inherited from the innovaTV-301 trial population without explicit description.

[6] The U.S. third-party public payer perspective is stated, but no justification is offered for why this perspective was selected over a broader societal or healthcare system perspective. Indirect costs, such as productivity loss and informal caregiving, which may be substantial in a population of women with a median age of 50 facing a terminal illness, are neither included nor discussed as a limitation.

#	Domain	Briceño-Casado et al. (2026) [9]	Huo et al. (2024) [10]
9	Time horizon	☑ Yes	⚠ Partial[7]
10	Discount rate	⚠ Partial[8]	☑ Yes
11	Selection of outcomes	☑ Yes	☑ Yes
12	Measurement of outcomes	☑ Yes	☑ Yes
13	Valuation of outcomes	⚠ Partial[9]	⚠ Partial[10]
14	Measurement & valuation of resources and costs	☑ Yes	☑ Yes
15	Currency, price date & conversion	☑ Yes	☑ Yes
16	Rationale & description of model	☑ Yes	⚠ Partial[11]
17	Analytics & assumptions	☑ Yes	☑ Yes

[7] A lifetime horizon is stated but never justified in relation to the specific clinical context. In a population with a median OS of roughly 10–11 months, a lifetime horizon is technically appropriate to capture tail survival, but the authors do not explain this reasoning. More importantly, the time horizon is never varied as a scenario in the sensitivity analyses, which CHEERS 2022 explicitly expects.

[8] A discount rate is included in the model and varied in the tornado diagram (0% vs. 5%), but the actual base case discount rate applied is never explicitly stated in the methods section. Readers have to infer it from the sensitivity analysis table.

[9] Utility values are borrowed from two non-Spanish studies (Thurgar et al. for endometrial cancer and Huo et al. for cervical cancer in a US context). No EQ-5D mapping, Spanish population norms, or primary utility elicitation were performed. The authors acknowledge that no Spanish cervical cancer utility data exist, but they make no attempt to bridge this gap (e.g., through a targeted literature review or mapping exercise).

[10] Utility values for PFS (0.817) and progressive disease (0.779) are taken from Thurgar et al., a US-based study on endometrial cancer, and AE disutilities for neutropenia are sourced from Nafees et al., a lung cancer study. No cervical cancer–specific or even gynaecological cancer–specific utility data are sought, discussed, or validated. The cross-indication transfer of utility values is not critically appraised, and no sensitivity analysis specifically tests the impact of alternative utility sources.

[11] The three-state Markov model is described, and a structural diagram is provided (Fig. S1). However, no rationale is given for choosing a Markov cohort model over a partitioned survival analysis approach, the alternative commonly used in this type of oncology evaluation. The model is built in TreeAge Pro 2022, a commercial software package, and no publicly available version of the model is provided or referenced.

#	Domain	Briceño-Casado et al. (2026) [9]	Huo et al. (2024) [10]
18	Characterising heterogeneity	✗ No[12]	✗ No[13]
19	Characterising distributional effects	✗ No[14]	✗ No[15]
20	Characterising uncertainty	⚠ Partial[16]	✓ Yes
21	Approach to engagement with patients and others	✗ No[17]	✗ No[18]
RESULTS			
22	Study parameters	✓ Yes	✓ Yes
23	Summary of main results	✓ Yes	✓ Yes

[12] No quantitative subgroup analyses are performed. The clinically relevant PD-L1 <1% subgroup, which is the primary remaining candidate population for second-line cemiplimab and potentially TV, is only discussed narratively. Disaggregated efficacy data for this subgroup were not available in innovaTV-301, but this absence is not formally addressed in the scenario or threshold analyses.

[13] No subgroup or heterogeneity analyses are performed or even discussed. Clinically meaningful subgroups exist in this population, notably by line of therapy (2nd vs. 3rd line), PD-L1 expression status, and prior immunotherapy exposure, all of which are likely to influence both clinical outcomes and cost-effectiveness. None of these is explored quantitatively or in scenario form.

[14] No analysis of how costs or health outcomes are distributed across different patient subgroups, socioeconomic strata, or priority populations is presented or discussed. Given that cervical cancer disproportionately affects younger and socioeconomically disadvantaged women, this is a notable omission from an equity perspective.

[15] No equity or distributional analysis is conducted. This is a noteworthy omission: the introduction itself highlights that approximately 90% of cervical cancer cases occur in lower- and middle-income countries and that geographic and socioeconomic disparities in incidence are substantial. Despite this framing, no attempt is made to explore how costs or outcomes may differ across racial, socioeconomic, or insurance-coverage subgroups within the U.S. population.

[16] Only deterministic one-way sensitivity analyses and scenario analyses are presented. No probabilistic sensitivity analysis (PSA) and no cost-effectiveness acceptability curve (CEAC) are produced. The time horizon is also not varied in any scenario. The authors acknowledge the PSA limitation but attribute it to the INES tool's constraints rather than offering an alternative approach.

[17] No patient or public involvement (PPI) in the design or conduct of the study is described. Stakeholder input was limited to clinical expert validation of survival curve projections and resource use assumptions by oncologists and hospital pharmacists, which does not constitute formal engagement as intended by this CHEERS item.

[18] No patient, public, or clinical stakeholder engagement is described at any stage of the study. Unlike Briceño-Casado et al., which at least involved medical oncologists and hospital pharmacists for clinical validation of survival curve projections and resource use assumptions, Huo et al. report no equivalent consultation. All model inputs appear to have been sourced exclusively from the published literature and databases without any expert review or validation step.

#	Domain	Briceño-Casado et al. (2026) [9]	Huo et al. (2024) [10]
24	Effect of uncertainty	⚠ Partial[19]	⚠ Partial[20]
25	Effect of engagement with patients and others	✗ No[21]	✗ No[22]
DISCUSSION			
26	Study findings, limitations, generalizability & current knowledge	✓ Yes	⚠ Partial[23]
OTHER			
27	Source of funding	✓ Yes	⚠ Partial[24]
28	Conflicts of interest	✓ Yes	✓ Yes

Table 5-4: CHEC list quality assessment [12]

#	Item	Briceño-Casado et al. (2026) [9]	Huo et al. (2024) [10]
1	Is the study population clearly described?	✓ Yes	✓ Yes
2	Are competing alternatives clearly described?	✓ Yes	✓ Yes
3	Is a well-defined research question posed in answerable form?	✓ Yes	✓ Yes

[19] Directly linked to item 20. The discount rate is varied, but the time horizon is not tested as a scenario. The absence of PSA means that the joint effect of simultaneous parameter uncertainty on the ICUR cannot be quantified, and no probability of cost-effectiveness at different willingness-to-pay thresholds is reported.

[20] The discount rate is varied in the DSA, and PSA with CEAC is conducted, which is commendable. However, the time horizon is never tested as a scenario despite being a structurally important assumption. No price threshold analysis is presented to inform the price reduction needed to bring TV below the $150,000/QALY WTP threshold — a highly policy-relevant output given the study's own conclusion that price reduction is the key lever for cost-effectiveness.

[21] This item is directly consequential on item 21, since no formal patient or stakeholder engagement took place; there is nothing to report regarding its effect on the study approach or findings.

[22] Directly consequential on item 21. Since no engagement occurred, there is nothing to report regarding its effect on the study approach or findings.

[23] Several important limitations are acknowledged: reliance on Medicare costs, restriction to grade ≥3 AEs with ≥5% incidence, and incomplete post-progression treatment data from the trial. However, several equally important limitations are not discussed: the use of utility values from different cancer indications; the absence of clinical expert validation of any model inputs; the fact that only conference-reported data from innovaTV-301 were available at the time (the full NEJM publication appeared after submission); the absence of subgroup analyses; and the non-inclusion of indirect costs. The discussion of generalizability is limited to the U.S. payer context without acknowledging that the conclusions may not transfer to other healthcare systems.

[24] Three funding sources are declared (China Anti-Cancer Association HER2 Target Research Fund, Tianjin Education Commission Key Science and Technology Development Fund, and the Tianjin Key Medical Discipline Construction Project). However, the authors provide no statement regarding the role, or the explicit absence of a role, of any of these funders in the study design, conduct, analysis, or reporting. CHEERS 2022 requires this to be explicitly addressed, not merely listed.

#	Item	Briceño-Casado et al. (2026) [9]	Huo et al. (2024) [10]
4	Is the economic study design appropriate to the stated objective?	☑ Yes	☑ Yes
5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	☑ Yes	☑ Yes
6	Is the actual perspective chosen appropriate?	☑ Yes	⚠ Partial[25]
7	Are all important and relevant costs for each alternative identified?	⚠ Partial[26]	⚠ Partial[27]
8	Are all costs measured appropriately in physical units?	☑ Yes	☑ Yes
9	Are costs valued appropriately?	☑ Yes	⚠ Partial[28]
10	Are all important and relevant outcomes for each alternative identified?	☑ Yes	☑ Yes
11	Are all outcomes measured appropriately?	☑ Yes	☑ Yes
12	Are outcomes valued appropriately?	⚠ Partial[29]	⚠ Partial[30]
13	Is an incremental analysis of costs and outcomes of alternatives performed?	☑ Yes	☑ Yes
14	Are all future costs and outcomes discounted appropriately?	⚠ Partial[31]	☑ Yes
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	⚠ Partial[32]	☑ Yes
16	Do the conclusions follow from the data reported?	☑ Yes	☑ Yes

[25] U.S. payer perspective stated without justification. Indirect costs neither included nor acknowledged as a limitation.

[26] Indirect costs (productivity loss, informal care) are excluded without quantifying their potential magnitude. Post-progression treatment costs are not clearly described, and it is unclear whether they are included in the progression health state.

[27] Indirect costs entirely absent with no acknowledgement. Post-progression treatment simplified to docetaxel and BSC only, excluding radiotherapy, surgery, and immunotherapy.

[28] Reliance on Medicare reimbursement rates only, which may not capture commercial payer rates — acknowledged as a limitation but not addressed in sensitivity analyses.

[29] Utility values are borrowed from a US endometrial cancer study (Thurgar et al.), with no systematic search for cervical cancer- or Spanish-specific utilities documented. Disutility for adverse events is not applied, and no scenario quantifies the combined impact of these omissions.

[30] Utility values from a US endometrial cancer study; neutropenia disutility from a lung cancer study. Cross-indication transfer neither justified nor discussed as a limitation.

[31] A discount rate is used and varied in sensitivity analysis, but the base case rate is never explicitly stated in the methods. It can only be inferred indirectly from the tornado diagram values.

[32] One-way DSA and scenario analyses are well conducted, but no PSA is performed, meaning joint parameter uncertainty cannot be quantified and no cost-effectiveness acceptability curve is produced. The time horizon is also never varied.

#	Item	Briceño-Casado et al. (2026) [9]	Huo et al. (2024) [10]
17	Does the study discuss the generalizability of the results to other settings and patient/client groups?	⚠ Partial[33]	⚠ Partial[34]
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	☑ Yes	⚠ Partial[35]
19	Are ethical and distributional issues discussed appropriately?	⚠ Partial[36]	⚠ Partial[37]

[33] The Spanish context is well described, and a comparison with the US setting is made. However, generalizability to other European systems is not discussed, and the clinically relevant PD-L1 and line-of-therapy subgroups are addressed only narratively, without any quantitative exploration.

[34] No discussion of applicability to other healthcare systems or to clinically relevant patient subgroups such as PD-L1 status or line of therapy.

[35] Authors declare no conflicts, but the role of three declared funding sources in the study is never addressed.

[36] System-level sustainability and outcome-based pricing are discussed, but patient-level equity considerations, such as the disproportionate burden of cervical cancer in younger and socioeconomically disadvantaged women, are entirely absent.

[37] Patient-level economic toxicity is discussed, which is a plus, but distributional issues across racial, socioeconomic, or geographic subgroups, highly relevant for cervical cancer, are not addressed.

6 Extended perspectives

6.1 Healthcare provider perspectives

Table 6-1: Questions for clinical experts [13]

Questions about the standard of care in Austria	
Question 1	Wie stellt sich die derzeitige Therapiesequenz in Österreich dar (1st-Line bis 3rd-Line), getrennt nach CPS ≥1 und CPS <1?
Question 2	Welche Therapieoptionen werden in der 2nd- bzw. 3rd-Line am häufigsten eingesetzt? Welches Zytostatikum stellt in der Praxis die dominante Monotherapie dar?
Question 3	Wo würden Sie Tisotumab vedotin im österreichischen Versorgungspfad verorten: eher als 2nd-Line- oder als 3rd-Line-Option?
Question 4	Welche klinischen Endpunkte halten Sie für besonders patientinnenrelevant (kritische Endpunkte)?
Questions about the population and the target group in Austria	
Question 5	Unsere vorläufige Schätzung für Österreich liegt bei etwa 40–95* Patientinnen pro Jahr in der Indikation „rezidiviertes oder metastasiertes Zervixkarzinom mit Progression unter oder nach systemischer Therapie“. ■ Wie hoch schätzen Sie den Anteil, der bereits eine Immuncheckpoint-Inhibition in der 1st-Line erhalten hat? ■ Welcher Anteil ist noch für eine weitere systemische Therapie geeignet? ■ Wie verteilen sich diese Patientinnen in der Praxis auf die verfügbaren Vergleichstherapien? ■ Und wie hoch ist der Anteil der Patientinnen, die primär Best Supportive Care erhalten?
Question 6	Wird der CPS-Status routinemäßig bei der Erstdiagnose bestimmt? ■ Wie verteilt sich dieser in Ihrer Erfahrung (CPS ≥ und CPS <1)? ■ Führt der positive CPS-Status in der Praxis konsistent zum Einsatz einer Immuncheckpoint-Inhibition (in Kombination mit Chemotherapie) in der 1st-Line?
Questions 7	Welche klinischen oder patientinnenbezogenen Kriterien sind aus Ihrer Sicht für die Indikationsstellung von Tisotumab vedotin besonders relevant? Zum Beispiel: ■ Progression unter einer Immuncheckpoint-Inhibition ■ CPS ≥1 und CPS <1 ■ Kontraindikation oder eingeschränkte Eignung für weitere Chemotherapie ■ Performance-Status oder relevante Komorbiditäten
Questions about organisational aspects	
Question 8	Wie schätzen Sie den realen organisatorischen und personellen Aufwand pro Patientin ein (Applikation, Monitoring, ophthalmologische Betreuung)? ■ Welche Abklärungen sind vor Therapiebeginn erforderlich? ■ Wie häufig erfolgen augenärztliche Kontrollen im realen Setting? ■ Wie relevant ist der Aufwand bei Nebenwirkungen wie okulärer Toxizität oder peripherer Neuropathie? ■ Kommt es aus Ihrer Erfahrung zu zusätzlichen ambulanten Kontakten oder zu stationären Aufenthalten?
Question 9	Würde Tisotumab vedotin aus Ihrer Sicht primär eine bestehende Therapie ersetzen oder eher die Sequenz systemischer Therapien insgesamt verlängern?
Question 10	Versorgungssetting: ■ Ambulante/tagesklinische Anwendung ■ Onkologische Einrichtungen mit Erfahrung in der systemischen Therapie gynäkologischer Tumoren. Weitere Spezialisierungen notwendig?
Question 11	Interdisziplinäre Betreuung: im Rahmen des interdisziplinären Teams (gynäkologische/internistische Onkologie, Ophthalmologie): Weitere Bereiche zu berücksichtigen?
Questions about ethical aspects	
Question 12	Welche Therapieziele stehen aus Ihrer Erfahrung für Patientinnen in dieser Therapielinie im Vordergrund – Lebensverlängerung, Symptomkontrolle oder Lebensqualität?
Question 13	Falls bereits eigene klinische Erfahrungen mit Tisotumab vedotin vorliegen: Welche Aspekte der Behandlung sind aus Ihrer Sicht im klinischen Alltag besonders relevant (zum Beispiel Nebenwirkungsprofil, organisatorischer Aufwand, ophthalmologische Betreuung, Lebensqualität)?
Questions about additional relevant aspects	
Question 14	Gibt es zusätzliche relevante Aspekte seitens der klinischen Expert:innen, die im Zuge der HTA-Erstellung berücksichtigt werden sollten?

Question 15	In Österreich gehen wir davon aus, dass sowohl die Tisotumab vedotin als auch die Chemotherapie in einem tagesklinischen Krankenhaussetting verabreicht werden; daher berücksichtigen wir die Verabreichungskosten anhand eines Tagessatzes von € 845. Könnten Sie diese Kostenschätzung validieren?
Question 16	Wir berücksichtigen die Kosten für die ophthalmologische Vorbehandlung aktuell nicht: In welchem Setting findet diese Vorbehandlung statt? In welcher Größenordnung liegen diese Kosten? (In Deutschland: € 300-400 pro Patientin pro Jahr)
Question 17	Indikationsbezogene Anwendungskriterien: ■ Therapieoption nach Progress unter Standardtherapien und bei begrenzten Therapiealternativen: ○ Einsatz bei Patientinnen mit rezidiviertem oder metastasiertem Zervixkarzinom nach vorangegangener systemischer Therapie, typischerweise nach platinbasierter Chemotherapie und Immuncheckpoint-Inhibition; ○ Verfügbarkeit weniger evidenzbasierter Therapieoptionen ■ Patientinnenselektion und Nutzen-Risiko-Abwägung entscheidend: Geeignet insbesondere für Patientinnen mit gutem Allgemeinzustand (ECOG 0–1) und ausreichender Organfunktion; eine individuelle Nutzen-Risiko-Abwägung ist erforderlich. ■ Spezifisches Nebenwirkungsprofil mit Bedarf an strukturiertem Management: Charakteristische okuläre Nebenwirkungen erfordern präventive Maßnahmen sowie eine interdisziplinäre Betreuung. Weitere patientinnenrelevante Kriterien?

*Note: * Own calculation based on the methodology of the Institute for Quality and Efficiency in Health Care for deriving the target population, taking into account Austrian incidence data and assumptions regarding the treatment sequence.*

Abbreviations: CPS ... combined positive score, ECOG ... Eastern Cooperative Oncology Group, HTA ...Health Technology Assessment

6.2 Patient perspective

Table 6-2: Questions for patients and relatives diagnosed with recurrent or metastatic cervical cancer

Questions for patients	
Hintergrundinformationen	
1	In welcher Rolle füllen Sie den Fragebogen aus? ■ Einzelne/r Patientin ■ Angehörige ■ Andere
2	Falls zutreffend, wie sind Sie an Informationen zu den Erfahrungen von Patientinnen gekommen? ■ Persönliche Erfahrungen ■ Erlebnisse von Patientinnen
3	In welchem Land befindet sich Ihr Hauptwohnsitz?
4	Sind Sie Mitglied einer Patientinnenorganisation? Wenn ja: ■ Bei welcher Patientinnenorganisation sind Sie Mitglied? ■ Welche Erkrankung(en) wird/werden von der Patientinnenorganisation vertreten? ■ Welche Rolle haben Sie in der Patientinnenorganisation?
5a	Wie lautet die Diagnose?
5b	In welchem Stadium der Erkrankung befinden Sie sich? Wie würden Sie den Schweregrad aktuell einschätzen?
5c	Welche Symptome haben Sie oder Ihre Angehörigen derzeit?
5d	Krankheitsgeschichte: ■ Seit wann leben Sie oder Ihre Angehörigen mit der Erkrankung? ■ Wann wurde sie diagnostiziert? ■ Welche Behandlungen wurden bisher durchgeführt?
5e	Zusätzliche Informationen, die Ihrer Meinung nach für den HTA-Bericht hilfreich wären.
Auswirkungen der Krankheit	
6	Wie beeinflusst die Erkrankung Ihr tägliches Leben (bzw. das Leben einer Patientin)?

7	Nur für Patientinnen: Wie wirkt sich die Erkrankung auf Ihr familiäres und soziales Umfeld aus?
8	Nur für Angehörige: Wie wirkt sich die Erkrankung auf das familiäre und soziale Umfeld der Patientinnen aus?
Erfahrung mit der derzeit verfügbaren Versorgung und Therapien	
9	Wie würden Sie die aktuelle Versorgungssituation in Österreich für Ihre Erkrankung beschreiben?
10	Wie geht es Ihnen und Ihren Angehörigen mit der derzeit angewandten Therapie? Falls keine spezifische Therapie zur Verfügung steht, geben Sie das bitte an.
Erwartungen an das zu bewertende neue Arzneimittel	
11	Was würden Sie und Ihre Angehörigen im Allgemeinen von einer neuen Therapie erwarten?
12	Kennen Sie das Medikament TIVDAK®?
13	Welche Gedanken haben Sie zum neuen Arzneimittel?
14	Für Personen, die Erfahrung mit TIVDAK®im Rahmen klinischer Studien haben: Welche Auswirkungen hatte bzw. hat es auf Ihr Leben (positiv und negativ)?
Weitere Angaben	
15	Was ist Ihrer Meinung nach noch wichtig? Gibt es weitere Aspekte, z.B. ethische oder soziale Aspekte, die noch nicht besprochen wurden? Bitte erläutern Sie diese.

Abbreviations: HTA ... health technology assessment

6.3 Further considerations

No additional figures or tables.

6.4 Registries and documentation of tisotumab vedotin

No additional figures or tables.

7 Development costs and public contributions

7.1 Public contributions to drug development

Table 7-1: Financing/patent deals/licensing/funding rounds of all companies involved in the development of TIVDAK®

Type of information	Details on collaboration, financing, and public funding	Year	Amount (in USD)	Funders/ Investors/Acquirers	Source
Genmab					
Co-Development agreement	In October 2011, Genmab entered into a license and collaboration agreement with Seagen, Inc. ("Seagen"), now Pfizer, per Pfizer's acquisition of Seagen in December 2023, that granted us rights to utilise Pfizer's antibody drug conjugate (ADC) technology with their tissue factor (TF) antibody in return for milestone payments and royalties.	2011	n.a.	Seagen	https://www.sec.gov/Archives/edgar/data/78003/000007800325000054/pfe-20241231.htm#i8531e747ebb543f3bf818166f157d26a_37
Co-Development agreement	In the 2011 deal, Genmab granted the right to exercise a co-development and co-commercialisation option at the end of Phase I clinical development for tisotumab vedotin. In August 2017, Seagen exercised this option to co-develop and co-commercialise tisotumab vedotin with Genmab.	2017	n.a.	Seagen	https://www.sec.gov/Archives/edgar/data/78003/000007800325000054/pfe-20241231.htm#i8531e747ebb543f3bf818166f157d26a_37
Join Commercial Agreement	Genmab and Pfizer entered into a Joint Commercialisation Agreement under which Genmab would co-promote tisotumab vedotin, marketed as Tivdak, in the U.S., and lead commercial operations and record sales in Japan, while Pfizer would lead operational commercial activities in the U.S., Europe, and China, with a 50:50 profit split in those markets. In all other markets, if any, Pfizer would be responsible for commercialising tisotumab vedotin, and Genmab would receive royalties based on a percentage of aggregate net sales ranging from the mid-teens to the mid-twenties.	2020	n.a.	Seagen	https://ir.genmab.com/static-files/c1fb13fb-65c5-486a-b744-d5d30869af2f
Amendment of licensing and collaboration agreement	Effective January 1, 2025, Genmab and Pfizer agreed to amend the License and Collaboration Agreement and the Joint Commercialisation Agreement for Tivdak, assigning Genmab sole responsibility for the development and commercialisation of Tivdak for second-line plus recurrent or metastatic cervical cancer in Europe and all other regions globally, excluding the United States and the China region.	2025	n.a.	Pfizer	https://ir.genmab.com/static-files/c1fb13fb-65c5-486a-b744-d5d30869af2f

Tisotumab vedotin (TIVDAK®) for the treatment of adult patients with recurrent or metastatic cervical cancer

Type of information	Details on collaboration, financing, and public funding	Year	Amount (in USD)	Funders/ Investors/Acquirers	Source
Licensing agreement	In 1999, Genmab entered into a license agreement with Medarex, now a wholly owned subsidiary of Bristol Myers Squibb, pursuant to which Genmab received access to the UI-tiMAb technology, the KM Mouse technology and the right to obtain antibody-exclusive licenses for an unlimited number of antigens and own the worldwide development and commercialisation rights to antibody products targeting such antigens. In addition, Medarex granted Genmab antigen-exclusive licenses in exchange for fully paid-up Genmab shares, subject to, in the event the products are generated in the KM Mouse, the pass-through of milestones and royalties payable by Medarex under its own license of the KM Mouse technology. However, no payments are required for tisotumab vedotin.	1999	n.a.	Medarex	https://ir.genmab.com/static-files/c1fb13fb-65c5-486a-b744-d5d30869af2f
Pfizer					
Collaboration and license agreement	In September 2022, Pfizer and Zai Lab announced an exclusive collaboration and license agreement for the development and commercialisation of Tivdak in mainland China, Hong Kong, Macau and Taiwan. Under the terms of the agreement, Pfizer received an upfront payment of $30 million and will receive development, regulatory and commercial milestone payments, as well as tiered royalties on net sales of Tivdak in the Zai Lab territory. Based on our agreement with Pfizer, all upfront, milestone payments and royalties have been and will continue to be shared 50:50 with Genmab.	2022	n.a.	Zailab	https://www.sec.gov/Archives/edgar/data/78003/000007800325000054/pfe-20241231.htm#i8531e747ebb543f3bf818166f157d26a_37

Abbreviations: ADC ...antibody drug conjugate, n.a. ... not available, TF ...tissue factor

Table 7-2: Search terms used to identify the development history and public contributions on TIVDAK®

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (yes/no)	Search period	Type of information extracted
https://www.ema.europa.eu/en/medicines	Tivdak Tisotumab vedotin	-	yes	Earliest mention – 04/2026	Active substance, Medical speciality, Pharmacotherapeutic group, Therapeutic area, Class, Orphan designation, Categorization, Additional monitoring, Conditional approval, Accelerated assessment, PRIME: priority medicines, Marketing authorisation issued
https://www.fda.gov/			yes		
https://adisinsight.springer.com/			yes		Alternative names/ Alternative Product identifiers
https://ihsi-horizonscandb.ecri.org/					
https://pubmed.ncbi.nlm.nih.gov/	HuMax-TF HuMax-TF-ADC		no		Development history, Researchers
https://clinicaltrials.gov/			no		Clinical trials

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https://euclinicaltrials.eu/	Humax®-TF-ADC TF-011-MMAE Tisotumab vedotin-tftv 1418731-10-8 gct1015-04 humaxtfadc humax-tf-adc igg1-1015-011-1006 t41737f88a Genmab Pfizer Seagen ZAI Lab European Network of Gynaecological Oncological Trial Groups (ENGOT) Belgian Gynaecological Oncology Group Gynecologic Oncology Group		no		
https://trialsearch.who.int/			no		
https://eudract.ema.europa.eu/			no		
https://cordis.europa.eu/			no		
https://reporter.nih.gov/		Johann de Bono Kristi Schmidt Keiichi Fujiwara Rutie Yin Guiling Li Bingzhong Zhang Qing Wen Meili Sun Jianhua Shi Dongqing Lv Tienan Yi Esther C.W. Breij The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust Genmab Saitama Medical University International Medical Center West China Second University Hospital Union Hospital, Tongji Medical College, Huazhong University of Science and Technology Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University Jinan Central Hospital Jinan Central Hospital Linyi Cancer Hospital Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University Xiangyang Central Hospital Genmab	no		
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm			no		Basic research. Authors selected based on literature found on PubMed
https://www.sec.gov/			yes		Collaborations, funding, financing, Series A-C funding, patent information, acquisitions, development history
https://competition-cases.ec.europa.eu/search			no		
https://www.ihi.europa.eu/			no		
https://eismea.ec.europa.eu/index_en			no		
https://eit.europa.eu/			no		
https://eic.ec.europa.eu/index_en			no		
https://www.eib.org/en/index			no		
https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls_en			no		
https://www.sbir.gov/			no		
https://www.nsf.gov/			no		
https://www.ukri.org/			no		
https://foerderportal.bund.de/			no		
https://www.health-holland.com/			no		
https://www.bpifrance.com/			no		
https://www.inserm.fr/en/home/			no		
https://innovationsfonden.dk/da			no		
https://www.ucc.ie/en/apc/			no		
https://www.amractionfund.com/about			no		
https://reporter.nih.gov/			no		
https://www.gatesfoundation.org/			no		
https://www.google.com/			no		
https://www.forbes.com/			no		
https://www.reuters.com/			no		
https://www.science.org/			no		
https://www.cafepharma.com/			no		
https://www.livescience.com/			no		
https://www.biospace.com/			no		
https://www.bioworld.com/			no		
https://www.biopharmadive.com/			no		
https://pharmaphorum.com/			no		
https://pharmatimes.com/			no		
https://pharmafile.com/			no		
https://www.fiercepharma.com/			no		
https://www.businesswire.com/			no		
https://www.businessinsider.com/			no		

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https://www.statnews.com/			no		

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8 Landscape overview

8.1 Ongoing studies on tisotumab vedotin

Table 8-1: List of ongoing studies with tisotumab vedotin

Title	Trial ID	Other IDs	Phase	Status	Estimated study completion date	Additional information
Ocular Assessments in Patients Treated With Tivdak® in Recurrent or Metastatic Cervical Cancer	NCT06952660	C5721005	4	Recruiting	13.12.2028	n.a.
Safety and Efficacy of Tisotumab Vedotin Monotherapy & in Combination With Other Cancer Agents in Subjects With Cervical Cancer	NCT03786081	GCT1015-05|InnovaTV 205|MK-3475-834|ENGOT-cx8|GOG-3024|KEYNOTE-834|2017-004758-40	1/2	Active not recruiting	31.03.2026	n.a.
Efficacy and Safety Study of Tisotumab Vedotin for Patients With Solid Tumours	NCT03485209	SGNTV-001|C5721001; innovaTV 207|2023-503812-34-00	2	Active not recruiting	31.03.2027	n.a.
Tisotumab Vedotin vs Chemotherapy in Recurrent or Metastatic Cervical Cancer	NCT04697628	SGNTV-003|C5721002|2023-503813-31-01	3	Active not recruiting	07.05.2026	n.a.
A Study to Compare Sacituzumab Tirumotecan (MK-2870) Monotherapy Versus Treatment of Physician's Choice as Second-line Treatment for Participants With Recurrent or Metastatic Cervical Cancer (MK-2870-020/TroFuse-020/Gog-3101/ENGOT-cx20)	NCT06459180	2870-020|MK-2870-020|TroFuse-020|2023-508323-12-00|U1111-1298-0563|GOG-3101|ENGOT-cx20|jRCT2031240201	3	Recruiting	15.06.2028	n.a.

Abbreviations: n.a. ... not available

8.2 Treatments in development

No content.

9 References

[1] Bhatla N., Aoki D., Sharma D. N. and Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. International Journal of Gynecology & Obstetrics. 2021;155(S1):28–44. DOI: https://doi.org/10.1002/ijgo.13865.

[2] European Medicines Agency (EMA). Tivdak: EPAR : Product information. 2025 [cited 09.02.2026]. Available from: https://www.ema.europa.eu/en/documents/product-information/tivdak-epar-product-information_en.pdf.

[3] Ali A., Shah A. A., Jeang L. J., Fallgatter K. S., George T. J. and DeRemer D. L. Emergence of ocular toxicities associated with novel anticancer therapeutics: What the oncologist needs to know. Cancer Treatment Reviews. 2022;105. DOI: 10.1016/j.ctrv.2022.102376.

[4] Avram S., Wilson T. B., Curpan R., Halip L., Borota A., Bora A., et al. DrugCentral 2023 extends human clinical data and integrates veterinary drugs. Nucleic Acids Research. 2023;51(1 D):D1276–D1287. DOI: 10.1093/nar/gkac1085.

[5] Vergote I., Gonzalez-Martin A., Fujiwara K., Kalbacher E., Bagameri A., Ghamande S., et al. Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer. New England Journal of Medicine. 2024;391(1):44–55. DOI: 10.1056/NEJMoa2313811.

[6] European Society For Medical Oncology (ESMO). ESMO-MCBS Scorecard. Tisotumab vedotin. innovaTV 301. 2025 [cited 2026-02-17]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=507.

[7] National Library of Medicine and ClinicalTrials.gov. Tisotumab Vedotin vs Chemotherapy in Recurrent or Metastatic Cervical Cancer (innovaTV 301). 2026 [cited 2026-02-17]. Available from: https://clinicaltrials.gov/study/NCT04697628.

[8] Sterne J. A. C., Savovic J., Page M. J., Elbers R. G., Blencowe N. S., Boutron I., et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898 Epub 20190828 DOI: 101136/bmjl4898. 2019.

[9] Briceño-Casado M. D. P., Sánchez Vegas A., Alegre-Del-Rey E. J. and Olry de Labry Lima A. Cost-effectiveness of second- or third-line treatment with tisotumab vedotin for metastatic or recurrent cervical cancer. Expert Rev Pharmacoecon Outcomes Res. 2026;26(2):203–210. Epub 20251218. DOI: 10.1080/14737167.2025.2603941 10.1080/14737167.2025.2603941. Epub 2025 Dec 18.

[10] Huo G., Liu W. and Chen P. Cost-effectiveness of tisotumab vedotin as a second- or third-line therapy for cervical cancer. J Gynecol Oncol. 2024;35(5):e58. Epub 20240124. DOI: 10.3802/jgo.2024.35.e58 10.3802/jgo.2024.35.e58. Epub 2024 Jan 24.

[11] Husereau D., Drummond M., Augustovski F., de Bekker-Grob E., Briggs A., Carswell C., et al. Cheers 2022 Checklist. 2022 [cited 03.03.2026]. Available from: https://www.equator-network.org/wp-content/uploads/2013/04/CHEERS-2022-checklist-1.pdf.

[12] Evers S., Goossens M., de Vet H., van Tulder M. and Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care. 2005;21(2):240–245.

[13] Clinical Experts. Personal communication with clinical experts. 2026.

10 List of abbreviations

ADA ……anti-drug antibody
ADC ……antibody drug conjugate
AE ……adverse event
AIC ……Akaike Information Criterion
AIHTA ……Austrian Institute for Health Technology Assessment
ALT ……alanine aminotransferase
ANC ……absolute neutrophil count
aPTT ……activated partial thromboplastin time
AST ……aspartate aminotransferase
C1D1 ……Cycle 1 Day 1
CC……cervical cancer
CA-125 ……Cancer-Antigen 125
CE ……Conformité Européenne
ChT ……chemotherapy
CI ……confidence interval
CNS ……central nervous system
CPS … ……combined positive score
CT ……computed tomography
CUA ……cost-utility analysis
DNA ……deoxyribonucleic acid
EC ……European Commission
ECOG ……Eastern Cooperative Oncology Group
eGFR ……estimated glomerular filtration rate
ENGOT ……European Network of Gynaecological Oncological Trial Groups
EOT ……end-of-treatment
EPAR ……European Public Assessment Report
ES ……Spain
ESMO-MCBS …European Society For Medical Oncology – Magnitude Of Clinical Benefit Scale
est. ……estimated
FDA ……U.S. Food and Drug Administration
FIGO ……International Federation of Gynecology and Obstetrics
GOG ……Gynecologic Oncology Group
HBV ……hepatitis B virus
HCVAb ……hepatitis C antibody
HER2 ……human epidermal growth factor 2
HIV ……human immunodeficiency virus,
HPV ……human papilloma virus
HR ……hazard ratio
HRQOL ……health-related quality of life
HTA ……Health Technology Assessment
ICI ……immune checkpoint inhibitor
ICUR … ……incremental cost-utility ratio
IDMC ……independent data monitoring committee
INR ……international normalized ratio
MDRD ……Modification of Diet in Renal Disease
MMAE ……monomethyl auristatin E
MRI ……magnetic resonance imaging
n ……number
OS … ……overall survival
OWSA ……one-way sensitivity analysis
p ……p-value
PD ……progressive disease
PD-1 ……programmed cell death 1
PD-L1 ……programmed cell death-ligand 1
PET ……positron emission tomography
PFS……progression-free survival
PK ……pharmacokinetics
PRO ……patient-reported outcome
PSA… ……probability sensitivity analysis
PSM ……partitioned survival model
pts……patients
QALY ……quality-adjusted life years
QoL ……quality of life
r/m ……recurrent/metastatic
RCT ……randomised controlled trial
RECIST ……Response Evaluation Criteria In Solid Tumours
RNA ……ribonucleic acid
RoB ……risk of bias
SA ……sensitivity analysis
SCC ……squamous cell carcinoma
TEAE ……treatment-emergent adverse event
TF ……tissue factor
TV ……tisotumab vedotin
ULN ……upper limit of normal

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