

Tisotumab vedotin (cervical cancer)

Benefit assessment according to §35a SGB V¹

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EXTRACT

Project: A25-112

Version: 1.0

Status: 26 Nov 2025

DOI: 10.60584/A25-112_en

¹ Translation of Sections I 1 to I 7 of the dossier assessment *Tisotumab vedotin (Zervixkarzinom)* – *Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Tisotumab vedotin (cervical cancer) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

29 August 2025

Internal Project No.

A25-112

DOI-URL

https://doi.org/10.60584/A25-112_en

Address of publisher

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Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Tisotumab vedotin (cervical cancer); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-112_en.

Keywords

Tisotumab vedotin, Uterine Cervical Neoplasms, Benefit Assessment, NCT04697628

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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² Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IDMC	independent data monitoring committee
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death-ligand 1
RCT	randomized controlled trial
RECIST v1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tisotumab vedotin. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 29 August 2025.

Research question

The aim of this report is to assess the added benefit of tisotumab vedotin in comparison with the appropriate comparator therapy (ACT) for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of tisotumab vedotin

Research question	Therapeutic indication	ACT ^a
1	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based first-line chemotherapy who have not received prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	cemiplimab
2	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after - platinum-free first-line chemotherapy without a PD-(L)1 antibody, - first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody, - sequential therapy with platinum-containing chemotherapy and a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	Individualized treatment with a choice of monotherapy ^{b, c} with - nab-paclitaxel - vinorelbine - ifosfamide - topotecan - pemetrexed - irinotecan - pembrolizumab (only for patients with PD-L1-positive cervical cancer [CPS score ≥ 1] who have not received prior treatment with a PD-(L)1 antibody)
3	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after prior systemic therapy for whom further antineoplastic therapy is not an option	Best supportive care ^d

a. Presented is the respective ACT specified by the G-BA.

b. The monotherapies nab-paclitaxel, vinorelbine, pemetrexed, ifosfamide, topotecan and irinotecan as well as the checkpoint inhibitor pembrolizumab as monotherapy are not authorized for this therapeutic indication. According to the G-BA, the authorized drugs (bleomycin, carboplatin, cisplatin and mitomycin, as well as the combination therapies bevacizumab in combination with paclitaxel and cisplatin or with paclitaxel and topotecan, ifosfamide in combination with cisplatin, pembrolizumab in combination with chemotherapy with or without bevacizumab, and topotecan in combination with cisplatin, cemiplimab) do not correspond to the guideline recommendations for this therapeutic indication or to the clinicians' comments on the standard of care in the reality of health care provision. In accordance with the generally accepted state of medical knowledge, the monotherapies with nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, ifosfamide, topotecan or pembrolizumab with off-label use are thus considered the standard of care and, in accordance with §6(2), sentence 3, number 2, AM-NutzenV, are generally preferable to the mono- and combination therapies authorized in the therapeutic indication.

c. In the given treatment situation, it is expected for the implementation of individualized treatment in a study of direct comparison that investigators have a choice of several treatment options at their disposal (multi-comparator study).

d. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1

In the remainder of the report, the research questions are referred to as follows:

- Research question 1: patients with platinum-based first-line chemotherapy, without prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option
- Research question 2: patients with platinum-free first-line chemotherapy without a PD-(L)1 antibody or first-line combination therapy consisting of chemotherapy and PD-(L)1 antibody or sequential therapy with platinum-containing chemotherapy and PD-(L)1 antibody and for whom further antineoplastic therapy is an option
- Research question 3: patients with prior systemic therapy for whom further antineoplastic therapy is not an option

The company followed the G-BA's specification of the ACT for research questions 1 and 2. The company did not address research question 3 in its dossier, justifying this by stating that, in its view, for patients for whom further antineoplastic therapy is not an option, treatment with tisotumab vedotin is also not an option. The company's approach was not appropriate. This benefit assessment was conducted in accordance with the 3 research questions specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit.

Research question 1: patients with platinum-based first-line chemotherapy, without prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option

Results

Concurring with the company, the review of the completeness of the study pool did not identify any relevant studies.

Results on added benefit

Since no relevant study was available for this research question, there is no hint of an added benefit of tisotumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients with platinum-free first-line chemotherapy without a PD-(L)1 antibody or first-line combination therapy consisting of chemotherapy and PD-(L)1 antibody or sequential therapy with platinum-containing chemotherapy and PD-(L)1 antibody and for whom further antineoplastic therapy is an option

Results

The review of the completeness of the study pool identified the study innovaTV 301 for the direct comparison of tisotumab vedotin versus investigator's choice chemotherapy. This study also included patients for research question 2 of this benefit assessment. The company also

identified this study, but considered the subpopulation of the study relevant for research question 2 to be unsuitable for the benefit assessment due to the small population size. The company therefore presented the results of the total population of the innovaTV 301 study as supportive evidence.

The data presented by the company were unsuitable to draw conclusions on the added benefit for research question 2 of this benefit assessment. Below, the study is first described and then reasons are provided as to why the data presented by the company were unsuitable for the benefit assessment.

Evidence presented by the company – innovaTV 301 study

The innovaTV 301 study is an ongoing, open-label, multicentre RCT comparing tisotumab vedotin with investigator's choice chemotherapy with a selection of topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed (hereinafter referred to as 'chemotherapy'). The chemotherapy was chosen prior to randomization. The study included adult patients with recurrent or metastatic cervical cancer of any histology (squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma) and disease progression during or after platinum-free or platinum-based chemotherapy. Patients had to have measurable disease according to the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1) and be in good general health, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with active eye disorders or a history of inflammatory eye disorders (conjunctivitis) were excluded.

The study included a total of 502 patients who were randomly allocated in a 1:1 ratio to the intervention arm (N = 253) or the comparator arm (N = 249). Randomization in the innovaTV 301 study was stratified according to ECOG PS (0 versus 1), prior bevacizumab therapy (yes versus no), geographical region (North America versus EU versus rest of the world) and prior therapy with a PD-(L)1 inhibitor (yes versus no).

Tisotumab vedotin was administered in compliance with the summary of product characteristics (SmPC). Since none of the drugs used in the comparator arm of the innovaTV 301 study is authorized as monotherapy for the therapeutic indication in question, the SmPCs do not provide any direct recommendation for treatment duration and dosage. Gemcitabine is not part of the ACT defined by the G-BA (see also comments on the relevant subpopulation of the study below). The treatment options nab-paclitaxel, ifosfamide and pembrolizumab, which were part of the individualized treatment defined by the G-BA as the ACT, were not used in innovaTV 301. The company did not provide any information on the extent to which this corresponded to the individualized treatment specified by the G-BA.

Treatment with the study medication continued until disease progression, unacceptable toxicity, decision by the investigator or the patient, withdrawal of consent by the patient,

initiation of subsequent anticancer therapy, study discontinuation by the sponsor, pregnancy, or death, whichever occurred first.

The primary outcome of innovaTV 301 was overall survival. Secondary outcomes included outcomes from the categories of morbidity, health-related quality of life and side effects.

Approach of the company

The company described the derivation of the analysis population relevant for research question 2 according to the population defined by the G-BA for this research question. For this purpose, the company first removed from the total study population the patients for whom gemcitabine had been selected as a potential comparator therapy prior to randomization (n = 109 patients in the intervention arm [43%] versus n = 99 patients in the comparator arm [40%]), as this drug was not an option of the ACT. In the next step, the company selected the patients who had received previous therapy according to the criteria defined by the G-BA. According to the information provided by the company, this applied to 32 patients in the intervention arm and 31 patients in the comparator arm. The subpopulation relevant for the assessment of research question 2 thus comprised 63 patients of the original 502 randomized patients.

The company explained, among other things, that the small population size led to major uncertainties with regard to the effect estimates of the analyses conducted and that the robustness of the conclusions drawn from them was limited. As a consequence, the company was of the opinion that the determined subpopulation was unsuitable for research question 2 and therefore only presented the results of the total population as supportive evidence for the assessment of the research question. The results of the subpopulation were not available in the dossier.

Assessment of the company's approach

The company's approach was not appropriate. The data of the total population presented by the company were unsuitable for answering research question 2.

72% of the total patient population had not received prior therapy with a PD-(L)1 inhibitor. The majority of these patients would have to be assigned to research question 1 due to their previous platinum-based therapy. However, cemiplimab was the ACT for this research question, which was not available in the innovaTV 301 study.

For the given research question, only analyses of the subpopulation of patients who had received prior therapy in accordance with the G-BA criteria and who had not been treated with gemcitabine as a comparator therapy would be suitable. It could be inferred from the available information that this only applied to 32 patients in the intervention arm versus 31

patients in the comparator arm. The company did not present the results for this subpopulation.

Results on added benefit

Since no suitable data were available for this research question, there is no hint of an added benefit of tisotumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: patients with prior systemic therapy for whom further antineoplastic therapy is not an option

Results

The company did not investigate research question 3 in its dossier. This was not appropriate.

However, this had no consequences for this benefit assessment, as no relevant study for research question 3 was identified in the review of the completeness of the study pool.

Results on added benefit

Since no relevant study was available for this research question, there is no hint of an added benefit of tisotumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

Table 3 shows a summary of the probability and extent of the added benefit of tisotumab vedotin.

³ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Tisotumab vedotin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
1	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based first-line chemotherapy who have not received prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	cemiplimab	Added benefit not proven
2	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after - platinum-free first-line chemotherapy without a PD-(L)1 antibody, - first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody, - sequential therapy with platinum-containing chemotherapy and a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	Individualized treatment with a choice of monotherapy ^{b, c} with - nab-paclitaxel - vinorelbine - ifosfamide - topotecan - pemetrexed - irinotecan - pembrolizumab (only for patients with PD-L1-positive cervical cancer [CPS score ≥ 1] who have not received prior treatment with a PD-(L)1 antibody)	Added benefit not proven
3	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after prior systemic therapy for whom further antineoplastic therapy is not an option	Best supportive care ^d	Added benefit not proven

Table 3: Tisotumab vedotin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. The monochemotherapies nab-paclitaxel, vinorelbine, pemetrexed, ifosfamide, topotecan and irinotecan as well as the checkpoint inhibitor pembrolizumab as monotherapy are not authorized for this therapeutic indication. According to the G-BA, the authorized drugs (bleomycin, carboplatin, cisplatin and mitomycin, as well as the combination therapies bevacizumab in combination with paclitaxel and cisplatin or with paclitaxel and topotecan, ifosfamide in combination with cisplatin, pembrolizumab in combination with chemotherapy with or without bevacizumab, and topotecan in combination with cisplatin, cemiplimab) do not correspond to the guideline recommendations for this therapeutic indication or to the clinicians' comments on the standard of care in the reality of health care provision. In accordance with the generally accepted state of medical knowledge, the monotherapies with nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, ifosfamide, topotecan or pembrolizumab with off-label use are thus considered the standard of care and, in accordance with §6(2), sentence 3, number 2, AM-NutzenV, are generally preferable to the mono- and combination therapies authorized in the therapeutic indication. c. In the given treatment situation, it is expected for the implementation of individualized treatment in a study of direct comparison that investigators have a choice of several treatment options at their disposal (multi-comparator study). d. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1			

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of tisotumab vedotin in comparison with the appropriate comparator therapy (ACT) for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of tisotumab vedotin

Research question	Therapeutic indication	ACT ^a
1	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based first-line chemotherapy who have not received prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	cemiplimab
2	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after - platinum-free first-line chemotherapy without a PD-(L)1 antibody, - first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody, - sequential therapy with platinum-containing chemotherapy and a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	Individualized treatment with a choice of monotherapy ^{b, c} with - nab-paclitaxel - vinorelbine - ifosfamide - topotecan - pemetrexed - irinotecan - pembrolizumab (only for patients with PD-L1-positive cervical cancer [CPS score ≥ 1] who have not received prior treatment with a PD-(L)1 antibody)
3	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after prior systemic therapy for whom further antineoplastic therapy is not an option	Best supportive care ^d

a. Presented is the respective ACT specified by the G-BA.

b. The monotherapies nab-paclitaxel, vinorelbine, pemetrexed, ifosfamide, topotecan and irinotecan as well as the checkpoint inhibitor pembrolizumab as monotherapy are not authorized for this therapeutic indication. According to the G-BA, the authorized drugs (bleomycin, carboplatin, cisplatin and mitomycin, as well as the combination therapies bevacizumab in combination with paclitaxel and cisplatin or with paclitaxel and topotecan, ifosfamide in combination with cisplatin, pembrolizumab in combination with chemotherapy with or without bevacizumab, and topotecan in combination with cisplatin, cemiplimab) do not correspond to the guideline recommendations for this therapeutic indication or to the clinicians' comments on the standard of care in the reality of health care provision. In accordance with the generally accepted state of medical knowledge, the monotherapies with nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, ifosfamide, topotecan or pembrolizumab with off-label use are thus considered the standard of care and, in accordance with §6(2), sentence 3, number 2, AM-NutzenV, are generally preferable to the mono- and combination therapies authorized in the therapeutic indication.

c. In the given treatment situation, it is expected for the implementation of individualized treatment in a study of direct comparison that investigators have a choice of several treatment options at their disposal (multi-comparator study).

d. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1

In the remainder of the report, the research questions are referred to as follows:

- Research question 1: patients with platinum-based first-line chemotherapy, without prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option
- Research question 2: patients with platinum-free first-line chemotherapy without a PD-(L)1 antibody or first-line combination therapy consisting of chemotherapy and PD-(L)1 antibody or sequential therapy with platinum-containing chemotherapy and PD-(L)1 antibody and for whom further antineoplastic therapy is an option
- Research question 3: patients with prior systemic therapy for whom further antineoplastic therapy is not an option

The company followed the G-BA's specification of the ACT for research questions 1 and 2. The company did not address research question 3 in its dossier, justifying this by stating that, in its view, for patients for whom further antineoplastic therapy is not an option, treatment with tisotumab vedotin is also not an option. The company's approach was not appropriate. This benefit assessment was conducted in accordance with the 3 research questions specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Research question 1: patients with platinum-based first-line chemotherapy, without prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option

I 3.1 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on tisotumab vedotin (status: 19 August 2025)
- Bibliographical literature search on tisotumab vedotin (last search on 19 August 2025)
- Search of trial registries / trial results databases for studies on tisotumab vedotin (last search on 19 August 2025)
- Search on the G-BA website for tisotumab vedotin (last search on 19 August 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on tisotumab vedotin (last search on 8 September 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, this review did not identify any relevant studies.

I 3.2 Results on added benefit

For research question 1, no data on the comparison with the ACT were available to assess the added benefit of tisotumab vedotin. There is no hint of an added benefit of tisotumab vedotin in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 3.3 Probability and extent of added benefit

No data for comparison with the ACT were available for the assessment of the added benefit of tisotumab vedotin in adult patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based first-line chemotherapy who have not received prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option. An added benefit of tisotumab vedotin in comparison with the ACT is thus not proven for these patients.

This concurs with the company's assessment.

I 4 Research question 2: patients with platinum-free first-line chemotherapy without a PD-(L)1 antibody or first-line combination therapy consisting of chemotherapy and PD-(L)1 antibody or sequential therapy with platinum-containing chemotherapy and PD-(L)1 antibody and for whom further antineoplastic therapy is an option

I 4.1 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on tisotumab vedotin (status: 19 August 2025)
- Bibliographical literature search on tisotumab vedotin (last search on 19 August 2025)
- Search of trial registries / trial results databases for studies on tisotumab vedotin (last search on 19 August 2025)
- Search on the G-BA website for tisotumab vedotin (last search on 19 August 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on tisotumab vedotin (last search on 8 September 2025); for search strategies, see I Appendix A of the full dossier assessment

The review identified the study innovaTV 301 [3] for the direct comparison of tisotumab vedotin versus investigator's choice chemotherapy. This study also included patients for research question 2 of this benefit assessment. The company also identified this study, but considered the subpopulation of the study relevant for research question 2 to be unsuitable for the benefit assessment due to the small population size. The company therefore presented the results of the total population of the innovaTV 301 study as supportive evidence.

The data presented by the company were unsuitable to draw conclusions on the added benefit for research question 2 of this benefit assessment. Below, the study is first described and then reasons are provided as to why the data presented by the company were unsuitable for the benefit assessment.

Evidence provided by the company

Study characteristics

Table 5 and Table 6 describe the innovaTV 301 study.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: tisotumab vedotin vs. chemotherapy of physician's choice^a (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^b
innovaTV 301	RCT, open-label, parallel	Ault patients (≥ 18 years) with recurrent or metastatic cervical cancer^c: - treated with 1 or 2 prior systemic therapy regimens^{d, e} - ECOG PS 0 or 1	tisotumab vedotin (N = 253) chemotherapy of physician's choice^a (N = 249)	Screening: up to 28 days Treatment: until disease progression, occurrence of unacceptable toxicity, treatment discontinuation at the patient's or investigator's decision, start of subsequent therapy, end of study, pregnancy or death Observation: outcome-specific, at most until death or end of study	25 centres in Argentina, Austria, Belgium, Brazil, Canada, China, Czech Republic, Finland, France, Germany, Hungary, Italy, Japan, Mexico, Netherlands, Norway, Peru, Poland, Singapore, South Korea, Spain, Sweden, Taiwan, United Kingdom, United states 3/2021–ongoing Data cut-offs: 24 July 2023^f (primary data cut-off) 16 January 2024^g	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 5: Characteristics of the study included by the company – RCT, direct comparison: tisotumab vedotin vs. chemotherapy of physician's choice^a (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^b
a. Topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed as monotherapy. b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. c. Measurable disease according to RECIST v1.1 as assessed by the investigator. d. Included patients had to have experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible) (see Table 6 for detailed information). e. Chemotherapies administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, were not counted as a prior systemic therapy regimen; monotherapy with a PD-(L)1 inhibitor were counted. f. Prespecified interim analysis for the outcome overall survival, planned after approx. 252 deaths in the total population (75% of events). g. Analyses on overall survival requested by the EMA (see explanations in the next section). AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; IDMC: independent data monitoring committee; N: number of randomized patients; PD-L1: programmed cell death-ligand 1; RCT: randomized controlled trial; RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1						

Table 6: Characteristics of the intervention – RCT, direct comparison: tisotumab vedotin vs. chemotherapy of physician's choice^a (multipage table)

Study	Intervention	Comparison
innovaTV 301	tisotumab vedotin 2.0 mg/kg BW IV every 3 weeks of a 21-day cycle ^b	topotecan 1 mg/m² or 1.25 mg/m² BSA IV on Days 1–5 of a 21-day cycle^b vinorelbine 30 mg/m² BSA IV, on Days 1 and 8 of a 21-day cycle^c gemcitabine 1000 mg/m² BSA IV, on Days 1 and 8 of a 21-day cycle^{c, d} irinotecan 100 or 125 mg/m² BSA IV, weekly for 28 days of a 42-day cycle^{c, e} pemetrexed 500 mg/m² BSA IV on Day 1 of a 21-day cycle^c
	Dose modification^c: ▪ Dose reduction allowed according to the SmPC ▪ Dose delay of up to 21 days; a delay of up to 6 weeks required consultation with the study sponsors	▪ topotecan: permanent dose reduction in case of toxicity ▪ vinorelbine: dose reduction in case of haematologic or hepatic toxicity ▪ gemcitabine, irinotecan and pemetrexed: dose reduction in case of toxicity
	Required prior therapy ▪ Systemic chemotherapy or platinum-based therapy (if eligible)^{f, g}: ▫ paclitaxel + cisplatin + bevacizumab + PD-(L)1 inhibitor or ▫ paclitaxel + carboplatin + bevacizumab + PD-(L)1 inhibitor or ▫ paclitaxel + topotecan/nogitecan + bevacizumab + PD-(L)1 inhibitor or ▪ Surgery or stereotactic brain radiotherapy > 8 weeks before the first dose of study treatment	
	Required concomitant treatment ▪ Intervention arm: prophylactic eye care according to the SmPC (eye drops^h, cold packs) and recommendation not to wear contact lenses	
	Permitted concomitant treatment ▪ Prophylaxis of alopecia ▪ Antiemetics and antipyretics, e.g. paracetamol ▪ Premedication for the treatment of infusion-related reactions ▪ G-CSF for neutropenic sepsis or neutropenia grade 3/4 ▪ Any treatments necessary for the patients' wellbeing ▪ Intervention arm: ▫ Anticoagulants, e.g. warfarin or other vitamin K-dependent anticoagulant agents ▫ Strong CYP3A or P-gp inhibitors	

Table 6: Characteristics of the intervention – RCT, direct comparison: tisotumab vedotin vs. chemotherapy of physician's choice^a (multipage table)

Study	Intervention	Comparison
	Prohibited prior and concomitant treatment - Intervention arm: chronic prophylactic treatment with acetylsalicylic acid (e.g. aspirin) or chronic antiplatelet therapy in combination with any other anticoagulation therapy - Other investigational products - Major surgery < 4 weeks, minor surgery < 7 days prior to study start - any prior treatment with MMAE - Radiotherapyⁱ within 21 days, other anticancer therapy, immunotherapy or monoclonal antibodies within 28 days prior to the first dose of study treatment - Antimicrobial therapy, systemic steroid therapy (≥ 10 mg prednisone or equivalent/day) and immunosuppressive therapy < 7 days prior to the first dose of study treatment	
	a. Topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed as monotherapy. b. The dose used does not correspond to the dosing recommendation in the S3 guideline 'Diagnosis, Therapy and Follow-up of Cervical Cancer' (1.5 mg/m² BSA) [4]. c. Dose modifications in the chemotherapy arm were allowed as per local labelling or guidelines. d. In this therapeutic indication, the S3 guideline 'Diagnosis, Therapy and Follow-up of Cervical Cancer' [4] recommends using gemcitabine not as monotherapy, but in combination with cisplatin. e. The S3 guideline [4] recommends the same dose once a week without further restriction. f. In cases where bevacizumab and/or a PD-(L)1 inhibitor is not a standard of care therapy or the participant is ineligible for such treatment, prior treatment with bevacizumab and/or a PD-(L)1 inhibitor is not required. g. Chemotherapies administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, were not counted as a prior systemic therapy regimen; monotherapy with a PD-(L)1 inhibitor were counted. h. Vasoconstrictor eye drops (brimonidine tartrate 0.2%) before each infusion, corticosteroid eye drops (e.g. dexamethasone 0.1%) before the infusion and for 3 days afterwards, lubricating eye drops during the treatment and until 30 days after the last dose of tisotumab vedotin. i. Radiation therapy of a symptomatic solitary non-target lesion or to the brain was allowed at the investigator's discretion, BBSA: body surface area; BW: body weight; CYP3A: cytochrome P450; G-CSF: granulocyte colony-stimulating factor; IV: intravenous; MMAE: monomethyl auristatin E; PD-L1: programmed cell death-ligand 1; P-gp: P-glycoprotein; RCT: randomized controlled trial	

The innovaTV 301 study is an ongoing, open-label, multicentre RCT comparing tisotumab vedotin with investigator's choice chemotherapy with a selection of topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed (hereinafter referred to as 'chemotherapy'). The chemotherapy was chosen prior to randomization. The study included adult patients with recurrent or metastatic cervical cancer of any histology (squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma) and disease progression during or after platinum-free or platinum-based chemotherapy. Patients had to have received 1 or 2 prior systemic therapy regimens with paclitaxel, bevacizumab and PD-(L)1 inhibitor, in combination with cisplatin, carboplatin or topotecan/nogitecan. In cases where bevacizumab and/or a PD-(L)1 inhibitor was not a standard of care therapy or the patients were ineligible for such treatment, these prior treatments were not required for inclusion in the study. Patients had to have measurable disease according to the Response Evaluation Criteria in Solid Tumours,

version 1.1 (RECIST v1.1) and be in good general health, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with active eye disorders or a history of inflammatory eye disorders (conjunctivitis) were excluded.

The study included a total of 502 patients who were randomly allocated in a 1:1 ratio to the intervention arm (N = 253) or the comparator arm (N = 249). Randomization in the innovaTV 301 study was stratified according to ECOG PS (0 versus 1), prior bevacizumab therapy (yes versus no), geographical region (North America versus EU versus rest of the world) and prior therapy with a PD-(L)1 inhibitor (yes versus no).

Tisotumab vedotin was administered in compliance with the summary of product characteristics (SmPC) [5]. Since none of the drugs used in the comparator arm of the innovaTV 301 study is authorized as monotherapy for the therapeutic indication in question, the SmPCs do not provide any direct recommendation for treatment duration and dosage. The dosages of the chemotherapeutic regimens used are presented in Table 6. The doses and intervals of chemotherapy with vinorelbine and pemetrexed corresponded to the recommendations of the S3 guideline for cervical cancer [4]. In contrast, the dosage of topotecan deviated from the recommendations of the S3 guideline. According to the guidelines, topotecan should be used at a daily dose of 1.5 mg/m² body surface area (BSA) for 5 days every 3 weeks, whereas in the innovaTV 301 study it was used at a daily dose of 1 or 1.25 mg/m² BSA for 5 days every 3 weeks. This means a lower dosage for topotecan than described in the S3 guideline. In the study, irinotecan was given at a dose of 125 mg/m² BSA weekly for 28 days in a 42-day cycle. The guideline recommends giving the same dosage once a week without further restriction. Gemcitabine is not part of the ACT defined by the G-BA (see also comments on the relevant subpopulation of the study below). The treatment options nab-paclitaxel, ifosfamide and pembrolizumab, which were part of the individualized treatment defined by the G-BA as the ACT, were not used in innovaTV 301. The company did not provide any information on the extent to which this corresponded to the individualized treatment specified by the G-BA.

Treatment with the study medication continued until disease progression, unacceptable toxicity, decision by the investigator or the patient, withdrawal of consent by the patient, initiation of subsequent anticancer therapy, study discontinuation by the sponsor, pregnancy, or death, whichever occurred first.

The primary outcome of innovaTV 301 was overall survival. Secondary outcomes included outcomes from the categories of morbidity, health-related quality of life and side effects.

Approach of the company

In Module 4 A, the company described the derivation of the analysis population relevant for research question 2 according to the population defined by the G-BA for this research

question. For this purpose, the company first removed from the total study population the patients for whom gemcitabine had been selected as a potential comparator therapy prior to randomization (n = 109 patients in the intervention arm [43%] versus n = 99 patients in the comparator arm [40%]), as this drug was not an option of the ACT. In the next step, the company selected the patients who had received previous therapy according to the criteria defined by the G-BA. According to the information provided by the company, this applied to 32 patients in the intervention arm and 31 patients in the comparator arm. The subpopulation relevant for the assessment of research question 2 thus comprised 63 patients of the original 502 randomized patients.

The company explained that the small population size led to major uncertainties with regard to the effect estimates of the analyses conducted and that the robustness of the conclusions drawn from them was limited. It added that the selection of this subpopulation meant that this highly selective population did not correspond to everyday practice. As a consequence, the company was of the opinion that the determined subpopulation was unsuitable for research question 2 and therefore only presented the results of the total population as supportive evidence for the assessment of the research question. The results of the subpopulation were not available in the dossier.

Assessment of the company's approach

The company's approach was not appropriate. The data of the total population presented by the company were unsuitable for answering research question 2.

72% of the total patient population had not received prior therapy with a PD-(L)1 inhibitor. The majority of these patients would have to be assigned to research question 1 due to their previous platinum-based therapy. However, cemiplimab was the ACT for this research question, which was not available in the innovaTV 301 study.

For the given research question, only analyses of the subpopulation of patients who had received prior therapy in accordance with the G-BA criteria and who had not been treated with gemcitabine as a comparator therapy would be suitable. It could be inferred from the available information that this only applied to 32 patients in the intervention arm versus 31 patients in the comparator arm. The company did not present the results for this subpopulation.

Further aspects

Two data cut-offs were prespecified for innovaTV 301:

- 1st data cut-off on 24 July 2023: prespecified interim analysis, planned after the occurrence of 252 deaths (approx. 75%) in the total population

- 2nd data cut-off: prespecified final analysis of overall survival, planned after the occurrence of 336 deaths in the total population

In the dossier, the company presented the data on the 1st data cut as the final analysis for overall survival (24 July 2023). At this point, 263 deaths had occurred in the total population (123 in the intervention arm and 140 in the comparator arm), thus reaching the prespecified 75% of overall survival events for the planned interim analysis. According to the company, the 1st data cut was determined post hoc as the final analysis, after an independent data monitoring committee (IDMC) had found that the events in the outcome overall survival had exceeded the prespecified efficacy threshold at that time. In the dossier, the company did not present analyses on the prespecified 2nd data cut. Furthermore, the company described that an additional, non-prespecified data cut from 16 January 2024 had been submitted to the EMA for the innovaTV 301 study, but that this had not been requested by the regulatory authority and had no influence on the marketing authorization. This data cut was not presented by the company.

The company's approach was not comprehensible. Contrary to the company's statement, an additional data cut for the outcome overall survival was submitted following a request by the EMA [6]. At the time of the subsequently submitted data cut from 16 January 2024, 350 deaths had occurred in the total population (176 in the intervention arm and 174 in the comparator arm) [7]. With this number of events, the final data cut of 336 deaths prespecified in the study protocol would have been reached. The omission of the data for this final analysis in the company's dossier was inappropriate.

I 4.2 Results on added benefit

For research question 2, no suitable data on the comparison with the ACT were available to assess the added benefit of tisotumab vedotin. There is no hint of an added benefit of tisotumab vedotin in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 4.3 Probability and extent of added benefit

No suitable data for comparison with the ACT were available for the assessment of the added benefit of tisotumab vedotin in adult patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-free first-line chemotherapy without a PD-(L)1 antibody, first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody or sequential therapy with platinum-containing chemotherapy and a PD-(L)1 antibody and for whom further antineoplastic therapy is an option. An added benefit of tisotumab vedotin in comparison with the ACT is thus not proven for these patients.

This deviates from the assessment of the company, which derived a hint of a minor added benefit for these patients, based on the total study population of innovaTV 301 as supportive evidence.

I 5 Research question 3: patients with prior systemic therapy for whom further antineoplastic therapy is not an option

The company did not investigate research question 3 in its dossier. This was not appropriate (see also Chapter I 2).

However, this had no consequences for this benefit assessment, as no relevant study for research question 3 was identified in the review of the completeness of the study pool (search in trial registries for studies on tisotumab vedotin [last search on 8 September 2025], for search strategies see I Appendix A of the full dossier assessment).

I 5.1 Results on added benefit

For research question 3, no data on the comparison with the ACT were available to assess the added benefit of tisotumab vedotin. There is no hint of an added benefit of tisotumab vedotin in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 5.2 Probability and extent of added benefit

No data for comparison with the ACT were available for the assessment of the added benefit of tisotumab vedotin in adult patients with recurrent or metastatic cervical cancer with disease progression during or after prior systemic therapy and for whom further antineoplastic therapy is not an option. An added benefit of tisotumab vedotin in comparison with the ACT is thus not proven for these patients.

This concurs with the company's assessment.

I 6 Probability and extent of added benefit – summary

Table 7 summarizes the result of the assessment of the added benefit of tisotumab vedotin in comparison with the ACT.

Table 7: Tisotumab vedotin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
1	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based first-line chemotherapy who have not received prior treatment with a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	cemiplimab	Added benefit not proven
2	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after ▪ platinum-free first-line chemotherapy without a PD-(L)1 antibody, ▪ first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody, ▪ sequential therapy with platinum-containing chemotherapy and a PD-(L)1 antibody and for whom further antineoplastic therapy is an option	Individualized treatment with a choice of monotherapy ^{b, c} with ▪ nab-paclitaxel ▪ vinorelbine ▪ ifosfamide ▪ topotecan ▪ pemetrexed ▪ irinotecan ▪ pembrolizumab (only for patients with PD-L1-positive cervical cancer [CPS score ≥ 1] who have not received prior treatment with a PD-(L)1 antibody)	Added benefit not proven
3	Adult patients with recurrent or metastatic cervical cancer with disease progression during or after prior systemic therapy for whom further antineoplastic therapy is not an option	Best supportive care ^d	Added benefit not proven

Table 7: Tisotumab vedotin – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. The monochemotherapies nab-paclitaxel, vinorelbine, pemetrexed, ifosfamide, topotecan and irinotecan as well as the checkpoint inhibitor pembrolizumab as monotherapy are not authorized for this therapeutic indication. According to the G-BA, the authorized drugs (bleomycin, carboplatin, cisplatin and mitomycin, as well as the combination therapies bevacizumab in combination with paclitaxel and cisplatin or with paclitaxel and topotecan, ifosfamide in combination with cisplatin, pembrolizumab in combination with chemotherapy with or without bevacizumab, and topotecan in combination with cisplatin, cemiplimab) do not correspond to the guideline recommendations for this therapeutic indication or to the clinicians' comments on the standard of care in the reality of health care provision. In accordance with the generally accepted state of medical knowledge, the monotherapies with nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, ifosfamide, topotecan or pembrolizumab with off-label use are thus considered the standard of care and, in accordance with §6(2), sentence 3, number 2, AM-NutzenV, are generally preferable to the mono- and combination therapies authorized in the therapeutic indication. c. In the given treatment situation, it is expected for the implementation of individualized treatment in a study of direct comparison that investigators have a choice of several treatment options at their disposal (multi-comparator study). d. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1			

The G-BA decides on the added benefit.

I 7 References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.
2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2016; 58(1): 43-58. <https://doi.org/10.1002/bimj.201300274>.
3. Vergote I, Gonzalez-Martin A, Fujiwara K et al. Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer. *N Engl J Med* 2024; 391(1): 44-55. <https://doi.org/10.1056/NEJMoa2313811>.
4. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom [online]. 2022 [Accessed: 28.10.2025]. URL: https://register.awmf.org/assets/guidelines/032-033OLI_S3_Diagnostik_Therapie_Nachsorge_Zervixkarzinom_2022-03.pdf.
5. Genmab. Fachinformation Tivdak 40 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung [online]. 06.2025 [Accessed: 15.09.2025]. URL: <https://www.fachinfo.de/fi/detail/25434/Tivdak-40-mg-Pulver-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsloesung>.
6. European Medicines Agency. Rapporteurs Day 150 Joint Assessment Report of the responses to the list of questions; Clinical Tivdak Tisotumab vedotin [unpublished]. 2024.
7. European Medicines Agency. Tivdak Assessment Report [online]. 2025 [Accessed: 01.09.2025]. URL: <https://www.ema.europa.eu/en/medicines/human/EPAR/tivdak>.

The full report (German version) is published at
<https://www.iqwig.de/en/projects/a25-112.html>.