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Austrian Institute for
Health Technology Assessment
GmbH

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

Health Technology Assessment

Final Report

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Conflict of interest

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Ergebnisse auf einen Blick

rezidivierendes oder metastasiertes (r/m) Zervixkarzinom

Bösartiger Tumor des **Gebärmutterhalses**, meist durch persistierende **HPV-Infektion** verursacht

Weltweit die **vierthäufigste** Krebserkrankung bei Frauen

r/m
= **erneutes Auftreten** des Tumors nach kurativem Therapieversuch oder das Vorliegen von **Fernmetastasen**

Indikation von Tisotumab vedotin:
Behandlung erwachsener Patientinnen mit r/m Zervixkarzinom

Standardversorgung

Leitlinien:
- Der Therapiestandard basiert auf nationalen und internationalen Leitlinien (AWMF-S3-Leitlinie, AGO-Empfehlungen, NCCN)

Standardversorgung:
- **Erstlinientherapie:** platinbasierte Chemotherapie + Pembrolizumab +/- Bevacizumab
- **Bei Progression:** nicht-platinbasierte Chemotherapie oder Best Supportive Care

Tisotumab vedotin (TIVDAK®)

Typ des Arzneimittels:
Antikörper-Wirkstoff-Konjugat

Positionierung in der Standardversorgung:
Einsatz bei Krankheitsprogression

Zulassung durch die Europäische Kommission: 28. März 2025

Verabreicherung:
- Alle drei Wochen intravenös
- Dosierung beträgt 2 mg/kg Körpergewicht

Monitoring:
Die Behandlung sollte von einer/m erfahrenen Ärzt:in verordnet & überwacht werden

Wirksamkeits- & Sicherheitsanalyse von Tisotumab vedotin
basiert auf einer einzelnen randomisierten kontrollierten Phase III Studie (*innovaTV 301*)

Wirksamkeit
(253 Pat. Tisotumab vedotin vs. 249 Pat. Chemo)

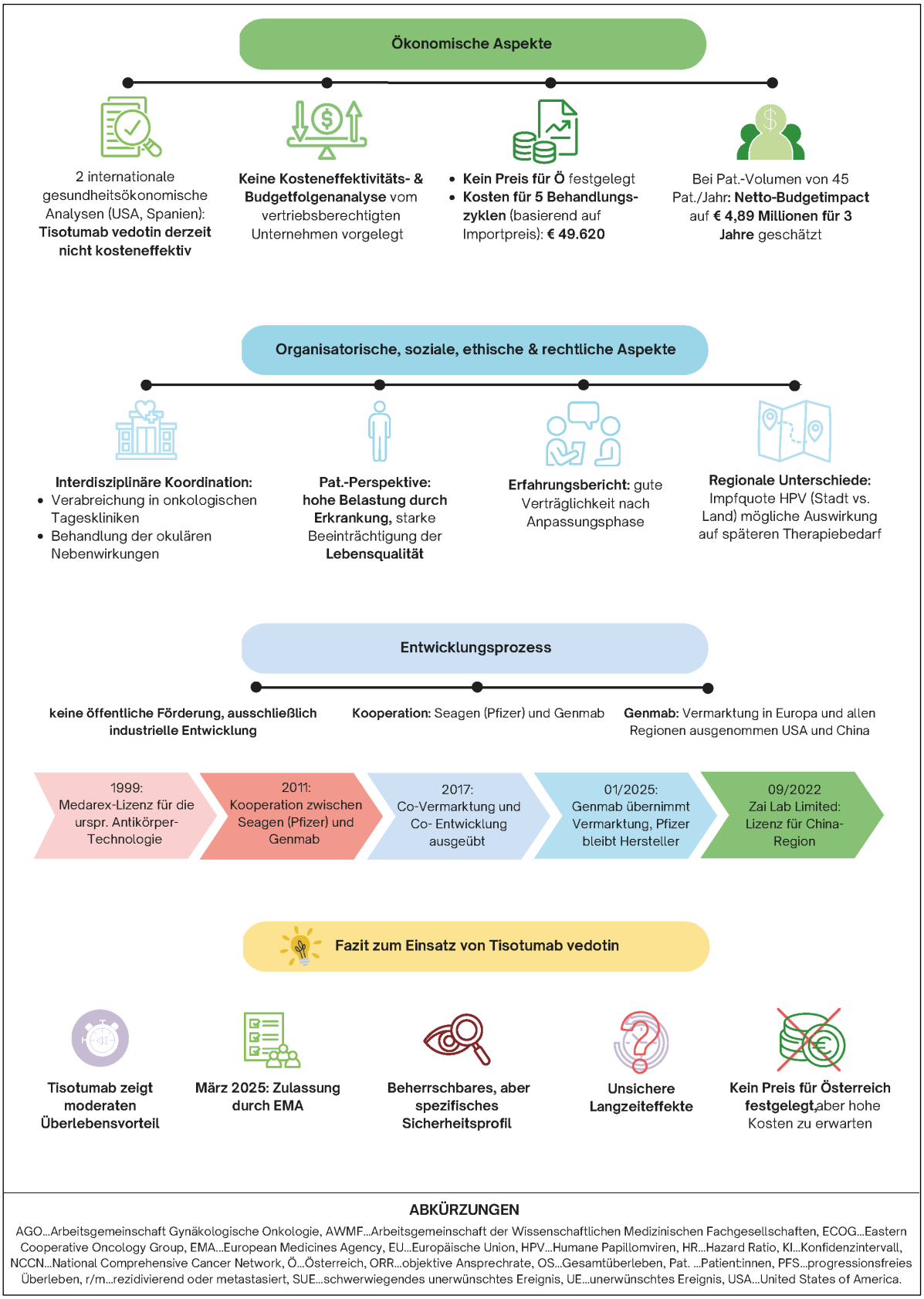
- Statistisch sign. OS-Vorteil für Tisotumab vedotin vs. Chemotherapie: medianes OS von 11,5 vs. 9,5 Monate
- Statistisch sign. PFS-Verbesserung von ca. 1,3 Monaten
- Statistisch sign. höhere bestätigte ORR für Tisotumab vedotin vs. Chemotherapie (17,8% vs. 5,2%)
- Keine eindeutige Verbesserung der gesundheitsbezogenen Lebensqualität nachgewiesen

Sicherheit
(ergänzende Sicherheitsdaten aus klinischem Entwicklungsprogramm)

- UEs in beiden Armen häufig; Grad≥3 UEs und SUEs unter Tisotumab vedotin seltener
- 12 Todesfälle (4,8%) im Tisotumab-vedotin-Arm vs. 19 (7,5%) im Chemo-Arm, überwiegend durch Krankheitsprogression
- Erhöhte Rate okulärer Toxizitäten: bei Tisotumab vedotin: überwiegend niedriggradig, gut beherrschbar → spezifische Präventionsmaßnahmen und Überwachung erforderlich

Studienqualität & Limitationen

- Einige Bedenken hinsichtlich des Verzerrungsrisikos, insbesondere auf fehlende Daten und Ergebnisberichterstattung
- Die Wirksamkeitsergebnisse sind abgeschlossen; jedoch bestehen Unsicherheiten hinsichtlich des langfristigen Sicherheitsprofils, da finale Sicherheitsdaten aus der Studie innovaTV 301 im Rahmen der Post-Authorisation-Pharmakovigilanz noch erwartet werden
- Wie bei den meisten anderen onkologischen Therapien war die Studienpopulation auf Patientinnen mit gutem Allgemeinzustand (ECOG 0-1) definiert



ABKÜRZUNGEN

AGO...Arbeitsgemeinschaft Gynäkologische Onkologie, AWMF...Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, ECOG...Eastern Cooperative Oncology Group, EMA...European Medicines Agency, EU...Europäische Union, HPV...Humane Papillomviren, HR...Hazard Ratio, KI...Konfidenzintervall, NCCN...National Comprehensive Cancer Network, Ö...Österreich, ORR...objektive Ansprechrate, OS...Gesamtüberleben, Pat. ...Patient:innen, PFS...progressionsfreies Überleben, r/m...rezidivierend oder metastasiert, SUE...schwerwiegendes unerwünschtes Ereignis, UE...unerwünschtes Ereignis, USA...United States of America.

Zusammenfassung

Der vorliegende Health Technology Assessment (HTA)-Bericht evaluiert Tisotumab vedotin (TIVDAK®) zur Behandlung erwachsener Patientinnen mit rezidivierendem oder metastasiertem (r/m) Zervixkarzinom und Krankheitsprogression unter oder nach systemischer Therapie.

Beschreibung der Erkrankung und Behandlungsoptionen

Das Zervixkarzinom ist weltweit die vierthäufigste Krebserkrankung bei Frauen und stellt trotz etablierter Screeningprogramme, der Verfügbarkeit prophylaktischer Impfungen gegen Hochrisiko-Humane Papillomaviren (HPV) sowie Weiterentwicklung von Behandlungsmöglichkeiten weiterhin ein bedeutendes Public-Health-Problem dar. Ein erheblicher Anteil der Patientinnen wird in einem lokal fortgeschrittenen oder metastasierten Stadium diagnostiziert, und bei etwa einem Drittel kommt es nach der initialen Therapie zu einem Rezidiv. In diesem Stadium der Erkrankung haben Patientinnen mit Zervixkarzinom eine schlechte Prognose. Die Pathogenese ist eng mit einer persistierenden HPV-Infektion verbunden, die nahezu alle Fälle invasiver Zervixkarzinome verursacht. Allerdings entwickelt sich nur ein kleiner Teil der HPV-Infektionen zu Krebs.

In Österreich werden jährlich rund 415 Neuerkrankungen diagnostiziert (8,5 pro 100.000 Frauen), davon etwa 35 Fälle in einem fortgeschrittenen Stadium. Etwa 135 Todesfälle pro Jahr (2,8 pro 100.000 Frauen) spiegeln die Krankheitslast und die hohe Mortalität in fortgeschrittenen Stadien wider.

Der Therapiestandard in Österreich basiert auf nationalen und internationalen Leitlinien, einschließlich der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)-S3-Leitlinie sowie aktualisierten Empfehlungen der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) und internationalen Leitlinien wie dem National Comprehensive Cancer Network (NCCN). Die Behandlung des r/m Zervixkarzinoms umfasst in der ersten Linie eine platinbasierte Chemotherapie in Kombination mit einem Immuncheckpoint-Inhibitor (Pembrolizumab) mit oder ohne Bevacizumab. Bei Krankheitsprogression stehen in weiteren Therapielinien nur begrenzte Therapieoptionen zur Verfügung. In der österreichischen klinischen Praxis werden in diesem Setting vor allem nicht-platinbasierte Monochemotherapien eingesetzt, die jedoch off-label angewendet werden; alternativ kommt Best Supportive Care infrage.

Überblick über das neue Arzneimittel

Tisotumab vedotin ist eine zielgerichtete Krebstherapie, die als Antikörper-Wirkstoff-Konjugat (Antibody-Drug Conjugates, ADC) bezeichnet wird, da sie einen Antikörper mit einem zytotoxischen Wirkstoff kombiniert. Es besteht aus einem monoklonalen Antikörper gegen den Tissue Factor (TF), ein Protein, das häufig in hoher Menge auf Tumorzellen vorkommt, der mit einem Mikrotubuli-Inhibitor gekoppelt ist. Der Antikörper bindet spezifisch an TF, woraufhin der Komplex in die Zelle aufgenommen und der zytotoxische Wirkstoff freigesetzt wird. Dieser hemmt die Mikrotubuli, die für die Zellteilung essenziell sind, und führt letztlich zum Absterben der Krebszellen.

Die empfohlene Dosierung beträgt 2 mg/kg Körpergewicht (bis maximal 200 mg bei Patientinnen ≥100 kg) und wird alle drei Wochen als intravenöse Infusion verabreicht, bis es zu einer Krankheitsprogression oder nicht tolerierbaren Nebenwirkungen kommt.

Tisotumab vedotin (TIVDAK®) ist als Monotherapie zur Behandlung erwachsener Patientinnen mit r/m Zervixkarzinom nach Progression unter oder nach systemischer Therapie indiziert. Im Jänner 2025 erhielt das Arzneimittel eine positive Empfehlung des Ausschusses für Humanarzneimittel (CHMP) der Europäischen Arzneimittel-Agentur (EMA) und wurde am 28. März 2025 von der Europäischen Kommission zugelassen. Es unterliegt einer zusätzlichen Überwachung. In den USA wurde im April 2024 eine reguläre Zulassung durch die Food and Drug Administration (FDA) für dieselbe Indikation erteilt.

Wirksamkeit und Sicherheit

Die Bewertung der klinischen Wirksamkeit und Sicherheit von Tisotumab vedotin basiert primär auf der randomisierten Phase-3-Studie 301 (Status zum Zeitpunkt des herangezogenen Datenschnitts (18. Februar 2026): noch laufend) bei erwachsenen Frauen mit r/m Zervixkarzinom nach vorheriger systemischer Therapie. Ergänzende Sicherheitsdaten stammen aus dem klinischen Entwicklungsprogramm, einschließlich der Phase-2-Studie innovaTV 204.

Die Studie innovaTV 301 zeigte einen statistisch signifikanten Vorteil im Gesamtüberleben (OS) für Tisotumab vedotin (n=253) im Vergleich zur Chemotherapie nach Wahl der Prüfärztin/des Prüfarztes (investigator's choice chemotherapy (ICC), n=249, HR 0,70; 95 %–KI 0,54-0,89), mit einer Verlängerung des medianen OS um etwa zwei Monate (11,5 vs. 9,5 Monate). Darüber hinaus zeigte Tisotumab vedotin im Vergleich zur Chemotherapie eine statistisch signifikante Verbesserung des progressionsfreien Überlebens (PFS) von ca. 1,3 Monaten sowie eine statistisch signifikant höhere bestätigte objektive Ansprechrate (ORR; 17,8 % vs. 5,2 %). Eine eindeutige Verbesserung der gesundheitsbezogenen Lebensqualität konnte nicht gezeigt werden.

Hinsichtlich der Sicherheit traten behandlungsbedingte unerwünschte Ereignisse (TEAEs) in beiden Behandlungsarmen häufig auf, jedoch waren Grad ≥3 TEAEs und schwerwiegende unerwünschte Ereignisse unter Tisotumab vedotin seltener. In der Zulassungsstudie wurden 12 Todesfälle (4,8 %) im Tisotumab-vedotin-Arm gegenüber 19 Todesfällen (7,5 %) im ICC-Arm berichtet, wobei die meisten Todesfälle auf Krankheitsprogression zurückzuführen waren. Das Sicherheitsprofil ist durch eine erhöhte Rate okulärer Toxizitäten gekennzeichnet, die engmaschige Überwachung erfordern. In der klinischen Studie waren diese Ereignisse überwiegend niedriggradig und gut beherrschbar, mit wenigen Therapieabbrüchen. Bezüglich der Qualität der Evidenz gibt es Bedenken hinsichtlich des Verzerrungsrisikos, insbesondere im Hinblick auf fehlende Daten und die Berichterstattung von Ergebnissen, während zentrale methodische Domänen nicht wesentlich beeinträchtigt waren. Unsicherheiten bestehen hinsichtlich des langfristigen Sicherheitsprofils, insbesondere da laut EPAR derzeit keine Langzeit-Sicherheitsdaten für Tisotumab vedotin vorliegen und finale Sicherheitsdaten aus der Zulassungsstudie innovaTV 301 im Rahmen der post-authorisation Pharmakovigilanz erwartet werden. Zudem gilt die vorliegende Evidenz primär für Patientinnen mit gutem Allgemeinzustand (ECOG 0–1), die für eine aktive systemische Therapie infrage kommen. Die primäre OS-Analyse basiert auf einem Datenschnitt mit etwa 52 % Ereignisreife; eine spätere OS-Auswertung lag vor, war jedoch lediglich deskriptiv und nicht α-kontrolliert.

Ökonomische Aspekte

Das vertriebsberechtigte Unternehmen hat für Tisotumab vedotin keine offizielle Preisangabe und kein pharmakoökonomisches Modell für Österreich vorgelegt, da das Produkt derzeit noch nicht am österreichischen Markt verfügbar ist. Tisotumab vedotin ist über Parallelimport zu einem Preis von € 2.481 pro 40 mg Durchstechflasche erhältlich. Bei einem medianen Behandlungsumfang von fünf Zyklen belaufen sich die gesamten direkten medizinischen Kosten auf € 53.849 pro Patientin, wovon 92% auf die Anschaffungskosten entfallen. Zum Vergleich: die gewichteten Durchschnittskosten der derzeitigen Standardtherapie (Topotecan 70 %, Gemcitabin 30 %) betragen € 17.663 pro Patientin.

Eine im Rahmen der HTA-Berichterstellung durchgeführte Budget-Folgen-Analyse schätzt die zusätzlichen Ausgaben auf rund € 1,63 Mio. pro Jahr bzw. € 4,89 Mio. über drei Jahre, unter der Annahme von 45 geeigneten Patientinnen jährlich für eine Therapie mit Tisotumab vedotin. Bei Anwendung des deutschen Lauer-Taxe-Preises (€ 1.821 pro Durchstechflasche) würde sich der jährliche Netto-Budgetimpact um ca. € 594.000 reduzieren. Diese Schätzungen unterliegen erheblichen Unsicherheiten hinsichtlich der Patientinnenzahl und verfügbaren Kostendaten für Österreich.

Soziale, organisatorische, ethische und rechtliche Aspekte

Tisotumab vedotin kann in bestehenden onkologischen Tageskliniken verabreicht werden, ohne dass wesentliche strukturelle Anpassungen erforderlich sind. Die Anwendung erfordert jedoch eine

interdisziplinäre Koordination zwischen Onkologie, gynäkologischer Onkologie und Ophthalmologie zur Behandlung der charakteristischen okulären Nebenwirkungen. Österreichische klinische Expert:innen wiesen darauf hin, dass die dreiwöchentliche ambulante Applikation im Vergleich zu den derzeitigen Chemotherapien den Ressourceneinsatz im Gesundheitswesen insgesamt reduzieren könnte.

Das r/m Zervixkarzinom geht mit einer erheblichen Krankheitslast einher und beeinträchtigt die Betroffenen in physischer, psychologischer, sozialer und finanzieller Hinsicht. Die Befragung von Patientinnen (n=2) zeigte, dass Tisotumab vedotin nach einer Anpassungsphase und mit geeigneten unterstützenden Maßnahmen als gut verträglich bewertet wurde. Aus der Literatur geht hervor, dass Patientinnen Gesamtüberleben und Krankheitskontrolle gegenüber Behandlungskosten deutlich priorisieren. Im Hinblick auf Versorgungsgerechtigkeit bestehen in Österreich ausgeprägte regionale Unterschiede bei der HPV-Impfquote (ca. 28 % in Salzburg vs. ca. 80 % in Wien) als auch in der Inanspruchnahme von Früherkennungsprogrammen, die sich mittelbar auf die Entstehung von Zervixkarzinomen und damit dem späteren Therapiebedarf auswirken können. Zur Verbesserung der Qualität der Behandlung und zur Dokumentation von diagnostischen und therapeutischen Parametern könnte das Klinische Tumorregister (KTR) Österreich für Mammakarzinome und gynäkologische Tumoren einen geeigneten Rahmen für die Erfassung der Anwendung von Tisotumab vedotin im Versorgungsalltag bieten.

Öffentliche Investition

Tisotumab vedotin entstand aus einer primär industriegetriebenen Kooperation zwischen Genmab und Seagen (heute Teil von Pfizer), bei der Genmabs TF-Antikörper mit der ADC-Technologieplattform von Seagen kombiniert wurde. Öffentliche Förderbeiträge zur Entwicklung konnten nicht identifiziert werden. Nach der Übernahme von Seagen durch Pfizer im Jahr 2023 wurden die kommerziellen Vereinbarungen neu geregelt: Seit Januar 2025 übernimmt Genmab die alleinige Vermarktungsverantwortung für die Zweit- und Folgelinie bei r/m Zervixkarzinom außerhalb der USA und China; die Herstellung verbleibt ausschließlich bei Pfizer. Der US-amerikanische Grundpatentschutz läuft bis 2033.

Weitere Entwicklungen

Es wurden fünf laufende klinische Studien zu Tisotumab vedotin, darunter eine Phase-4-Studie mit gezieltem Fokus auf okuläre Nebenwirkungen (voraussichtlicher Abschluss Dezember 2028), identifiziert. Unter den rund 20 Therapien, die aktuell für r/m Zervixkarzinom entwickelt werden, gehören sieben, darunter u. a. Sacituzumab tirumotecan, Trastuzumab deruxtecan and Ifinatamab deructecan, derselben Wirkstoffklasse (ADC) wie Tisotumab vedotin an. Da sich diese Klasse in der Onkologie rasch weiterentwickelt, könnten zukünftige Wirkstoffe mit günstigerem Sicherheitsprofil die Positionierung von Tisotumab vedotin beeinflussen. Die früheste erwartete Entscheidung der Europäischen Kommission für eine Therapie in vergleichbarer Indikation betrifft Trastuzumab deruxtecan (bereits zugelassen als ENHERTU® in den Anwendungsgebieten Brustkrebs, NSCLC, Magenkrebs) im April 2026. Weitere Zulassungen werden zwischen 2027 und 2033 erwartet.

Schlussfolgerung

Insgesamt stellt Tisotumab Vedotin eine zielgerichtete Therapieoption für Patientinnen mit r/m Zervixkarzinom und begrenzten Behandlungsalternativen dar, wobei die vorliegende Evidenz aus der innovaTV 301 Studie auf einen Überlebensvorteil gegenüber Chemotherapie hinweist. Aufgrund der nur moderaten Ereignisreife der primären OS-Analyse, der lediglich deskriptiven und nicht alpha-kontrollierten späteren OS-Auswertung, fehlender konsistenter Ergebnisse zur gesundheitsbezogenen Lebensqualität sowie limitierter Übertragbarkeit auf den österreichischen Versorgungskontext bestehen jedoch relevante Unsicherheiten hinsichtlich des patientinnenrelevanten Zusatznutzens. Darüber hinaus bestehen Unsicherheiten hinsichtlich des langfristigen Sicherheitsprofils, da laut EPAR Langzeit-Sicherheitsdaten derzeit noch nicht vorliegen und finale Sicherheitsdaten aus der Zulassungsstudie erst post-authorisation erwartet werden. Zudem ist die ökonomische Bewertung aufgrund fehlender nationaler Preisinformationen und belastbarer Analysen für Österreich nur eingeschränkt möglich.

Executive summary

This Health Technology Assessment (HTA) report evaluates Tisotumab vedotin (TIVDAK®) for the treatment of adult patients with recurrent or metastatic (r/m) cervical cancer (CC) with disease progression on or after systemic therapy.

Disease background

CC is the fourth most common cancer in women worldwide and remains a major public health concern despite established screening programmes, the availability of prophylactic high-risk human papillomavirus (HPV) vaccination and the development of novel therapies. A large proportion of patients are diagnosed with locally advanced or metastatic disease, and recurrence occurs in about one-third of patients after initial therapy. Most recurrences occur in the pelvis, although distant metastases are also frequent. Patients in this stage of the disease have a poor prognosis. Pathogenesis is strongly linked to persistent infection with HPV, which accounts for nearly all cases of invasive CC. However, only a minority of HPV infections progress to cancer.

The prognosis of r/m CC remains poor, particularly after progression on first-line treatment, with an estimated overall survival of approximately 13-17 months. In Austria, about 415 new cases are diagnosed annually (8.5 per 100,000 women), with 35 cases presenting at a disseminated stage, and approximately 135 deaths per year (2.8 per 100,000 women), reflecting the disease burden and its high mortality in advanced stages.

Standard of care in Austria is based on national and international guidelines, including the guideline of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF S3), updated recommendations from the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), as well as international guidelines such as the National Comprehensive Cancer Network (NCCN) guideline. First-line treatment of r/m CC includes platinum-based chemotherapy in combination with an immune checkpoint inhibitor (pembrolizumab) with or without bevacizumab. Upon disease progression, only limited treatment options are available in subsequent lines of therapy. In Austrian clinical practice, this setting is primarily managed with non-platinum single-agent chemotherapies, which are, however, used off-label; alternatively, best supportive care may be considered.

Overview of the new medicinal product

Tisotumab vedotin (TIVDAK®) is a targeted cancer therapy known as an antibody-drug conjugate (ADC), meaning it combines an antibody with a cytotoxic drug. It consists of an anti-tissue factor (TF) monoclonal antibody linked to a microtubule inhibitor. The antibody specifically binds to TF, a protein that is often present at high levels on cancer cells. Once attached, the complex enters the cancer cell, where the microtubule inhibitor is released. This inhibitor blocks microtubules, that are essential for cell division, ultimately leading to cancer cell death.

The recommended posology is 2 mg/kg (up to a maximum of 200 mg in patients ≥100 kg), administered as an intravenous infusion every three weeks until disease progression or unacceptable toxicity.

Tisotumab vedotin is indicated as monotherapy for the treatment of adult patients with r/m CC after disease progression on or after systemic therapy. It received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) in January 2025 and was granted marketing authorisation by the European Commission (EC) on 28 March 2025. It is subject to additional monitoring. In the United States (US), the Food and Drug Administration (FDA) granted traditional approval for the same indication in April 2024.

Clinical effectiveness and safety

The clinical effectiveness and safety of tisotumab vedotin are primarily based on the phase 3 randomised controlled trial innovaTV 301[1] in adult women with r/m CC after prior systemic therapy, with supportive safety data from the clinical development programme, including the phase 2 study innovaTV 204.

The innovaTV 301 trial demonstrated a statistically significant overall survival (OS) benefit for tisotumab vedotin (n=253) compared to investigator's choice chemotherapy (ICC, n=249, HR 0.70; 95% CI 0.54-0.89), with a median OS prolongation of approximately two months (11.5 vs 9.5 months). Furthermore, tisotumab vedotin showed a statistically significant improvement in progression-free survival (PFS) of approximately 1.3 months, as well as a statistically significantly higher confirmed objective response rate (ORR; 17.8% vs 5.2%) compared to chemotherapy. A clear improvement in health-related quality of life could not be demonstrated.

Regarding safety, treatment-emergent adverse events (TEAEs) were common in both arms, although grade ≥3 TEAEs and serious adverse events (SAEs) occurred less frequently with tisotumab vedotin. In the pivotal study, 12 deaths (4.8%) were reported in the tisotumab vedotin arm compared with 19 deaths (7.5%) in the ICC arm, with most deaths attributed to progressive disease. The safety profile is characterised by a higher incidence of ocular toxicity, requiring specific preventive measures and monitoring. In the trial setting, these events were mostly low grade and manageable, with few discontinuations.

The study was assessed as having some concerns regarding risk of bias, mainly related to missing data and outcome reporting, while key methodological domains were not substantially affected. Uncertainty remains regarding the long-term safety profile, as no long-term safety data are currently available according to the EPAR, and final safety data from the pivotal study are expected as part of post-authorisation pharmacovigilance activities. In addition, the available evidence primarily applies to patients with good performance status (ECOG 0–1) who are eligible for active systemic treatment. The primary OS analysis was based on a data cut-off with approximately 52% event maturity; a subsequent OS analysis was available but was descriptive in nature and not alpha-controlled.

Economic aspects

The marketing authorisation holder did not submit a price proposal, or a pharmacoeconomic model for Austria, as it is currently not marketed in Austria. Tisotumab vedotin is available via parallel import at €2,481 per 40 mg vial. Based on a median of five treatment cycles, the total direct medical cost per patient amounts to €53,849, of which 92% is attributable to drug acquisition. By comparison, the weighted average cost of the current standard of care (topotecan 70%, gemcitabine 30%) is €17,663 per patient.

A Budget Impact Analysis (BIA) conducted as part of the HTA report preparation estimated additional expenditures of approximately €1.63 million per year, totaling €4.89 million over three years, assuming 45 eligible patients annually. Applying the German Lauer-Taxe price (€1,821 per vial) would reduce the annual net budget impact by approximately €594,000. These estimates are subject to considerable uncertainty regarding patient numbers and available cost data.

Social, organisational, ethical and legal aspects

Tisotumab vedotin can be administered in existing oncology day-care settings without substantial structural changes. However, its use requires interdisciplinary coordination between oncology, gynaecological oncology and ophthalmology services to manage the characteristic ocular adverse reactions. Austrian clinical experts noted that 3-weekly outpatient administration may reduce overall healthcare resource utilisation compared with current chemotherapy regimens.

R/m CC imposes a substantial burden on patients across physical, psychological, social, and environmental domains. Patient input (n=2) indicated good tolerability of tisotumab vedotin after an initial adjustment period. Evidence from the literature suggests patients prioritise overall survival and disease control

[1] At the time of the data cut-off used for this document (18 February 2026), the innovaTV 301 study was still ongoing.

over treatment costs. Regarding equity in healthcare provision, Austria shows pronounced regional disparities in HPV vaccination coverage (approximately 28% in Salzburg vs around 80% in Vienna) as well as in the uptake of screening programmes, which may indirectly influence the incidence of CC and, consequently, future treatment needs. To improve the quality of care and to document diagnostic and therapeutic parameters, the Austrian Clinical Tumour Registry (KTR) for breast cancer and gynaecological malignancies provides a suitable framework for capturing the use of tisotumab vedotin in routine clinical practice.

Public investment aspect

Tisotumab vedotin was developed through a primarily industry-led collaboration between Genmab and Seagen (now part of Pfizer), combining Genmab's tissue factor-targeting antibody with Seagen's ADC technology platform. No public funding contributions to its development were identifiable. Following Pfizer's acquisition of Seagen in 2023, commercial arrangements were restructured in January 2025, with Genmab assuming sole commercialisation responsibility for second- and subsequent-line treatment in r/m CC outside the US and China, while Pfizer remains the sole manufacturer. The US basic product patent expires in 2033.

Landscape overview

Five ongoing clinical studies evaluating tisotumab vedotin were identified, including a phase 4 trial specifically addressing ocular adverse events (estimated completion December 2028). Among approximately 20 therapies in development for r/m CC, seven are ADCs, the same drug class as tisotumab vedotin, including sacituzumab tirumotecan, trastuzumab deruxtecan, and ifinatamab deruxtecan. Furthermore, a total of 20 therapies were identified as under development for r/m CC in adults. The earliest anticipated EC decision in a similar indication is for trastuzumab deruxtecan (already approved as ENHERTU® for breast cancer, NSCLC, and gastric cancer) in April 2026, with several others expected between 2027 and 2033.

Conclusion

Overall, tisotumab vedotin represents a targeted treatment option for patients with r/m CC with limited therapeutic alternatives, with current evidence from the innovaTV 301 trial suggesting a survival benefit compared to chemotherapy. However, relevant uncertainties remain regarding the patient-relevant added benefit due to the limited event maturity of the primary OS analysis, the descriptive and non-alpha-controlled nature of the subsequent OS update, and inconsistent evidence on health-related quality of life. Additional uncertainty relates to the long-term safety profile, as no long-term safety data are currently available according to the EPAR and final safety data from the pivotal study are expected as part of post-authorisation pharmacovigilance activities. Furthermore, the economic evaluation is restricted by the lack of country-specific price information and robust analyses for Austria.

1 Introduction

The objective of this report is to evaluate tisotumab vedotin (TIVDAK®) as monotherapy for the treatment of adult patients with recurrent or metastatic (r/m) cervical cancer (CC) whose disease progressed on or after systemic therapy.

Tisotumab vedotin bei rezidiviertem oder metastasiertem Zervixkarzinom (r/m CC)

1.1 Disease background

Overview

CC is the fourth most common cancer in women worldwide and one of the most common causes of cancer-related deaths among women worldwide. Despite screening programmes for early detection, the approval of prophylactic vaccines and significant advances in the treatment of cervical lesions, CC is still a growing global burden and a significant public health problem. [1, 2].

CC: vierthäufigste Krebsart unter Frauen weltweit, erhebliches Problem für die öffentliche Gesundheit

Classification and disease staging

CC is classified as a primary malignant neoplasm involving the cervix. According to the International Statistical Classification of Diseases and Related Health Problems (ICD), it is coded as 2C77 in ICD-11 [3].

ICD-11 2C77: primäre maligne Neoplasie des Gebärmutterhalses

The disease is staged by the International Federation of Gynaecology and Obstetrics (FIGO) classification. Stages are assigned after completing all imaging and pathology tests. Once assigned, the stage should not be changed, even if the cancer recurs. The revised FIGO staging is closely aligned with the latest tumour, node and metastasis (TNM) staging system. The most recent version of FIGO staging of CC (2018) [4] is presented in the Appendix, Chapter 1.1. An overview of the four stages of CC, according to FIGO (2018), is presented in Figure 1-1.

CC-Staging nach FIGO-Klassifikation (2018)

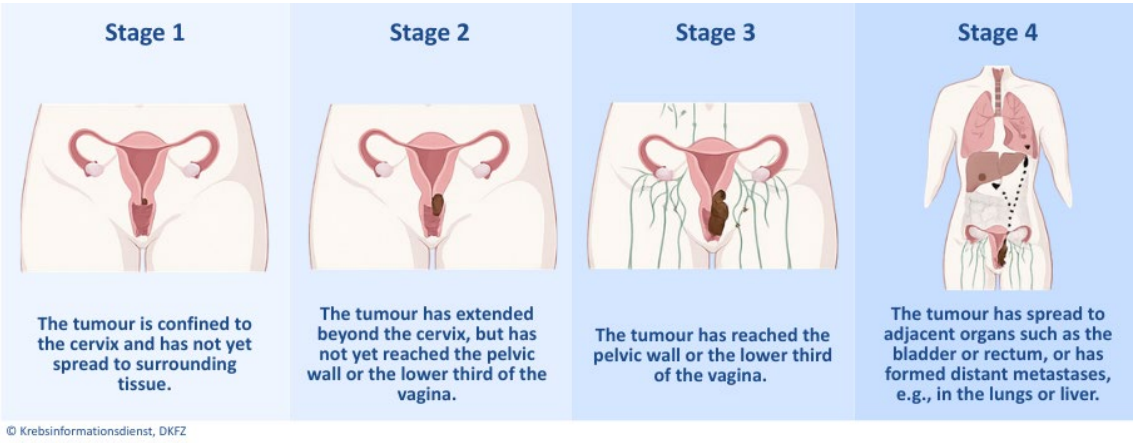


Figure 1-1: Stages of cervical cancer showing tumour spread, according to FIGO (2018) [4, 5]

Rezidivrisiko ist erheblich und abhängig vom initialen Krankheitsstadium

Recurrent CC is defined as local tumour re-growth or development of lymph nodal or distant metastases at least six months after the primary lesion has regressed. Despite the high cure rate of primary treatment for CC, the risk of recurrence is substantial and correlates with the initial disease stage [2, 6, 7]. One-third of the patients receiving therapy for locally advanced disease will experience a recurrence. Ultimately, the vast majority of r/m CC that cannot be treated with locoregional methods are considered incurable diseases with a very poor prognosis [1, 2].

Rezidive meist im Becken

The most frequent sites of recurrence are classified as local or central-pelvic, regional, or distant organ metastasis [2, 6, 7]; however, the majority of recurrences occur in the pelvis [8].

Fernmetastasen oder mehrere Rezidivstellen bei 15-61 % der Patientinnen

Distant metastases or multiple recurrence sites can develop in 15-61% of patients [9].

Pathogenesis and histopathology

Entwicklung von CC

The development of CC takes place in four steps. While additional risk factors contribute to cervical cancer, the vast majority of cases are attributable to human papillomavirus (HPV) infection. Figure 1-2 depicts the progression of cervical cancer in the context of HPV infection.

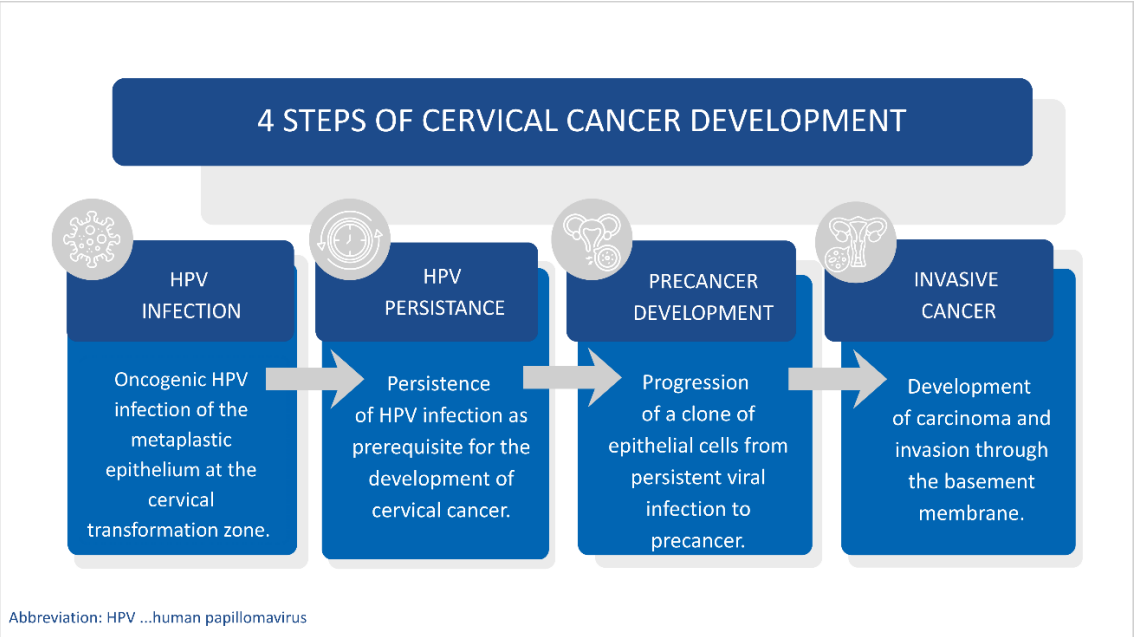


Figure 1-2: Four steps of cervical cancer development [2, 6, 7, 10]

80 % aller CC sind Plattenepithelkarzinome

The most common histologic type of CC is squamous cell carcinoma [6], which accounts for 80% of all CC. With 12-15%, adenocarcinomas represent the second most common type of CC, with several further histological subtypes accounting for the remainder [8].

Diagnosis

15 % haben Fernmetastasen bei Diagnosestellung

Rezidive meist ≤3 Jahren nach Diagnosestellung

At the time of diagnosis, approximately 43% of patients have localised disease, 35% have regional disease, and 15% present with distant metastases [9]. As this report focuses on the r/m stage of the disease, the initial diagnosis of CC will not be discussed. Most recurrences of CC are diagnosed within the first three years after diagnosis. The diagnosis is based on the clinical indications or examination findings shown in Table 1-1 [8].

Table 1-1: Diagnostic steps for diagnosis of recurrent or metastatic cervical cancer [8]

Clinical symptoms	**Pain, bleeding, discharge, swelling**
External physical examination	Swelling of the abdomen, lower extremities or lymph nodes, tenderness on percussion of the renal area
Gynaecological examination	Visible and/or palpable tumour
Kidney examination (urinary retention)	Early diagnosis of hydronephrosis (recurrence, ureteral stenosis, ureteral stricture) can prevent loss of kidney function, which would limit palliative cytostatic treatment options
Tumour markers	Possible elevation of SCC tumour markers (squamous cell carcinoma antigen) in squamous cell carcinoma or CA-125 in adenocarcinoma
Imaging	CT thorax/abdomen or PET-CT if recurrence is suspected
	MRI of the pelvis if recurrence is suspected

Abbreviations: CA-125 … Cancer-Antigen 125, CT … computed tomography, MRI … magnetic resonance imaging, PET … positron emission tomography, SCC … squamous cell carcinoma

Risk factors and prevention

persistierende HPV-Infektion als größter Risikofaktor für CC

A persistent infection with oncogenic high-risk HPV – predominantly HPV16 and HPV18 – is the cause of nearly 100% of cases of invasive CC (see Figure 1-3). Risk factors that are associated with HPV-related cancers include the early onset of sexual activity, multiple sexual partners, a high-risk sexual partner, a history of sexually transmitted infections (e.g., chlamydia trachomatis, genital herpes, and a history of vulvar or vaginal squamous intraepithelial neoplasia or cancer) [6, 10, 11]. Although a HPV infection is strongly linked to CC, only 10-20% of women develop the persistent infection required for carcinogenesis, as approximately 75% of infections are subclinical and transient, resolving spontaneously without progression [10, 11].

nicht-HPV-assoziierte Risikofaktoren, z. B. Rauchen

Other, not HPV-related factors that have been implicated to increase the risk of developing CC are tobacco use, oral contraceptives, genetics and a low socioeconomic status [6, 11, 12].

HPV-Impfung als effektive und sichere Primärprävention

For primary prevention, prophylactic HPV vaccines are available. They effectively prevent infection with high-risk HPV types, thereby reducing the incidence of precancerous cervical lesions and invasive cervical cancer. To achieve the greatest effect, it is recommended to vaccinate females and males as early as possible before the onset of sexual activity ('HPV-naïve') at a young age, around 9-12 years old [13, 14].

Prognosis

ungünstige Prognose für Patientinnen mit r/m Erkrankung: Medianes OS von ca. 13-17 Monate

Patients with CC who have progressed after first-line treatment have limited effective subsequent treatment options and, therefore, a dismal prognosis. In particular, women who experience distant metastases, either at initial diagnosis (FIGO stage IVB) or at recurrence, have poor prognoses. This is reflected by 5-year overall survival (OS) rates of 65% and 17% for locally advanced and metastatic disease, respectively. The estimated median OS of patients with recurrent disease is around 13-17 months [1, 15].

Epidemiology

2 Altersgipfel

CC typically occurs at certain ages: the first peak is between the ages of 35 and 40, and the second peak is between the ages of 60 and 70. The average annual incidence for the period 2022-2024 was 415 women, corresponding to an age-standardised rate of approximately 8.5 per 100,000 women. Of particular concern, the average annual incidence of disseminated-stage CC during this same period was 35 women, representing approximately 0.7 per 100,000 women [7, 16, 17].

Inzidenz: 415 Frauen/Jahr
Inzidenz disseminiertes Stadium: 35 Frauen/Jahr

Mortalität: 135 Frauen/Jahr

The mortality data for 2022-2024 showed an average of 135 deaths per year, corresponding to an age-standardised mortality rate of approximately 2.8 per 100,000 women [17]. The prognosis for patients with metastatic disease is particularly poor, with a 5-year survival rate of only 19% [18].

1.2 Standard of care

primäre Leitlinie: deutsche AWMF S3-Leitlinie (2022)

aktuelle Ergänzung für Österreich: AGO-Therapiemanual (2025)

In Austria, the clinical management of r/m CC is primarily based on the "S3 guideline on diagnosis, treatment and follow-up care for patients with cervical cancer, version 2.2" [12]. It is published by the Oncology Guidelines Programme of the Association of Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF), with the participation of various professional associations, including the Gynaecological Oncology Working Group (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO) from Austria. The AGO additionally published an updated therapy manual in 2025, providing current treatment recommendations for the clinical practice [8].

aktuelle internationale Referenzen: NCCN-Leitlinie (2026) und ESGO/ESTRO/ESP-Leitlinie (2023)

The most recent international guidelines identified are the "Cervical Cancer, Version 2.2026" from the National Comprehensive Cancer Network (NCCN) [19] and the European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Pathology (ESP) "Guidelines for the management of patients with cervical cancer" (update 2023) [20]. The European Society for Medical Oncology (ESMO) guideline for cervical cancer (2017, updated 2020) has also been identified but was considered outdated (an update is awaited) [21]. Overall, the international guidelines align with the Austrian standard therapy.

Österreich: platinbasierte Chemo + Pembrolizumab + Bevacizumab, danach Topotecan, Gemcitabin, Tisotumab vedotin oder BSC

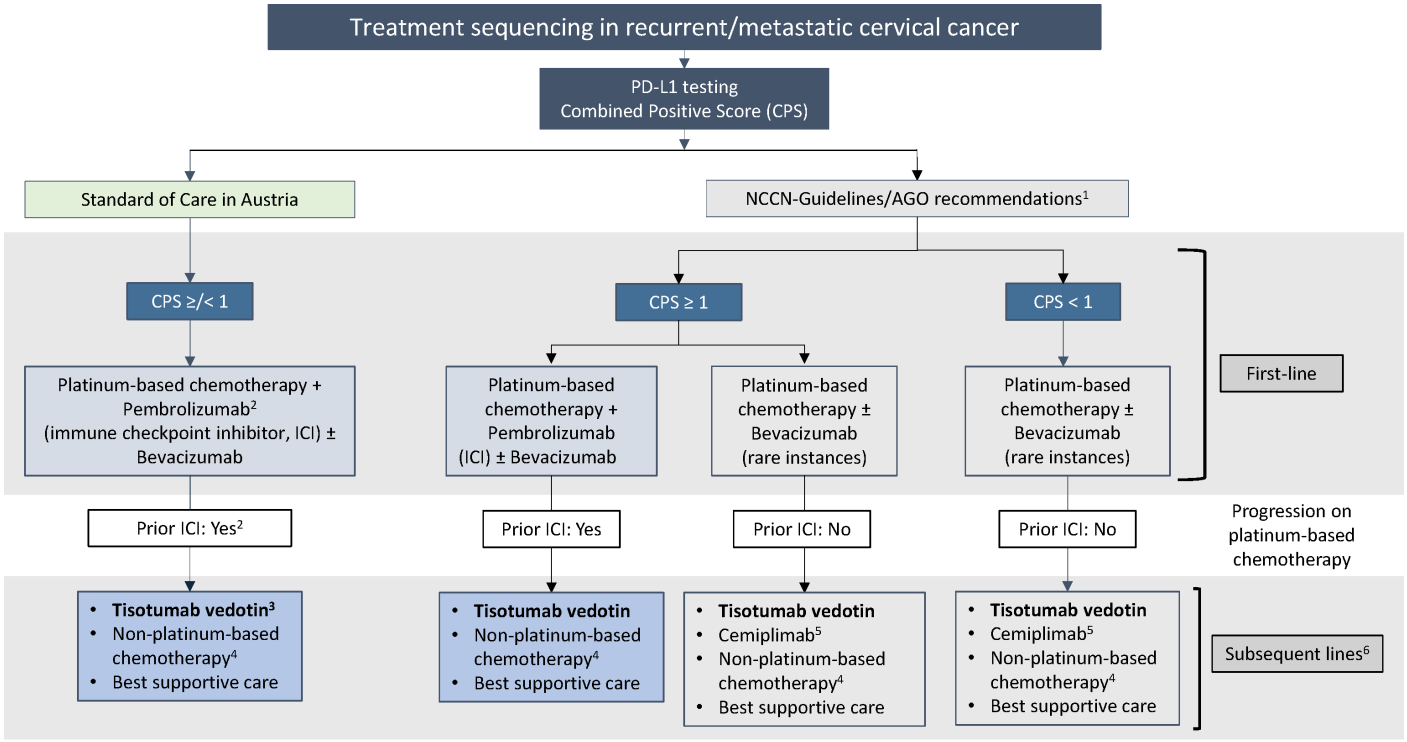
According to the consulted Austrian clinical experts, patients in the r/m CC setting first receive platinum-based chemotherapy in combination with an immune checkpoint inhibitor (ICI, pembrolizumab)[2] and bevacizumab, independent of their combined positive (CPS) status [22]. Pembrolizumab, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥1 [23]. However, despite being approved for tumours expressing CPS ≥1, pembrolizumab is used in Austria in almost all patients for the first-line therapy, independent of their CPS-status. It is administered with or without bevacizumab, a monoclonal antibody approved for the use in combination with chemotherapy [24]. In case of progression, options in subsequent treatment lines include non-platinum-based chemotherapy (mainly topotecan or gemcitabine), or best supportive care (BSC) [22]. While topotecan is approved in combination with cisplatin and is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease[3], gemcitabine is currently not approved for this indication [25]. Tisotumab vedotin offers a new treatment option for the assessed indication. Details can be found in Chapter 1.3.

Behandlungsalgorithmus in Abb. 1-3

Figure 1-3 summarises the Austrian standard of care given from the clinical experts, as well as recommendations from the latest guidelines (NCCN guidelines and the AGO manual), offering a detailed overview of treatment lines and therapeutic approaches in an international context. Of note, the medicinal product under evaluations is already included in the algorithm, as it is used in some Austrian hospitals on a patient-specific level.

[2] Although ICIs are widely used in this setting, in rare cases, they may not be suitable in patients with contraindications (e.g., active autoimmune diseases or conditions requiring systemic immunosuppression).

[3] Of note, topotecan is not approved as a single agent for the treatment of cervical carcinoma.



[1] NCCN Guideline "Cervical Cancer, V.2.2026" available from Cervical Cancer - Guidelines Detail; AGO Manual „Zervixkarzinom – Therapie, 2025" available from VIII. THERAPIE | AGO –AUSTRIA.
[2] Although immune checkpoint inhibitors (ICIs) are widely used in first-line treatment, they may not be suitable in patients with contraindications (e.g., active autoimmune diseases or conditions requiring systemic immunosuppression).
[3] The use of tisotumab vedotin in Austria depends on its availability and reimbursement status.
[4] Cisplatin, Carboplatin, Paclitaxel, **Topotecan**, Bevacizumab, **Gemcitabine**, Fluorouracil, Docetaxel, Pemetrexed, Vinorelbine, Irinotecan, Capecitabine, Mitomycin, Albumin-bound Paclitaxel (**bold**: chemotherapeutic agents predominantly used in Austria)
[5] Cemiplimab may be considered after progression on platinum-based therapy irrespective of prior ICI exposure. In clinical practice, treatment sequencing may vary depending on individual patient characteristics, tolerability, and available alternatives.
[6] The order of treatment options does not represent a recommendation, but is individual and depends on the patient's individual status.
Abbreviations: AGO ... Arbeitsgemeinschaft für gynäkologische Onkologie, CPS ... combined positive score, ICI ... immune checkpoint inhibitor, NCCN ... National Comprehensive Cancer Network

Figure 1-3: Treatment sequencing in recurrent/metastatic cervical cancer. Own illustration based on [8, 19, 22]

1.3 Medicinal product under evaluation

HTA-Bericht zu Tisotumab vedotin (TIVDAK®)

The medicinal product under evaluation in this HTA is tisotumab vedotin (TIVDAK®), an antibody-drug conjugate (ADC). Table 1-2 summarises the most important information on this product.

Table 1-2: Pharmacological characteristics of tisotumab vedotin (TIVDAK®) [26]

INN	
Product name	TIVDAK®
Active substance(s)	Tisotumab vedotin
ATC code	L01FX23
Pharmacologic class	Antineoplastic agent, other monoclonal antibodies and antibody-drug conjugates
MAH	Genmab A/S

Abbreviations: ATC ... Anatomical Therapeutic Chemical,
IN ... international non-proprietary name, MAH ... marketing authorisation holder

Tisotumab vedotin is an ADC that is targeted to the tissue factor (TF), a cell surface protein that is expressed at elevated levels on a variety of solid tumours in comparison to normal tissue. The mechanism of action of tisotumab vedotin involves binding to tumour cells that express TF, leading to internalisation of the ADC-TF complex. This leads to the local release of monomethyl auristatin E (MMAE). MMAE is a microtubule-disrupting agent that has been shown to disrupt the microtubule network in actively dividing cells, resulting in cell cycle arrest and subsequent apoptotic cell death [9].

Konjugat aus einem gegen den Gewebefaktor gerichteten Antikörper und einem Mikrotubuli-Inhibitor → induziert Zelltod der Krebszellen

Regulatory status

On 30 January 2025, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the tisotumab vedotin, intended for the treatment of adult patients with r/m CC with disease progression on or after systemic therapy [27]. The marketing authorisation for the medicinal product has been issued by the European Commission on 28 March 2025 [28]. Tisotumab vedotin is included in the EMA's additional monitoring list, meaning that it is being monitored even more intensively than other medicines. [9, 29]. The regulatory information for tisotumab vedotin is summarised in Table 1-3 [26].

Tisotumab vedotin am 28. März 2025 zugelassen für Erwachsene mit r/m CC und Progression unter/nach syst. Therapie

On 29 April 2024, the US Food and Drug Administration (FDA) granted traditional approval to tisotumab vedotin-tftv (TIVDAK®), indicated for the treatment of r/m CC with disease progression on or after chemotherapy [31].

frühere FDA-Zulassung für dieselbe Indikation: 29. April 2024

Table 1-3: EMA regulatory information for tisotumab vedotin (TIVDAK®)

Medicinal product	
Conditional marketing authorisation	No
Specific obligations of the conditional marketing authorisation	No
Additional monitoring	Yes
Accelerated approval	No
Exceptional circumstances	No
ATMP	No
PRIME	No
First approved indication	Yes; indicated as monotherapy for the treatment of adult patients with r/m CC with disease progression on or after systemic therapy

Abbreviations: ATMP ... advanced therapy medicinal product, CC ... cervical cancer, PRIME ... priority medicines

Note: Currently, tisotumab vedotin is available in Austria via parallel import [30]

Posology and method of administration

The recommended dose of tisotumab vedotin is 2 mg/kg (up to a maximum of 200 mg for patients ≥ 100 kg), administered by intravenous infusion (IV) over 30 minutes every three weeks until disease progression or unacceptable toxicity. The treatment should be initiated and supervised by a physician experienced in the use of anti-cancer therapies [32].

2 mg/kg IV alle 3 Wochen bis zur Krankheitsprogression oder inakzeptabler Toxizität

Requirements for pre- and post-treatment evaluation and monitoring

Eye care

According to the EMA Assessment Report, prior to the first infusion with tisotumab vedotin and as clinically indicated, patients should be referred to an eye care professional for a full eye exam, including visual acuity and slit lamp exam. In addition, prior to each infusion, the treating healthcare provider should inspect the patient's eyes. Patients should be monitored for and be instructed to report new or worsening ocular signs and symptoms and referred to an eye care professional as soon as warranted. If adverse reactions occur, tisotumab vedotin should be withheld, the dose reduced or permanently discontinued based on the severity of the reaction. The patient should be advised to avoid wearing contact lenses for the entire duration of therapy [32].

Augenuntersuchung durch Augenspezialist:in zu Behandlungsbeginn

+ durch den/die behandelnde/n Ärzt:in vor jeder Infusion

+ Überwachung von Symptomen

To reduce the risk of ocular adverse reactions, patients should adhere to a specific eye care plan, including recommendations for the application of (topical, preservative-free) corticosteroid eye drops, ocular vasoconstrictor drops, lubricating eye drops and cooling eye pads. Detailed information on the administration can be found in the Appendix, Chapter 1.3, and a schematic presentation of the eye care plan can be found in Figure 1-4 [32].

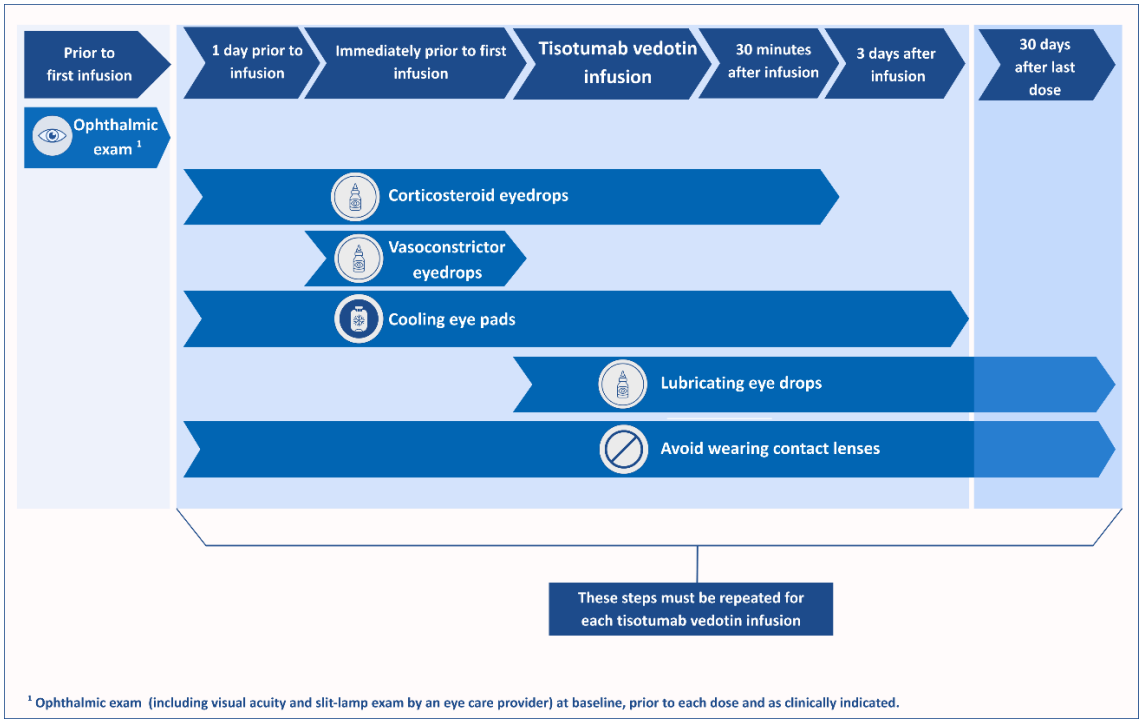


Figure 1-4: Required eye care to mitigate the risk of ocular adverse events in patients treated with tisotumab vedotin, adapted from according to recommendations from the European Medicines Agency [32]

Further requirements

Besides eye care, the EMA Assessment Report also recommends that patients should be monitored for signs and symptoms of peripheral neuropathy and severe cutaneous adverse reactions after tisotumab vedotin administration [32].

weiteres Monitoring: periphere Neuropathie und Hautreaktionen

The prescribing information for tisotumab vedotin published by the FDA further includes recommendations to monitor patients for signs and symptoms of haemorrhage and for pulmonary symptoms indicative of pneumonitis [33].

FDA empfiehlt zusätzliche Überwachung auf Blutungen und Lungenbeschwerden

Use in specific populations

Information on the use of tisotumab vedotin in specific populations, derived from the EPAR product information, is summarised in Table 1-4 [32].

Spezifische Populationen gemäß EPAR

Table 1-4: Use of tisotumab vedotin in specific populations [32]

	Tisotumab vedotin can cause foetal harm when administered to a pregnant woman, including embryo-foetal toxicity and structural malformations. It should not be used during pregnancy unless the clinical condition of the woman requires treatment with tisotumab vedotin.
	The safety and efficacy of tisotumab vedotin in children and adolescents ≤18 years have not been established (no data are available). It should not be used in children and adolescents below 18 years of age.
	No dose adjustment is required in patients aged ≥65 years.

eingeschränkte Anwendung bei Schwangeren

keine Anwendung bei Kindern ≤ 18 Jahren

keine Dosisanpassungen bei ≥ 65-Jährigen

2 Scope of assessment

This report aims to evaluate the clinical effectiveness, safety, economic and other aspects of tisotumab vedotin (TIVDAK®) for the treatment of adult patients with r/m CC with disease progression on or after systemic therapy.

Analyse der Wirksamkeit, Sicherheit und anderer Aspekte zu Tisotumab vedotin

2.1 Research questions

The following research questions will be answered in the present report:

Clinical domain:

1. In patients with r/m CC with disease progression on or after systemic therapy, is tisotumab vedotin more effective and safer compared to the current standard treatment regarding patient-relevant outcomes?

klinische Domäne: Wirksamkeit und Sicherheit

Non-clinical domains:

2. What are the economic, ethical, organisational and social consequences of implementing tisotumab vedotin into the Austrian healthcare system?
3. What were the key contributions of publicly funded research institutions and private companies in discovering and developing tisotumab vedotin as a therapy for disease, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

nicht-klin. Domänen: ökonomisch, ethisch, organisatorisch, sozial, sowie öffentliche Beiträge zu Entwicklungskosten

2.2 Inclusion criteria

Inclusion criteria for relevant clinical studies are summarised in Table 2-1.

Einschlusskriterien für relevante klinische Studien

Regarding the non-clinical domains, relevant economic literature was included with information about tisotumab vedotin prices, other direct medical costs and health economic evaluations. In addition, relevant literature for the organisational, ethical and social domains, as well as literature on public investment, such as information on public grants, funding and contributions, were considered.

zusätzlich Literatur für nicht klin. Bereiche berücksichtigt

Table 2-1: Assessment scope, including the patient, intervention, comparison and outcome (PICO) question for the clinical domain

P	Adult patients with recurrent or metastatic cervical cancer on or after systematic therapy Relevant subgroup: Previous platinum-based chemotherapy with or without immune checkpoint inhibitor
I	Tisotumab vedotin/TIVDAK/1418731-10-8/gct1015-04/humax-tf-adc/humaxtfadc/igg1-1015-011-1006/ t41737f88a/tf-011-mmae
C	■ Non-platinum-based single-agent chemotherapy (e.g., topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed) (off-label) ■ Immune checkpoint inhibitor (e.g., cemiplimab for patients who did not receive prior ICIs) ■ Best supportive care
O	*Efficacy:* Mortality (**overall survival**) Morbidity (**progression-free survival, objective response rate**, duration of response) *PROs:* **Quality of life** *Safety:* Adverse events (≥ Grade 2) **Adverse events (≥ Grade 3)** Serious adverse events **Death** Treatment discontinuation/interruption due to adverse events
Studies	Randomised control trials, non-randomised control studies, observational studies, and single-arm trials
Languages	English, German

Abbreviations: ICI ... immune checkpoint inhibitor, PRO ... patient reported outcomes

Notes: Outcomes in **bold** *indicate critical efficacy and safety endpoints based on clinical expert consultation.*

3 Methods

This HTA employed a multi-domain assessment approach, following the European Network for Health Technology Assessment (EUnetHTA) methodology (see guiding question in Chapter 3 of the Appendix) [34]. Methods were tailored to address the three research questions identified in Chapter 2, with a data cut-off date of 18 February 2026.

Multi-Methoden-Ansatz: EUnetHTA-Leitfragen Daten-Cut-off: 18. Februar 2026

Systematic literature search and study selection

For the clinical effectiveness and safety domain, evidence was identified through a systematic literature search. For the remaining domains, relevant information was identified through targeted hand searches of regulatory documents, HTA reports, guideline documents, and other publicly available sources.

Wirksamkeit und Sicherheit: systematische Literatursuche; andere Domänen: gezielte Handsuche

The systematic search was performed on 6 February 2026, across four electronic databases (MEDLINE via Ovid, Embase, The Cochrane Library, and INAHTA). The search was restricted to English and German publications and excluded conference abstracts (detailed search strategies are provided in Chapter 3 of the Appendix). After deduplication, 292 citations were identified. In addition, three clinical trial registries (ClinicalTrials.gov, WHO ICTRP, and EU Clinical Trials Register) were searched to identify ongoing or unpublished studies, yielding five potentially relevant records. Besides, the manufacturer dossier submitted on February 18th, 2026, did not provide additional eligible citations.

1 systematische Literatursuche in 4 Datenbanken: 290 Treffer; Suche in klinischen Studienregistern: 5 Treffer

Dossier des vertriebsberechtigten Unternehmens

The study selection process was conducted using a structured two-stage process. Two researchers (TM, ER) independently screened titles/abstracts and full texts, with arbitration solved by a third reviewer (SGG) in case of disagreement. The study selection process for the clinical effectiveness and safety assessment is presented in a PRISMA flow diagram in Chapter 3 of the Appendix.

Literaturauswahlprozess im 4-Augenprinzip

Clinical effectiveness and safety assessment

Data extraction was systematically performed by one reviewer (TM) and cross-checked by a second reviewer (ER).

system. Datensynthese im 4-Augenprinzip

The risk of bias (RoB) of the included clinical evidence was assessed at outcome level using the Cochrane Risk of Bias 2.0 tool. The assessment covered five predefined domains and followed the structured signalling-question approach of RoB 2.0. Domain-level judgements ("low risk," "some concerns," or "high risk") were assigned and synthesised into an overall RoB judgement for each outcome.

RoB 2.0-Tool angewendet

Due to limited availability of comparative data, the evidence synthesis was conducted narratively. Consequently, the certainty of evidence was not assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

keine GRADE-Bewertung

Economic evaluation methods

Preis-Infos von GÖG

To collect price information on tisotumab vedotin, the Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) was contacted. In addition, the Pharmaceutical Pricing and Reimbursement Information (PPRI) network conducted a confidential survey to gather data on the economic aspects of tisotumab vedotin, including pricing and managed entry agreements, across multiple European member states.

Umfrage im PPRI-Netzwerk (vertraulich)

zusätzliche Handsuche nach ökonomischen Analysen zu Tisotumab vedotin + Qualitätsbewertung der identifizierten Analysen

Regarding health economic evaluations of tisotumab vedotin, both the MAH submissions and published analyses were considered. For the latter, we screened the literature identified through systematic and additional manual Google searches. Furthermore, we did a quality assessment of the included economic evaluations using two checklists. Namely, the CHEERS 2022 checklist [35], which assesses the reporting standard of whether a study has transparently documented all methodological choices and inputs, and the CHEC-list [36], which assesses the quality and conduct standard by evaluating whether the methodological choices themselves were appropriate and sound.

Budgetfolgenanalyse: zahlreiche Annahmen getroffen

In addition, pursuant to the implementation regulation §4(2) of the Austrian Appraisal Board, a 3-year budget impact analysis (BIA) was conducted, including the gross drug budget impact and additional administration-related costs. Overall, we made the following assumptions in the BIA:

- We derived the patient population estimates from Austrian clinical experts, as no real-world data were available for this specific patient population in Austria.

  … epidemiologische Daten (Expert:innenschätzungen)

- We received price information from a parallel import to Austria, which we used for the primary analysis.

  … Preis für Parallelimport

- For the cost calculations, we used drug ex-factory prices from the Austrian "Warenverzeichnis Apothekerverlag" and inpatient treatment cost data from the Austrian procedure- and diagnosis-related groups (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) catalogue.

  … Kostendaten: Fabriksabgabepreise und LKF-Daten

- Minor cost categories, such as corticosteroid therapies, as well as costs related to diagnostics and end-of-life treatments, were excluded from the analysis due to the individualised nature of diagnostic testing and BSC.

  … Diagnostik und BSC-Kosten in Analyse nicht berücksichtigt

Organisational, ethical, and social assessment

Bewertung nach EUnetHTA-Methodik, 3 Quellen:

The assessment of organisational, ethical and social aspects utilised the EUnetHTA methodology [34]. Data was gathered from three sources:

- Firstly, we used structured patient questionnaires (see details in Chapter 6.2 in the Appendix). Initially, we searched for eligible patients, carers and/or representatives of patient organisations in Austria. The search was then extended to other German-speaking countries, including Germany and Switzerland. In addition, patients were also identified through clinical experts.

  schriftliche Patientinnen-Befragungen

- Secondly, we conducted expert consultations with eight leading clinicians (see Chapter 6.1 in the Appendix).

  Expert:innen-Konsultationen,

- Thirdly, we retrieved relevant literature from the systematic literature results and manual search findings.

  & Literaturquellen

Development costs and public contributions

Entwicklungskosten und öffentliche Beiträge erhoben

The methodology for assessing development costs and public contributions involved several steps:

Identifizierung generischer oder (nicht) geschützter Bezeichnungen

- Identifying product origins through searches for generic/non-proprietary names and trade names.

Produktherkunft & Grundlagenforschung

- Searching for the earliest references to identify basic research and development (R&D) support and research grants.
- Exploring databases on clinical trials and research funding.

Finanzierungsrunden, Fusionen & Übernahmen

- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.
- Searching Securities and Exchange Commission (SEC) reports for information on acquisitions, patents and shareholders.
- Reviewing business news sources for additional information.
- If funding amounts are reported in another currency than €, they will be converted to €.

Landscape overview

Überblick zu laufenden Studien und weiteren Therapien in Entwicklung für r/m CC bei Erwachsenen

Ongoing studies (active and recruiting) evaluating tisotumab vedotin independent of origin found in ClinicalTrials.gov were shortly summarised and reported. Additionally, we compiled a landscape overview of other therapies, which are in the development for r/m CC in adults, using the International Horizon Scanning Initiative (IHSI) database [37].

4 Clinical effectiveness and safety

innovaTV 301-Studie als zentrale Grundlage der EU-Zulassung

The clinical evidence base for tisotumab vedotin is primarily derived from the pivotal phase 3 randomised controlled trial (RCT) innovaTV 301 (also referred to as SGNTV-003; ClinicalTrials.gov identifier: NCT04697628) [9, 38]. This study forms the basis of the marketing authorisation granted by the European Commission following EMA assessment and constitutes the only source of comparative evidence in the present assessment. At the time of the data cut-off for this assessment (18 February 2026), the study was still ongoing, with completion expected in Q1-Q2 2026.

ergänzende Sicherheitsdaten aus gepoolten EPAR-Analysen

Supportive evidence for the safety profile is derived from the clinical development programme as summarised in the European Public Assessment Report (EPAR), including data from the single-arm phase 2 study innovaTV 204 (ClinicalTrials.gov identifier: NCT03438396) [9, 39].

CSR-Prüfung ohne relevante Zusatzbefunde

The confidential Clinical Study Report (CSR) submitted by the MAH [40] was reviewed to complement the information available from the EPAR and the published study report. However, no material discrepancies or additional clinically relevant findings were identified.

4.1 Characteristics of the included studies

The main characteristics of the pivotal study, innovaTV 301, are summarised in Table 4-1.

Table 4-1: Main characteristics of the innovaTV 301 study [9, 38]

Reference/ID	innovaTV 301 (SGNTV-003); ClinicalTrials.gov: NCT04697628
Study type and design	Phase 3, global, multicentre, randomised (1:1), open-label, active-controlled trial comparing tisotumab vedotin with the investigator's choice of single-agent chemotherapy in second- or third-line r/m CC
Study population	Adult women with r/m CC (squamous, adenocarcinoma or adenosquamous histology) with disease progression during or after systemic therapy
Key inclusion criteria	■ 1-2 prior systemic regimens in the r/m setting ■ Prior platinum-based chemotherapy (unless contraindicated) ■ ECOG performance status 0-1 ■ Measurable disease per RECIST v1.1 ■ Prior anti-PD-(L)1 therapy permitted
Key exclusion criteria	■ Primary neuroendocrine, lymphoid, sarcomatoid, or other histologies ■ Clinically significant bleeding issues or risks ■ Active CNS metastases ■ Clinically significant ocular surface disease ■ Grade ≥2 peripheral neuropathy ■ Uncontrolled comorbidities
Study arms	■ Tisotumab vedotin (n=253) ■ Investigator's choice chemotherapy (n=249): topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed ■ Total randomised population: n=502

Reference/ID	innovaTV 301 (SGNTV-003); ClinicalTrials.gov: NCT04697628
Stratification factors	■ ECOG performance status (0 vs 1) ■ Prior bevacizumab (yes vs no) ■ Prior anti-PD-1/PD-L1 (yes vs no) ■ Histology ■ Geographic region (Note: excluded from the stratified Cox model due to sparse strata)
Study duration, data cut-off and location	■ 24 July 2023 (median follow-up 10.8 months; 52% OS maturity) ■ Updated OS analysis: 16 January 2024 (descriptive OS update; median follow-up 16.8 months; not part of hierarchical testing procedure)
Study protocol amendments	The study protocol underwent three amendments during study conduct; no changes to the primary endpoint (OS) or overall study design were reported
Available documentation	■ CSR: provided by MAH (not publicly available) ■ EPAR ■ Registry entry: NCT04697628 ■ Sponsoring status: industry-sponsored

Abbreviations: CNS ... central nervous system, CSR ... clinical study report, ECOG ... Eastern Cooperative Oncology Group, EPAR ... European Public Assessment Report, MAH ... Marketing Authorisation Holder, n ... number of patients, NCT ... National Clinical Trial identifier (ClinicalTrials.gov), OS ... overall survival, PD-(L) ... programmed death (ligand) 1, r/m CC ... recurrent or metastatic cervical cancer, RECIST ... Response Evaluation Criteria in Solid Tumors, v1.1 ... version 1.1

Note: A complete list of inclusion and exclusion criteria, as well as study protocol amendments are provided in Chapter 4 of the Appendix.

4.1.1 Study population

Patient baseline characteristics

vergleichbare Baseline-Charakteristika in der ITT-Population

Baseline characteristics of the intention-to-treat (ITT) population of the innovaTV 301 trial were broadly comparable between treatment arms. Key demographic and disease-related characteristics are summarised in Table 4-2; the full baseline table is provided in Chapter 4.3 of the Appendix.

Table 4-2: Baseline demographics and characteristics of the intention-to-treat population in innovaTV 301 [9, 38]

Characteristic	innovaTV 301	
Parameter	**Tisotumab vedotin (n=253)**	**Investigator's choice chemotherapy (n=249)**
Age in years, median (range)	51 (26-80)	50 (27-78)
≥65 years, n (%)	42 (16.6%)	41 (16.5%)
ECOG performance status		
0, n (%)	137 (54.2%)	136 (54.6%)
1, n (%)	116 (45.8%)	113 (45.4%)
Histology		
Squamous cell carcinoma, n (%)	160 (63.2%)	157 (63.1%)
Adenocarcinoma, n (%)	85 (33.6%)	75 (30.1%)
Adenosquamous carcinoma, n (%)	8 (3.2%)	17 (6.8%)
Number of prior systemic regimens		
1 prior line, n (%)	159 (62.8%)	149 (59.8%)
2 prior lines, n (%)	93 (36.8%)	100 (40.2%)
Unknown, n (%)	1 (0.4%)	0 (0%)

Characteristic	innovaTV 301	
Parameter	**Tisotumab vedotin (n=253)**	**Investigator's choice chemotherapy (n=249)**
Prior bevacizumab exposure, n (%)	164 (64.8%)	157 (63.1%)
Prior anti-PD-1/PD-L1 therapy, n (%)	71 (28.1%)	67 (26.9%)
Region		
USA, n (%)	16 (6.3%)	14 (5.6%)
EU, n (%)	106 (41.9%)	104 (41.8%)
Asia, n (%)	85 (33.6%)	88 (35.3%)
Other, n (%)	46 (18.2%)	43 (17.3%)

Abbreviations: ECOG ... Eastern Cooperative Oncology Group, EU ... European Union, n ... number of patients, PD-(L)1 ... programmed death (ligand) 1, USA ... United States of America

4.1.2 Treatment regimens

502 Patientinnen randomisiert (1:1) Tisotumab vedotin vs. ICC

In the tisotumab vedotin arm, 250 of 253 randomised patients (98.8%) received at least one dose of study treatment. In the investigator's choice chemotherapy (ICC) arm, 239 of 249 randomised patients (96.0%) received at least one dose of one of the prespecified single-agent chemotherapy options. Among patients treated in the ICC arm, the most frequently administered agents were gemcitabine (45.6%) and pemetrexed (33.5%), followed by topotecan (7.9%), vinorelbine (7.1%), and irinotecan (5.9%)[9, 40].

protokollverpflichtende okuläre Prophylaxe aufgrund bekannter Augentoxizität

Due to the known ocular toxicity profile of tisotumab vedotin, protocol-mandated ocular prophylaxis was implemented, including pre- and post-infusion eye drops, cold packs during infusion, and mandatory ophthalmologic monitoring [9, 38].

Details on treatment exposure and treatment duration are presented in Section 4.2.

4.1.3 Outcomes

Outcome priorisation (PICO and GRADE-informed approach)

The endpoints reported in innovaTV 301 are presented as defined in the original study protocol and the EPAR. For this HTA, these endpoints were mapped to the outcome domains specified in the PICO framework (Chapter 2).

In line with a GRADE-informed approach, outcomes were prioritised according to their relevance for decision-making and this prioritisation was applied consistently throughout the assessment. Overall survival (OS), progression-free survival (PFS), quality of life (QoL), and key safety outcomes (including grade ≥3 adverse events (AEs) and fatal AEs) were classified as critical outcomes, while other endpoints were considered important but not critical.

Definitions and reporting of efficacy outcomes

primärer Endpunkt: OS

In the innovaTV 301 trial, the primary efficacy endpoint was OS, defined as the time from randomisation to death from any cause.

wichtige sekundäre Endpunkte: PFS, ORR

Key secondary endpoints were PFS and objective response rate (ORR). PFS was defined as the time from randomisation to investigator-assessed

radiologically confirmed disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or death from any cause. ORR was defined as the proportion of patients achieving a confirmed complete or partial response.

OS, PFS and ORR were included in the prespecified hierarchical testing procedure.

weitere wichtige Endpunkte: DoR und TTR

Additional important secondary endpoints included duration of response (DoR) and time to response (TTR). DoR was defined as the time from first documented response to disease progression or death, and TTR as the time from randomisation to first confirmed complete or partial response.

Tumorbewertung nach RECIST v1.1

Tumour assessments were performed according to RECIST v1.1. All efficacy analyses were conducted in the ITT population.

PROs explorativ; deskriptive Auswertung

Patient-reported outcomes (PROs) were assessed using the European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire (EORTC QLQ-C30), the cervical cancer-specific module QLQ-CX24, and the EQ-5D instrument. PRO analyses were conducted in the PRO full analysis set, prespecified as exploratory endpoints, and evaluated descriptively without multiplicity adjustment [9, 38].

Definitions and reporting of safety outcomes

Sicherheitsanalyse im Safety-Set (≥1 Dosis), TEAEs nach CTCAE v5.0 klassifiziert

Safety was assessed in the safety population, including all patients who received at least one dose of study treatment. Adverse events were reported as treatment-emergent adverse events (TEAEs) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Safety analyses included overall TEAEs, grade ≥3 TEAEs, treatment-emergent serious adverse events (TESAEs), treatment-related events, treatment discontinuations due to TEAEs, and fatal TEAEs (grade 5 events). Deaths occurring during the safety observation period were captured and classified according to TEAE definitions [9, 38]. A comprehensive overview of all study endpoints of innovaTV 301 is provided in Chapter 4.2 of the Appendix.

4.1.4 Safety analysis set

EPAR-basierte gepoolte Sicherheitsanalyse über das klinische Entwicklungsprogramm (n=628)

In addition to the pivotal RCT, the EPAR reports integrated safety analyses pooling patients treated with tisotumab vedotin across the clinical development programme. Two pooled populations are presented: a cervical cancer population (pool 1) and a broader population across all tumour types (pool 2).

Pool 1 includes patients with cervical cancer from the pivotal phase 3 study innovaTV 301 and the single-arm phase 2 study innovaTV 204. Pool 2 comprises all patients from pool 1 as well as additional patients from earlier-phase studies in other solid tumour indications.

In total, 628 patients were exposed to tisotumab vedotin in the pooled analyses [9].

4.2 Results on relative efficacy and safety

Results are presented for the ITT and safety populations. The prespecified primary analysis was performed at the data cut-off (DCO) of 24 July 2023. An updated OS analysis at the later DCO of 16 January 2024, is reported in the EPAR only and is descriptive in nature (nominal p-value; not alpha-controlled).

primäre Analyse zum DCO Juli 2023; Update-OS-Analyse nur deskriptiv (nicht alpha-kontrolliert)

At the primary DCO, the median duration of treatment was longer in the tisotumab vedotin arm compared with ICC (3.7 vs 2.8 months), corresponding to a median of 5 versus 4 treatment cycles, respectively. Updated exposure data were not reported for the later DCO [9].

längere mediane Behandlungsdauer unter Tisotumab vedotin (3,7 vs. 2,8 Monate)

4.2.1 Clinical efficacy outcomes

Efficacy outcomes are reported for the ITT population. Detailed numerical results are summarised in Table 4-3.

Overall survival

At the prespecified primary analysis (DCO 24 July 2023), median OS was 11.5 months in the tisotumab vedotin arm compared with 9.5 months in the ICC arm, corresponding to a stratified hazard ratio (HR) of 0.70 (95% CI 0.54-0.89; p=0.0038; alpha-controlled). At this time point, 263 deaths had occurred in the ITT population, corresponding to approximately 52% of randomised patients.

signifikanter OS-Vorteil unter Tisotumab vedotin (HR 0,70; alpha-kontrolliert)

In the descriptive OS update (DCO 16 January 2024), median OS was 11.7 months in the tisotumab vedotin arm vs 9.2 months in the ICC arm, corresponding to a stratified HR of 0.79 (95% CI 0.63-0.97; nominal p=0.0280). This analysis was not part of the prespecified hierarchical testing procedure.

OS-Update bestätigt Effekt, jedoch nur deskriptiv (nicht hierarchisch geprüft)

Prespecified subgroup analyses for OS at the primary DCO (24 July 2023) showed no evidence of heterogeneity across clinically relevant strata, including prior bevacizumab exposure, prior anti-programmed death [ligand] 1 (anti-PD-(L)1) therapy, Eastern Cooperative Oncology Group (ECOG) performance status, histology and the number of prior systemic regimens. The descriptive OS update at the later DCO (16 January 2024) did not indicate a materially different pattern across subgroups. Subgroup analyses according to the ICC demonstrated some variability in effect estimates in small subgroups, including patients receiving vinorelbine. However, confidence intervals were wide, no statistically significant interaction was detected. These analyses were exploratory and not adjusted for multiplicity [9, 38].

konsistenter Behandlungseffekt über Subgruppen hinweg; explorativ ohne Multiplizitätsanpassung

Progression-free survival

At DCO 24 July 2023, tisotumab vedotin improved PFS compared with ICC (stratified HR 0.67; 95% CI 0.54-0.82; p<0.0001; alpha-controlled) [9, 38].

PFS signifikant zugunsten von Tisotumab vedotin (p<0,0001)

Tumour response

signifikanter ORR-Vorteil vs. ICC

At DCO July 24th, 2023, confirmed ORR was higher with tisotumab vedotin than with ICC (stratified odds ratio 4.0; 95% CI 2.1-7.6; p<0.0001). Detailed results on the complete and partial response are given in Table 4-3.

DoR und TTR zwischen den Armen vergleichbar

Among confirmed responders, DoR and TTR were comparable between treatment arms and are reported descriptively in Table 4-3 [9, 38].

Table 4-3: Efficacy results of the innovaTV 301 clinical study [9, 38]

Efficacy endpoints	Data cut-off	Tisotumab vedotin	ICC	Effect estimate
OS, median (95% CI), months	24 July 2023	11.5 (9.8-14.9)	9.5 (7.9-10.7)	HR 0.70 (0.54-0.89); p=0.0038 (α-controlled; threshold 0.0226)
OS, median (95% CI), months	16 January 2024	11.7 (9.9-13.1)	9.2 (8.0-10.3)	HR 0.79 (0.63-0.97); nominal p=0.0280 (descriptive)
PFS (INV), median (95% CI), months	24 July 2023	4.2 (4.0-4.4)	2.9 (2.6-3.1)	HR 0.67 (0.54-0.82); p<0.0001 (α-controlled; threshold 0.0453)
ORR (INV), n/N (%) (95% CI)	24 July 2023	45/253 (17.8) (13.3-23.1) complete: 2.4% partial: 15.4%	13/249 (5.2) (2.8-8.8) complete: 0% partial: 5.2%	OR 4.0 (2.1-7.6); p<0.0001
DoR (INV; responders only), median (95% CI), months	24 July 2023	5.3 (4.2-8.3)	5.7 (2.8-NR)	descriptive
TTR (INV; responders only), median, months	24 July 2023	1.6	1.7	descriptive

Abbreviations: CI ... confidence interval, DoR ... duration of response, HR ... hazard ratio, ICC...investigator's choice chemotherapy, INV ... investigator-assessed, N ... total number of patients, n ... number of patients, NR ... not reached, OR ... odds ratio, ORR ... objective response rate, OS ... overall survival, PFS ... progression-free survival, TTR ... time to response

Patient-reported outcomes (exploratory)

höhere PRO-Teilnahmeraten unter Tisotumab vedotin

hohe Compliance in beiden Armen trotz unterschiedlicher Rücklaufquoten

Completion rates between baseline and cycle 5 (corresponding approximately to the median number of treatment cycles received in the tisotumab vedotin arm) among patients included in the PRO full analysis set were consistently higher in the tisotumab vedotin arm than in the ICC arm: For the EORTC QLQ-C30 questionnaire, the completion rate between baseline and cycle 5 was ≥57.6% in the tisotumab vedotin arm and ≥38.4% in the ICC arm. For the EORTC QLQ-CX24 module, completion rates were ≥56.3% and ≥37.9%, respectively. For the EQ-5D questionnaire, completion rates were ≥57.1% in the tisotumab vedotin arm and ≥40.4% in the ICC arm. Compliance rates were generally high in both treatment arms (≥88.8% in the tisotumab vedotin arm and ≥82.4% in the ICC arm).

Lebensqualität unter Tisotumab vedotin überwiegend stabil; klinisch relevante Verbesserungen häufiger

Between baseline and cycle 5, health-related quality of life (HRQoL), functioning, and symptom scales were generally maintained in the tisotumab vedotin arm, although interpretation is limited by decreasing completion rates over time. A ≥10-point improvement from baseline to cycle 5 in the QLQ-C30 Global Health Status/Quality of Life scale was reported in 13.9% of patients treated with tisotumab vedotin compared with 3.4% in the ICC arm [9].

4.2.2 Safety outcomes

Safety outcomes are reported for the safety population (n=250 vs n=239). A summary of key safety outcomes is presented in Table 4-4.

Sicherheitsanalyse im Safety-Set (250 vs. 239 Patientinnen)

Overall adverse events

TEAEs were common in both treatment arms. The incidence of any TEAE was 98.4% in the tisotumab vedotin arm and 99.2% in the ICC arm. Grade ≥3 TEAEs occurred less frequently with tisotumab vedotin than with ICC (52.0% vs 62.3%). TESAEs were reported in 32.8% and 39.3% of patients, respectively. Grade 5 TEAEs (all-cause) were infrequent and occurred at similar rates in both groups (1.6% vs 2.1%). Treatment-related grade 5 TEAEs were rare, occurring in 0.8% of patients receiving tisotumab vedotin and 0.4% receiving ICC.

TEAEs häufig in beiden Armen; weniger Grad ≥3 unter Tisotumab vedotin

Most frequent adverse events

The most common TEAEs (≥25%) in the tisotumab vedotin arm were nausea, conjunctivitis, peripheral sensory neuropathy, and epistaxis.

häufigste TEAEs: Übelkeit, Konjunktivitis, Neuropathie, Epistaxis

Severe (grade ≥3) adverse events

Common grade ≥3 AEs in the tisotumab vedotin arm included anaemia (8.4%), urinary tract infection (4.4%), abdominal pain (4.0%) and neutropenia (3.6%), whereas in the ICC arm anaemia (27.6%), neutropenia (13.4%) and urinary tract infection (7.1%) were most frequent.

Severe cutaneous adverse reactions were reported in 2.4% of patients in the tisotumab vedotin arm, including one grade 5 event.

schwere und schwerwiegende TEAEs numerisch geringer vs. ICC

Deaths

In the pivotal study, 12 deaths (4.8%) were reported in the tisotumab vedotin arm compared with 19 deaths (7.5%) in the ICC arm. Most deaths were attributed to progressive disease. In the tisotumab vedotin arm, four deaths were reported due to AEs (acute kidney injury, pneumonia, sepsis, and Stevens-Johnson syndrome), two of which were considered treatment-related [9, 38].

Todesfälle im Zusammenhang mit AEs selten; 2 davon als behandlungsbedingt eingestuft)

Treatment discontinuations

TEAEs leading to permanent treatment discontinuation occurred more frequently in the tisotumab vedotin arm (14.8%) than in the ICC arm (3.8%).

At the preferred term level, the most frequent TEAEs leading to discontinuation in the tisotumab vedotin arm were [9, 38]:

- peripheral sensory neuropathy (3.6%),
- keratitis (2.4%),
- conjunctivitis (1.2%).

häufigere Therapieabbrüche unter Tisotumab vedotin (14,8 % vs. 3,8 %)

Adverse events of special interest

Ocular adverse events

Ocular TEAEs were reported more frequently with tisotumab vedotin than with ICC (all grades: 52.8% vs 6.3%). Grade ≥3 ocular TEAEs occurred in 4.0% of patients in the tisotumab vedotin arm and were not reported in the ICC arm.

okuläre Ereignisse deutlich häufiger unter Tisotumab vedotin

The median time to onset of ocular TEAEs was 1.22 months (range 0.0-4.9), and the median time to resolution among resolved AEs was 0.59 months (range 0.1-12.6). At the primary DCO, 69.7% of ocular TEAEs had fully resolved or improved, 24.2% had partially resolved or improved, and 6.1% were ongoing.

okuläre TEAEs mit frühem Auftreten überwiegend reversibel

Among the ten patients with grade ≥3 ocular events, eight had a relevant ocular history at baseline, and all had previously experienced grade 1-2 ocular events. The EPAR concludes that ocular AEs were generally manageable and frequently reversible under the implemented eye-care plan [9, 38].

ophthalmologische Toxizität überwiegend beherrschbar; Grad ≥ 3 selten (4 %)

Peripheral neuropathy

Peripheral neuropathy was more frequently observed with tisotumab vedotin than with ICC (all grades: 38.4% vs 4.2%; grade ≥3: 5.6% vs 0.4%). The median time to onset was 2.38 months (range 0.0-9.3), and the median time to resolution was 1.12 months (range 0.0-12.1). Among affected patients, 18.8% experienced resolution of neuropathy by the primary DCO.

periphere Neuropathie häufiger unter Tisotumab vedotin (38,4 %; Grad ≥ 3: 5,6 %)

Bleeding events

Bleeding events were more frequently reported with tisotumab vedotin than with ICC (all grades: 42.0% vs 14.2%). Grade ≥3 bleeding events were infrequent and occurred at similar rates in both arms (2.4% vs 2.9%).

erhöhte Blutungsrate, jedoch vergleichbare Grad ≥3-Häufigkeit vs. ICC

Dose modifications

Dose modifications due to TEAEs occurred in 53.2% of patients treated with tisotumab vedotin and 56.9% of patients treated with ICC. Dose delays were reported in 39.2% and 31.0%, and dose reductions in 29.6% and 24.7%, respectively. The median relative dose intensity in the tisotumab vedotin arm was 96.1% [9, 38].

häufige Dosisanpassungen in beiden Armen, vergleichbare Raten

Table 4-4: Summary of treatment-emergent adverse events in innovaTV 301 clinical study [9, 38]

Outcome	innovaTV 301	
	Tisotumab vedotin (n=250)	ICC (n=239)
Overall TEAEs		
Subjects with any TEAE	246 (98.4%)	237 (99.2%)
Treatment-related TEAE (all grades)	219 (87.6%)	204 (85.4%)
Subjects with ≥ grade 3 TEAE	130 (52.0%)	149 (62.3%)
≥ grade 3 treatment-related TEAE	73 (29.2%)	108 (45.2%)
Subjects with any TESAE	82 (32.8%)	94 (39.3%)
Treatment-related TESAE	26 (10.4%)	35 (14.6%)
TEAE leading to permanent treatment discontinuation	37 (14.8%)	9 (3.8%)
Treatment-related TEAE leading to discontinuation	34 (13.6%)	4 (1.7%)

Outcome	innovaTV 301	
	Tisotumab vedotin (n=250)	ICC (n=239)
Subjects with grade 5 TEAE	4 (1.6%)	5 (2.1%)
Treatment-related grade 5 TEAE	2 (0.8%)	1 (0.4%)
Adverse events of special interest		
Ocular events (all grades)	132 (52.8%)	15 (6.3%)
Ocular events (≥ grade 3)	10 (4.0%)	0 (0%)
Peripheral neuropathy (all grades)	96 (38.4%)	10 (4.2%)
Peripheral neuropathy (≥ grade 3)	14 (5.6%)	1 (0.4%)
Bleeding events (all grades)	105 (42.0%)	34 (14.2%)
Bleeding events (≥ grade 3)	6 (2.4%)	7 (2.9%)

Abbreviations: ICC … investigator's choice chemotherapy, n … number of patients, TEAE … treatment-emergent adverse event, TESAE … treatment-emergent serious adverse event

Integrated safety analyses (EPAR)

gepoolte EPAR-Analyse bestätigt bekanntes Sicherheitsprofil aus innovaTV 301

In the pooled EPAR analyses, the overall incidence of TEAEs and grade ≥3 TEAEs was comparable to that observed in innovaTV 301. The pattern of AEs was consistent with the known safety profile of tisotumab vedotin, with ocular, peripheral neuropathy and bleeding events representing the most frequently reported AEs of special interest. No additional safety signals were identified in the integrated datasets. According to the EPAR, long-term safety data from tisotumab vedotin are not available at present, and final safety data from the pivotal study will be provided post-authorisation [9].

In addition, post-marketing data from the USA, including approximately 1,500 treated patients, did not identify any new safety signals, supporting the consistency of the established safety profile [9].

4.2.3 ESMO-MCBS scorecard for tisotumab vedotin

ESMO-MCBS Score 3 (unterhalb der Schwelle für einen erheblichen klinischen Nutzen)

According to the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS), tisotumab vedotin received an ESMO-MCBS score of 3 (Form 2a; non-curative setting; OS as primary endpoint) as the observed survival gain of approximately two months and the HR did not meet the predefined thresholds required for a higher score [41]. A short summary can be found in Table 4-5. Further details on the ESMO-MCBS scorecard are presented in Chapter 4.4 of the Appendix.

Table 4-5: ESMO-MCBS v2.0 evaluation of tisotumab vedotin (innovaTV 301) [41]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation1	PM	Toxicity	QoL	AJ	FM
ESMO-MCBS v2.0	NC	2a	OS: 9.5 months	OS: +2.0 months	0.70 (0.54-0.89)	HR ≤0.65 AND gain ≥2-<3months	3	No AJ	No AJ	None	**3**

Abbreviations: AJ … adjustment, CI … confidence interval, ESMO-MCBS … European Society for Medical Oncology-Magnitude of Clinical Benefit Scale, FM … final magnitude of clinical benefit grade, HR … hazard ratio, Int … intention, MG … median gain, NC … non-curative, PM … preliminary grade, QoL … quality of life, ST … standard treatment

Note: [1] According to the ESMO-MCBS v2.0 methodology, score assignment is based on the lower limit of the 95% confidence interval of the HR (0.54 in this study).

4.3 Certainty of the evidence

4.3.1 Risk of bias

insgesamt: gewisse Bedenken (RoB Tool Version 2.0)

The RoB of the innovaTV 301 RCT was assessed using the Cochrane Risk of Bias 2.0 tool at study outcome level [42-44]. Overall, the study was judged to raise *some concerns* regarding RoB. No major issues were identified in the domains related to the randomisation process or measurement of the primary endpoint. Some concerns were noted in selected domains, including missing outcome data, particularly for PRO outcomes due to decreasing completion rates over time, and in the selection of the reported results, as certain outcomes (e.g., PROs and subgroup analyses) were analysed descriptively without multiplicity adjustment and were not part of the hierarchical testing procedure. Protocol amendments were transparently reported and did not materially affect the pre-specified endpoints or alter the overall RoB judgement.

Detailed domain-level assessments are presented in Chapter 4.5 of the Appendix.

4.3.2 Statistical analysis and inconsistencies

hierarchisches Testverfahren

The primary study endpoint (OS) and the selected key secondary endpoints (PFS, ORR) were evaluated within a pre-specified hierarchical testing procedure to control for multiplicity. At the primary DCO (24 July 2023), OS and PFS were tested within the alpha-controlled framework.

OS-Update und Subgruppenanalysen explorativ

The OS update (16 January 2024) was descriptive and not part of the hierarchical testing strategy; reported p-values are therefore nominal. Subgroup analyses were exploratory and not adjusted for multiplicity. No statistically significant treatment-by-subgroup interactions were reported. Patient-reported outcomes were analysed descriptively without multiplicity adjustment.

OS-Daten moderat reif (52 % Events); Langzeitdaten zur Sicherheit noch ausstehend

At the time of the primary analysis, approximately 52% of patients had experienced an OS event, indicating moderate maturity of the survival data. The updated OS analysis at the 16 January 2024 data cut-off provides supportive information but is limited due to its descriptive nature and lack of alpha control. With regard to safety, the EPAR states that long-term safety data are not available at present and that final safety data from the pivotal study will be provided post-authorisation [9, 38].

5 Price comparisons, treatment costs and budget impact

The Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) found prices for Germany at a pharmacy retail price of €2,289.66 per vial and an NHS price of £1,995.00 per vial for the UK.

Preise für Deutschland und Großbritannien verfügbar

This part includes confidential information!

The MAH did not submit a proposed price for Austria in the submitted dossier, stating that the market launch and commercialisation of tisotumab vedotin in Austria are not planned for the next three years. The ex-factory price of tisotumab vedotin in Germany that was reported in the submitted dossier is €1,821 per vial. Nevertheless, tisotumab vedotin is available in Austria via a parallel import. The import price per vial is therefore €2,481.

Angaben des Unternehmens: Deutscher Listenpreis von € 1.821 pro Durchstechflasche vs. Parallelimport-Preis € 2.481

5.1 Pharmacoeconomic model(s)

5.1.1 Submitted pharmacoeconomic model

The MAH did not submit a pharmacoeconomic model to assess the cost-effectiveness of tisotumab vedotin in Austria.

kein Modell für Ö übermittelt

5.1.2 Economic evaluation based on pharmacoeconomic models

Characteristics of the economic evaluations and applied models

Countries and perspectives

Two completed cost-utility analyses (CUAs) were identified: one [45] conducted from a Spanish National Health System perspective, and another [46] adopting a US third-party public healthcare payer (Medicare reimbursement) perspective. Notably, neither study was conducted from a societal perspective.

2 Kosten-Nutzwert-Analysen mit der Gesundheitssystem-/ Zahlerperspektive

Intervention, comparator, and target population

Both studies evaluated tisotumab vedotin as the intervention. The Spanish analysis [45] compared tisotumab vedotin against single-agent chemotherapies of the clinician's choice, using the ratios from the innovaTV 301 trial control arm (gemcitabine 44%, pemetrexed 32%, topotecan 8%, vinorelbine 7%, iri-

Tisotumab vedotin vs. Einzelwirkstoff-Chemotherapie (± Pembrolizumab)

notecan 6%)[4] with or without pembrolizumab, assuming that PD-L1-positive patients currently receive first-line chemotherapy combined with pembrolizumab. The US study [46] also extracted efficacy data from the innovaTV 301 clinical trial comparing tisotumab vedotin against the investigator's choice of single-agent chemotherapy. In addition, it assumed that patients would receive post-progression treatment (50% docetaxel and 50% BSC), with all patients receiving a single end-of-life visit.

Population: r/m CC

Both analyses focused on patients with r/m CC receiving second- or third-line treatment after failure of first-line chemotherapy with or without pembrolizumab [45], or chemotherapy with or without bevacizumab and/or PD-(L)1 inhibitors [46].

Model structure and time horizon

Markov-Modelle mit 3 Gesundheitszuständen (Progressionsfrei, Progression, Tod)

The two studies employed different modelling approaches. The Spanish analysis [45] employed a partitioned survival model with three mutually exclusive health states: progression-free (PF/baseline), progression, and death (end state), using a 60-month time horizon. A generalised F-function was selected for OS and an exponential function for PFS, based on Akaike Information Criterion (AIC), visual comparison with trial curves, and independent clinical expert validation. Estimated hazard ratios were 0.6928 for OS and 0.6708 for PFS. The US study [46] employed a 3-state Markov cohort model with health states of PFS, progressive disease (PD), and death, using a lifetime horizon. Log-logistic functions were selected for both PFS and OS based on AIC criteria, with half-cycle correction applied.

Cost categories and utility values

Spanien: Tisotumab vedotin-Preis basierend auf Cemiplimab-Preis;

USA: Tisotumab vedotin-Kosten basierend auf selbstberechneten Medicare-Erstattungssätzen

The Spanish analysis [45] included costs of tisotumab vedotin, which was not yet marketed in Spain, based on the assumption that its price would be equivalent to that of cemiplimab (€1,536.57 per administration). Grade ≥3 AEs observed in the clinical trial were included, and associated costs were estimated using the Boletín Oficial de la Junta de Andalucía. Drug costs were sourced from national databases. In comparison, the US study [46] based the costs on self-calculated Medicare reimbursement rates, noting this cost source may not be applicable to other US providers. Tisotumab vedotin was assumed to cost $168.26 per mg, i.e. $6,730 per vial.

Nutzwerte aus der Literatur herangezogen

Utility values in both studies were extracted from published literature rather than directly from the innovaTV 301 trial, as trial-based utility data were unavailable. The Spanish analysis [45] referenced Thurgar et al. (2021) and Huo et al. (2024), while the US study [46] referenced Thurgar et al. (2021), Liu et al. (2022), and Jem et al. (2008), applying utility values of 0.817 for PFS and 0.779 for PD. The Spanish analysis did not consider disutility, while the US study applied AE disutilities of 0.073 for anaemia, and 0.090 for neutropenia. Neither study applied a severity modifier.

[4] These numbers slightly differ from the original numbers reported in the innovaTV 301 trial control arm: gemcitabine (45.6%), pemetrexed (33.5%), topotecan (7.9%), vinorelbine (7.1%) or irinotecan (5.9%).

Uncertainty testing and discount rates

The Spanish analysis [45] did not explicitly report a base-case discount rate; the 0-5% range was explored only in the deterministic sensitivity analysis (SA). The US study [46] applied a 3% per annum discount rate for both costs and health outcomes, with variations of 0-5% explored in sensitivity analyses. Both studies conducted SA, though the Spanish analysis noted that using a partitioned survival model limited the feasibility of probabilistic sensitivity analysis (PSA).

Spanien: Diskontrate nur in SA (0-5 %)

USA: Diskontrate 3 % p.a. SA: 0-5 %

Model assumptions and limitations

Both studies relied on efficacy data from the innovaTV 301 RCT. Key limitations shared by both studies include the absence of utility values derived directly from the trial and the restriction of AEs to those of grade ≥3 with an incidence rate ≥5%. In addition, the Spanish analysis [45] noted the lack of a direct clinical comparison with cemiplimab due to unreliable PD-L1 <1% subgroup data, the assumption that tisotumab vedotin's price was equivalent to cemiplimab in the absence of official Spanish market pricing, and the absence of Spanish-specific utility values for CC. In comparison, the US analysis [46] also highlighted incomplete trial results, reliance on reconstructed Kaplan-Meier data for transition probabilities, and the limited generalisability of Medicare-based cost sources to other US healthcare providers.

beide Studien: fehlende studieneigene Nutzwerte; Berücksichtigung von lediglich AEs Grad ≥ 3 mit Inzidenz ≥ 5 %

Quality assessment

The quality assessment of the two included economic evaluations using the CHEERS and CHEC lists showed that both evaluations [45, 46] are of moderate quality. Collectively, the two studies converge on a consistent finding: the cost-effectiveness of tisotumab vedotin is critically dependent on the acquisition price of the drug. However, neither study fully meets the methodological standards required for HTA submissions. Key limitations shared across both analyses include the absence of a prespecified analytical protocol, the use of utility values derived from nonrepresentative patient populations, a lack of clinically relevant subgroup analyses, and a lack of patient involvement, all of which constrain the validity of the reported estimates. Overall, Spanish evaluation [45] demonstrates greater methodological transparency and policy relevance for European HTA contexts, underpinned by independent authorship and clinical expert validation, but is limited by the absence of a PSA. In comparison, the US analysis [46] addresses uncertainty quantification more rigorously through a full PSA, but is undermined by reliance on immature conference-reported trial data and unjustified cross-indication utility transfer. The detailed assessment is presented in Appendix, Chapter 5.

beide Evaluationen von moderater Qualität (CHEERS, CHEC-Liste)

Results of the economic evaluations

The Spanish analysis reported incremental costs of €12,138 (tisotumab vedotin: €19,900 vs chemotherapy: €7,762) and an incremental effect of 0.341 quality-adjusted life years (QALYs) (tisotumab vedotin: 1.229 vs chemotherapy: 0.889). Consequently, the base-case incremental cost-effectiveness ratio (ICER) was €35,600 per QALY gained. As Spain has not formally adopted a cost-effectiveness threshold, the authors cited literature-based values ranging from €21,000 to €60,000 per QALY gained [45]. In comparison, the US analysis reported incremental costs of $206,779 (tisotumab vedotin: $293,641 vs chemotherapy: $86,862), with incremental effects of 0.25 QALYs (tisotumab vedotin: 1.15 vs chemotherapy: 0.90), resulting in a base-case ICER

Basis-ICER: Spanien: € 35.600/QALY – kein nationaler Schwellenwert; USA: $ 839.108/QALY – nationaler Schwellenwert ($ 150.000/QALY) deutlich überschritten

of $839,108 per QALY gained, substantially exceeding the applied threshold of $150,000 per QALY gained in the US [46].

SA: Spanien: größter Einfluss OS-HR, PFS-Nutzwert und Tisotumab vedotin-Preis USA: stärkste Einflussfaktoren Tisotumab vedotin-Kosten/mg, Nutzwerte und Diskontrate

Regarding the uncertainty analysis, the deterministic one-way sensitivity analyses (OWSA) of the Spanish analysis identified the HR for OS as the most influential parameter, with the ICER ranging from €23,283 per QALY gained (HR 0.54, lower CI) to €95,626 per QALY gained (HR 0.89, upper CI). The second most influential parameter was the PFS utility of tisotumab vedotin, with the ICER ranging from €31,609 (utility 0.90) to €68,966 (utility 0.50) per QALY gained. Variations in tisotumab vedotin prices yielded ICERs ranging from €31,476 (tisotumab vedotin price: €1,306) to €39,924 per QALY gained (tisotumab vedotin price: €1,767) [45]. In the US study, the OWSA identified the per-milligram cost of tisotumab vedotin as the most influential parameter, followed by the utilities of PD and PFS, and the discount rate. The PSA indicated a 0% probability that tisotumab vedotin is cost-effective at the $150,000-per-QALY-gained threshold [46].

Kosteneffektivität von Tisotumab vedotin in beiden Analysen primär preisgetrieben

Overall, both health economic analyses consistently demonstrate that tisotumab vedotin's cost-effectiveness is highly sensitive to its price, suggesting that outcome-based pricing agreements or price reductions may be necessary conditions for tisotumab vedotin to become cost-effective in either the Spanish or US healthcare context [45, 46].

Below, Table 5-1 presents an overview of the main results. The detailed data of the included health economic evaluations are presented in Chapter 5.1 in the Appendix.

Excursus: Health economic model submitted to the National Institute for Health and Care Excellence (NICE) in the UK[5]

Modell des Unternehmens für NICE (UK):

Additionally, we report the main characteristics and results of the economic model that was submitted by the MAH to NICE for the purposes of reimbursement of tisotumab vedotin in the NHS in England. The draft guidance document concludes that due to the uncertainties in the submitted model, the cost-effectiveness estimates for tisotumab vedotin could not be determined.

Semi-Markov-Modell (basierend auf innovaTV 301 Studie)

ICER über NHS-Schwellenwert (£ 20.000 – £ 30.000/QALY)

Listenpreis vertraulich

The MAH presented a semi-Markov model with a 30-year time horizon and a 1-week cycle length, comprising three health states: PF, PD, and death. Transition probabilities were derived from the innovaTV 301 trial using a parametric multistate modelling approach. For the first 12 months, the company used Kaplan-Meier trial data to directly estimate OS rather than modelled OS predictions. Based on the available document [47], the reported results are quite limited due to commercial confidentiality. The document states only that the MAH base case ICERs (both deterministic and probabilistic) were higher than the range normally considered acceptable for NHS resources (£20,000-£30,000 per QALY gained). The list price of tisotumab vedotin, which has not yet been approved, was also considered confidential and not disclosed in the document.

finale NICE-Empfehlung im Juni 2026 erwartet

The committee requested additional analyses from the MAH, including exploration of a partitioned survival model structure and updated chemotherapy administration costs. The final guidance document is expected to be published on 12 June 2026.

[5] The draft guidance of NICE for tisotumab vedotin for treating r/m CC was published after our cut-off date on 18 February 2026.

Table 5-1: Overview of main results of published health economic evaluations of tisotumab vedotin

Author, Year [Ref]	Country	Main assumptions	Incremental costs	Incremental effects	ICER & cost-effectiveness (national threshold)	Main sensitivity analysis results
Briceno-Casado et al., 2026 [45]	**Spain:** Spanish National Health System perspective	■ 3 health states (PF, PD, death); 60-month horizon ■ OS: generalised F-function (HR 0.6928); PFS: exponential function (HR 0.6708) ■ TV price assumed equal to cemiplimab (€1,536.57/administration) ■ Comparators: single-agent chemotherapies at the clinician's choice, including gemcitabine, pemetrexed, topotecan, vinorelbine, and irinotecan ■ Utility values from Thurgar et al. (2021) & Huo et al. (2024) ■ AEs ≥ Grade 3 ■ Discount rate reported in SA only (0-5%)	**€12,138** (TV: €19,900 vs chemo: €7,762)	**0.341 QALYs** (TV: 1.229 vs chemo: 0.889)	**€35,600/QALY gained** No formal national threshold; literature-based range: €21,000-€60,000/QALY	Largest drivers: ■ OS HR: €23,283-€95,626/QALY ■ PFS utility: €31,609-€68,966/QALY ■ TV price: €31,476-€39,924/QALY PSA not feasible (noted as a limitation)
Huo et al, 2024 [46]	**USA:** US third-party public payer (Medicare) perspective	■ Post-progression: 50% docetaxel + 50% BSC; one-time end-of-life care for all ■ 3-state Markov cohort model (PFS, PD, death); lifetime horizon; half-cycle correction ■ PFS & OS: log-logistic functions (AIC-based) ■ TV costs: self-calculated Medicare rates (USD $93,641; $6,730/vial) ■ Comparators: investigator's choice of single-agent chemotherapy, including gemcitabine, vinorelbine, topotecan, pemetrexed, or irinotecan ■ Utility values from Thurgar et al. (2021), Liu et al. (2022), Nafees et al. (2008): PFS 0.817, PD 0.779, anaemia disutility 0.073, neutropenia disutility 0.090 ■ AEs ≥ grade 3, incidence ≥5% only ■ Discount rate: 3% p.a. (SA: 0-5%)	**$206,779** (TV: $293,641 vs chemo: $86,862)	**0.25 QALYs** (TV: 1.15 vs chemo: 0.90)	**$839,108/QALY gained** National threshold: $150,000/QALY	Largest drivers: ■ Per-mg cost of TV ■ Utility of progressive disease ■ Utility of PFS ■ Discount rate PSA: **0% probability** of cost-effectiveness at $150,000/QALY threshold

Abbreviations: AE … adverse event; BSC … best supportive care; HR … hazard ratio, ICER … incremental cost-effectiveness ratio; OS … overall survival; PD … progressive disease; PF … progression-free; PFS … progression-free survival; PSA … probabilistic sensitivity analysis; QALY … quality-adjusted life year; SA … sensitivity analysis; TV … tisotumab vedotin

5.2 Budget impact analysis

5.2.1 Budget impact analysis submitted by the marketing authorisation holder

The MAH did not submit a BIA of tisotumab vedotin for Austria.

Unternehmen hat keine Budgetfolgenanalyse für Österreich übermittelt

5.2.2 Austrian budget impact analysis

Eligible population and market share in years 1-3

To derive the eligible population for tisotumab vedotin treatment, it would be necessary to sum the incidence of metastatic CC cases with the estimate of recurrent, initially non-metastatic cases, and further restrict the resulting r/m CC population to those with progression on or after systemic therapy.

Ableitung der anspruchsberechtigten r/m CC-Population nach Systemtherapie

According to Statistik Austria, patients with disseminated CC in Austria account for an average of 8.5% of overall CC incidence, amounting to 35 patients annually [48]. To derive the recurrent arm of the eligible population, we assumed that the remaining 91.5% of the incident population is initially non-metastatic (n=380). The likelihood of recurrence of CC among initially non-metastatic cases was adopted from the IQWiG report and reported as a 22-31% range [49]. Consequently, there are an estimated 119-153 patients with r/m CC in Austria. The eligible population is further restricted to patients who have progressed after or during a systemic therapy; again, in the IQWiG report, the MAH estimated this population by using a range, with lower bound adopted from a publication by Musa et al. from 2022 [50] and corresponding to 33%; the upper bound from an abstract publication by Denschlag et al. from 2024 [51] corresponding to 62% [49]. Hence, the resulting Austrian eligible population derived from literature estimates can be expressed as a range of 39-95 patients per year.

Statistik Austria: 35 Fälle/Jahr metastasiert (8,5 %); 380 initial nicht metastasiert

nach Einschränkung auf Progression nach Systemtherapie: 39-95 anspruchsberechtigte Patientinnen/Jahr

In contrast, the consulted clinical experts provided a qualified estimate of the eligible population of 40 to 50 patients per year. We decided to proceed with this estimate and applied the average of 45 patients treated per year in the presented BIA.

klinische Expert:innen-Schätzung: 40-50 Patientinnen/Jahr

Direct medical costs of tisotumab vedotin treatment

The direct medical costs of tisotumab vedotin treatment include drug acquisition and administration costs.

Medikamentenkosten sowie Administrationskosten

Acquisition costs of tisotumab vedotin

Tisotumab vedotin is obtained for use in Austria via a parallel import arrangement at a price of €2,481 per 40 mg vial. Given the dosing regimen of 2 mg/kg IV every 21 days [32], four vials are needed on average per treatment cycle. Assuming a median of five treatment cycles from the pivotal innovaTV 301 trial (range: 1-26), the overall acquisition cost per patient is €49,620.

Bezug via Parallelimport à € 2.481/Flasche; 4/Zyklus; Median 5 Zyklen (innovaTV 301): € 49.620/Patientin

Administration costs of tisotumab vedotin

The recommended dose is administered as an IV over 30 minutes in a hospital daycare clinic setting. We accounted for the administration costs via a per-diem hospital daycare clinic tariff of €845.71. Given the median of five treatment cycles, the administration costs of tisotumab vedotin in Austria amount to €4,229.

Applikation IV über 30 Min.; Tagesklinikpauschale € 845,71/Tag; 5 Zyklen: € 4.229/Patientin

There are additional recommended procedures associated with ocular adverse reactions (see detailed information in Chapter 1.3) [32]. These ophthalmological procedures were deemed cost-irrelevant and therefore not included in the BIA.

empfohlene ophthalmologische Begleitmaßnahmen nicht in der BIA berücksichtigt

Additional treatment costs

We did not assume any additional treatment costs.

keine zusätzlichen Kosten

Direct medical costs of standard of care treatments

To date, patients in Austria with r/m CC receive individualised off-label monotherapy treatments with chemotherapy agents. According to the consulted experts, topotecan is the most used chemotherapy regimen for this indication in Austria (estimated share: 70%), followed by gemcitabine (estimated share: 30%). The combined costs of these two chemotherapy regimens represent standard of care costs that are assumed to be replaced by costs of tisotumab vedotin treatment in the present BIA. In addition, a non-negligible number of patients with r/m CC for whom further antineoplastic therapy is not an option receive BSC, consisting of measures aimed at symptom alleviation. However, given the highly individualised nature of BSC measures, the associated costs could not be quantified.

derzeitiger Standard: Off-label-Monotherapien: Topotecan (70 %) und Gemcitabin (30 %)

BSC-Kosten wurden aufgrund ihres individuellen Einsatzes nicht quantifiziert

Topotecan direct medical costs

The recommended dose of topotecan for this indication is 1.5 mg/m^2 IV on five consecutive days of each 21-day cycle [52]. The median number of treatment cycles in the chemotherapy comparator arm in the innovaTV 301 trial was four. Given the price of topotecan (Topotecan Hospira®) at €237 per 4 mg vial, the overall per-patient acquisition cost is €4,740.

Topotecan (Hospira®): Median 4 Zyklen, € 237/Flasche → € 4.740/Patientin

Similar to tisotumab vedotin, topotecan is administered in Austria in hospital daycare clinics at a per-diem tariff of €845.71. With the median of 20 treatment days per patient, the administration costs of topotecan treatment amount to €16,914.

Tagesklinikpauschale € 845,71; Median 20 Behandlungstage: € 16.914/Patientin

Gemcitabine direct medical costs

Recommended dosing of gemcitabine in this indication is 1000 mg/m^2 IV on days 1 and 8 of each 21-day cycle [44]. Assuming the median of four treatment cycles and a price of €99 per 1,000 mg vial of gemcitabine (Gemzar®), the overall per-patient acquisition cost averages €1,584.

Gemcitabin (Gemzar®): Median 4 Zyklen, € 99/Flasche (1.000 mg) → € 1.584/Patientin

Given the eight treatment days per patient, the administration costs of gemcitabine treatment in hospital daycare clinics amount to €6,766.

8 Behandlungstage: € 6.766/Patientin

Overall treatment costs and per-patient comparison

Overall, **the direct medical costs of tisotumab vedotin treatment per patient amount to €53,849**, 92% of which are attributable to drug acquisition. By comparison, direct medical costs for the standard of care treatments are €21,654 for topotecan and €8,350 for gemcitabine.

Tisotumab vedotin Gesamtkosten, davon 92 % Medikamentenkosten

Given the 70-30% distribution among eligible patients receiving antineo plastic therapies, **the average direct medical cost of the standard of care mix is €17,663**, with only 21% attributable to drug acquisition. A detailed breakdown by cost categories is presented graphically on Figure 5-1 and in Table 5-2 below .

Chemotherapie-Gesamtkosten, davon 21 % Medikamentenkosten

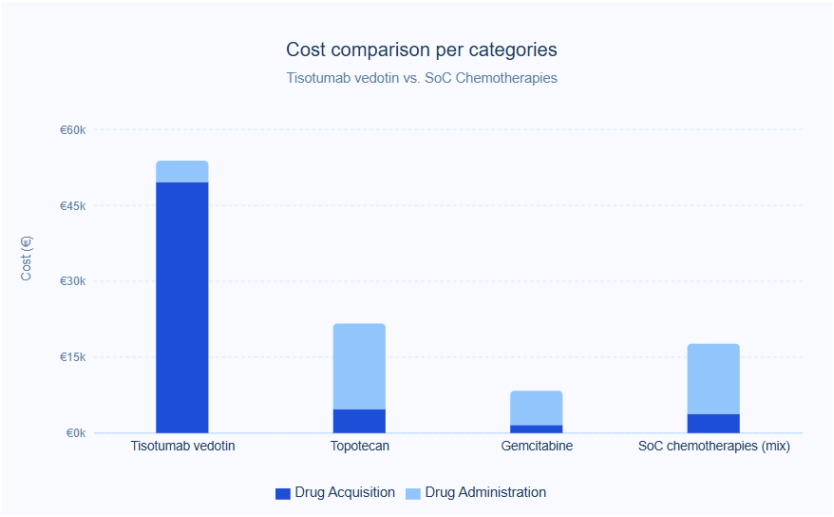


Figure 5-1: Comparison of per-patient annual direct medical costs

Table 5-2: Breakdown of per-patient treatment costs

Cost categories	Tisotumab vedotin	Topotecan (70%)	Gemcitabine (30%)	Mixed ChT comparator
Drug acquisition	€49,620	€4,740	€1,584	€3,793
Drug administration	€4,229	€16,914	€6,766	€13,869
Sum: Total direct medical costs, including additional treatment costs	**€53,849**	**€ 21,654**	**€8,350**	**€17,663**

Net budget impact in years 1-3

The actual budget impact of reimbursing tisotumab vedotin will depend on the number of eligible patients and the uptake rate. If we apply clinical experts' estimate of an average of 45 eligible patients per year and assume that all patients currently receiving the individualised off-label standard of care treatment would switch to tisotumab vedotin, the net budget impact of reimbursing tisotumab vedotin will be approximately €4.89 million over the first three years compared to the amount spent on the chemotherapy mix. A detailed breakdown by cost categories is presented in Figure 5-2 and Table 5-3.

bei 45 Patientinnen/Jahr und vollständiger Umstellung auf Tisotumab vedotin beträgt der Netto-Budgetimpact ca. € 4,89 Mio. über 3 Jahre

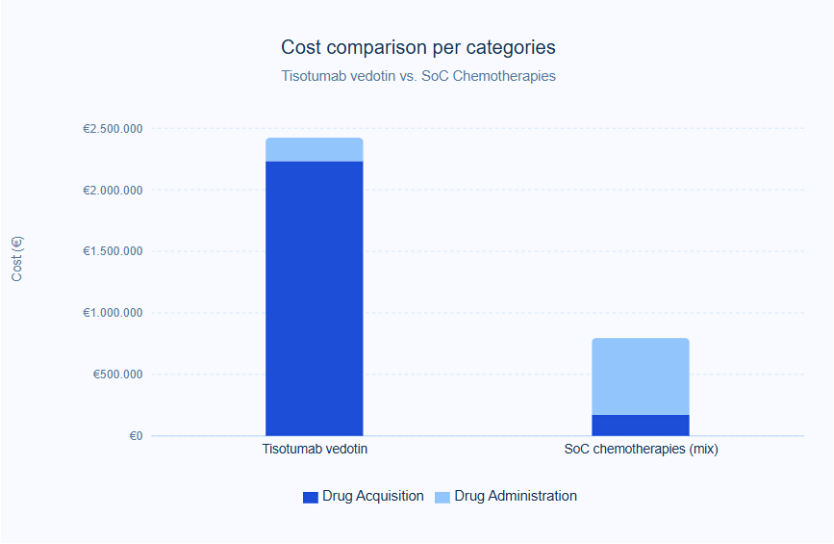


Figure 5-2: Comparison of the budget impact for 45 patients treated

Table 5-3: Net budget impact of tisotumab vedotin over 3 years

Cost category	Year 1	Year 2	Year 3	Total
New pts. treated p.a.	45	45	45	135
Acquisition costs	€2,232,900	€2,232,900	€2,232,900	€6,698,700
Administration costs	€190,285	€190,285	€190,285	€570,854
Total tisotumab vedotin costs	€2,423,185	€2,423,185	€2,423,185	€7,269,554
Standard of care costs (ChT mix)	€794,828	€794,828	€794,828	€2,384,484
NET BUDGET IMPACT	**€1,628,357**	**€1,628,357**	**€1,628,357**	**€4,885,070**

Abbreviations: ChT ... chemotherapy, p.a ... per annum, pts ... patients

Scenario analysis

This scenario analysis illustrates a possible future price for tisolumab vedotin in Austria, assuming Austria will receive the same price as Germany. Thus, according to the lowest available net price following the Lauer-Taxe, a price of €1,821 per vial was applied in the BIA while keeping all other parameters fixed. This price reduction of around €660 reduced per-patient acquisition costs to €36,420 for a median of five treatment cycles, corresponding to a net budget impact of around €1.6 million for the 45 expected patients per year. Finally, this price reduction would result in a net BIA reduction of around €594,000 per year and €1.782.000 for three years (see Figure 5-3 and Table 5-4).

Szenarioanalyse: Preisanpassung lt. Lauer-Taxe (lgn); € 1.821/Flasche

Netto-BIA-Reduktion: ~ €594.000/Jahr

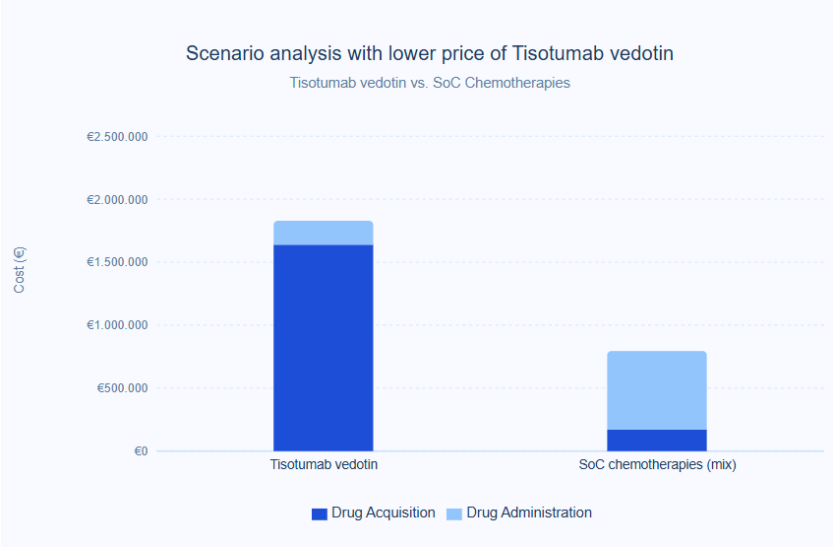


Figure 5-3: Comparison of the budget impact for 45 patients treated (scenario analysis)

Table 5-4: Net budget impact of tisotumab vedotin over 3 years (scenario analysis: confidential)

Cost category	Year 1	Year 2	Year 3	Total
New pts. treated p.a.	45	45	45	135
Acquisition costs	€1,638,900	€1,638,900	€1,638,900	€4,916,700
Administration costs	€190,285	€190,285	€190,285	€570,854
Total tisotumab vedotin costs	€1,829,185	€1,829,185	€1,829,185	€5,487,554
Standard of care costs (ChT mix)	€794,828	€794,828	€794,828	€2,384,484
NET BUDGET IMPACT	**€1,034,357**	**€1,034,357**	**€1,034,357**	**€3,103,070**

Abbreviations: ChT ... chemotherapy, p.a ... per annum; pts ... patients

Limitations

Limitationen:

The presented BIA is subject to several limitations, primarily attributable to the uncertainties in the Austrian eligible population and cost data:

große Unsicherheit bei Patientinnen-Zahlen

As noted previously in the relevant subchapter, the size of the eligible population remains highly uncertain. The expert estimates (40-50 patients/year) applied in the presented BIA are provisional. Given the lack of Austrian epidemiological data to reliably estimate the number of patients meeting the approved indication, the actual number of eligible patients may differ from the assumed average of 45 per year.

Dosierungen basieren auf Off-Label-Anwendung und Zulassungsstudie;

Abweichungen sind Unsicherheitsquellen

In addition, the considered standard of care chemotherapy agents used in this indication are off-label; consequently, there is no recommended posology for this population. The applied dosing was adapted from the pivotal trial [44] and cross-checked against the product information (for different approved indications) [52]. However, the clinical dosing of chemotherapy regimens and the agents used in the Austrian practice may differ slightly, altering the standard of care costs. In addition, chemotherapy may be administered on an inpatient basis to patients who live far from the treatment centre, which would

increase the standard of care costs. The same uncertainty arises when using the median number of cycles from the pivotal trial.

Unsicherheiten hinsichtlich Kostendaten; Augenvorbehandlungen (kosten-irrelevant) und BSC-Kosten (individualisiert) wurden nicht in der BIA berücksichtigt

Further uncertainties arise regarding the cost data used. The chosen costing approach relied on ex-factory drug prices and an estimation of a daycare clinic day based on LKF catalogue reimbursement codes. In addition, some cost categories – namely, pre-treatment and AE management – were not considered in the BIA, the former being deemed cost-irrelevant by the clinical experts. For example, the costs of pre-treatment eye procedures were deemed cost-irrelevant by the clinical experts. Additionally, BSC costs could not be included in the BIA due to the highly individualised nature of the associated measures.

keine indirekten Kosten berücksichtigt

Finally, the analysis was conducted from a healthcare payer perspective and therefore considered only direct medical costs. Standardised and widely accepted data on indirect healthcare costs are unavailable in Austria, limiting the possibility of applying a societal perspective.

6 Extended perspectives

This chapter summarises the perspectives of healthcare providers (HCP) and patients, along with other relevant considerations. It outlines existing registries and describes frameworks for documenting the use of tisotumab vedotin in Austria.

6.1 Healthcare provider perspective

Identification of eligible patients

Identifikation geeigneter Patientinnen durch Monitoring des systemischen Therapieansprechens

Eligible patients are identified through assessment of treatment response and follow-up care within the framework of the close monitoring the Austrian cancer patients are integrated in.

Implementation considerations

Infrastruktur für die Anwendung von Tisotumab vedotin besteht größtenteils schon

organisatorische Anforderungen an Tisotumab vedotin

The integration of tisotumab vedotin into clinical practice requires careful consideration of healthcare infrastructure, HCP readiness, and patient support needs. Tisotumab vedotin requires specialised resources for storage, administration, and management [32]. Nevertheless, substantial structural changes are not anticipated, as most centres administering targeted infusion therapies already have the necessary infrastructure in place. However, organisational adjustments may be required to accommodate treatment protocols specific to tisotumab vedotin. Effective treatment also requires interdisciplinary coordination to manage AEs, including ocular complications, neuropathy, and bleeding events. Furthermore, patient education and support are also required [32, 53].

Austrian clinical practice context

Einschätzung von 8 klin. Expert:innen für den österr. Kontext

As part of the assessment, eight clinical experts were consulted to provide specific guidance for the Austrian clinical practice context (see Chapter 3). The consultation addressed organisational aspects and patient-relevant outcomes of tisotumab vedotin use. In addition, clinical experience with tisotumab vedotin was discussed. The questions addressed during the two clinical expert meetings are provided in Appendix 6.1.

Entlastung der Infrastruktur durch tagesklinische Behandlung und längere Intervalle zw. den Behandlungszyklen

Regarding organisational aspects, the clinical experts indicated that administering tisotumab vedotin in a day-clinic setting at 3-week intervals could positively impact healthcare resource utilisation, including fewer patient visits, reduced demand for inpatient beds, and lower HCP staffing requirements (e.g., for intravenous access). The current standard of care with chemotherapies generally involves frequent administration with longer infusion times and is often delivered in an day-clinic setting [22].

klin. Expert:innen bewerten OS, PFS, ORR und QoL als zentrale patient:innen-relevante Endpunkte;

In the r/m setting, the clinical experts considered OS, PFS, ORR, and QoL, particularly regarding symptom control, to be closely interrelated patient-relevant outcomes. The clinical experts noted that while improvements in response rate may not necessarily translate into gains in OS, tumour response was considered relevant, particularly when associated with improvements in

QoL. Increasing experience with ADCs in oncology and in the management of associated AEs was reported. Initial clinical experience with tisotumab vedotin in Austria was described as positive. The feasibility of AE management was highlighted by the consulted experts [22].

bisher positive Erfahrungen mit Tisotumab vedotin in der klin. Praxis in Österreich

6.2 Patient perspective

The following section outlines the patient perspective, integrating evidence from the literature and insights gained through a patient questionnaire. The combined approach provides a more multidimensional view of patient experiences, expectations, and concerns relevant to the HTA report.

Findings from the literature

Treatment preferences

A discrete choice experiment (DCE)[6] conducted by Thaker et al. (2025) evaluated patient trade-offs between treatment efficacy, risks, and burden in r/m CC and modelled perceived financial and logistical impacts on treatment preferences. The findings suggest that patients prioritise OS and disease control. Patients with prior experience of ocular TEAEs attributed greater importance to the risk of corneal side effects. The authors conclude that individual patient preferences should be considered in shared decision-making, as they also affect treatment satisfaction and potentially adherence [55].

Berücksichtigung individueller Präferenzen in der Entscheidungsfindung beeinflusst Zufriedenheit und Adhärenz

Joseph et al. (2026) evaluated patient priorities by asking respondents to rank OS, emotional well-being, functional dependence, healthcare costs, and treatment experience. OS was consistently ranked as the highest priority, whereas treatment costs were ranked lowest in importance. The ranking of priorities of greatest and lowest importance was comparable across metastatic and non-metastatic disease settings, as well as among patients who had received chemotherapy or surgery. Differences emerged across stages of survivorship regarding the three highest-ranked priorities in each group. Short-term survivors (<1 year) prioritised OS, functional independence, and emotional well-being, whereas long-term survivors (>5 years) placed greater emphasis on OS, treatment experience, and emotional well-being [56].

Priorität der Patientinnen:
… höchste: OS
… niedrigste: Behandlungskosten

Burden of treatment and quality of life

Health-related QoL in patients with CC is multidimensionally impacted, affecting physical, psychological, social, and environmental domains, depending on the treatment modality. Soares and Dantas (2024) conducted a systematic review examining QoL outcomes in women with CC. Additionally, Liberacka-Dwojak et al. (2024) compared QoL in patients with CC after their diagnosis with that of healthy women using the 36-Item Short Form Survey and the six-item Female Sexual Function Index (FSFI) and Membrilla-Beltran et al. (2023) evaluated the impact of CC on QoL and sexuality in female survivors with the FSFI, Golombok Rust Inventory of Sexual Satisfaction, and European

bei Pat. mit CC zeigte sich eine reduzierte QoL in den körperlichen, psychologischen, sozialen und Umwelt-Domänen

[6] A DCE is a quantitative research method used to explore participants' preferences without asking them directly. The participants are presented with a series of alternative hypothetical scenarios and are asked to rank their preferences [54].

Organisation for Research and Treatment of Cancer QoL questionnaire. To synthesise the findings, outcomes were structured using the domains of the World Health Organization Quality of Life (WHOQOL) framework [57]. An overview of the affected domains is presented in Figure 6-1.

Figure 6-1: Schematic representation of the quality of life domains affected by cervical cancer (created using CANVA, based on [57]

- **Physical domain:** Women with CC scored significantly lower on physical functioning (mean 53.56 vs 69.69) [58]. Reported symptoms included gynaecological problems, urinary incontinence, intestinal issues, physical changes to the vagina, and swelling of the legs [59]. Other symptoms, such as appetite, fatigue, insomnia, and pain were also reported [60]. Women with CC also scored significantly lower on sexual functioning (mean 32.50 vs 88.50) [58]. Manifestations of sexual dysfunction included loss of libido, lack of sexual excitement, and pain during sexual intercourse. Fear of pain during penetration often resulted in avoidance of sexual intercourse and subsequent impairment of sexual functioning [59]. Findings showed that CC survivors experienced sexual dysfunction [60].

körperliche Domäne: z. B. gynäkologische Probleme, Harninkontinenz, Magen-/Darmbeschwerden, Erschöpfung, Schlaflosigkeit

- **Psychological domain:** Women with CC scored significantly lower on psychological functioning (mean 35.33 vs 85.67) [58]. Patients experienced aggression, anger, anxiety, and worry. Sadness and frustration related to infertility, difficulty discussing fertility issues, and grief associated with the loss of the ability to have children following treatment [59].

psychische Domäne: z. B. Wut, Angst, Trauer und Frustration

- **Level of independence domain:** Consequences included loss of ability to work and consequently of employment, and high medical expenses [59].
- **Social relationships domain:** Feelings of shame and self-criticism were also associated with isolating behaviours. Patients experienced isolation from family or community following diagnosis or disease progression. Perceived social support was a key determinant of QoL, with lower support associated with poorer outcomes [59].
- **Environmental domain:** With reduced independence, patients became increasingly financially reliant on family members. Furthermore, experiences of discrimination and stigmatisation were reported. Stigma related to HPV infection, misconceptions regarding transmission of HPV, and assumptions about women's sexual behaviour contributed to stigmatising labels and social ostracisation [59].

Unabhängigkeit: z. B. Verlust der Arbeitsfähigkeit

soziale Beziehungen: z. B. Isolation

Umwelt: z. B. finanzielle Abhängigkeit, Stigmatisierung und soziale Ausgrenzung

Patient perspective – results from a questionnaire

Patient characteristics

Patient perspectives were collected as part of this HTA using a questionnaire, as described in the Methods section (see Chapter 3). Two patients, who were not affiliated with any patient organisations, completed the patient questionnaire (see Appendix 6.1). Both patients reported a long history of treatment. The characteristics of the patients are presented in Table 6-1.

Patientinneninvolvierung: 2 Patientinnen haben Fragebögen ausgefüllt

Table 6-1: Characteristics of participants of the structured patient questionnaires (n=2) [61]

Patient characteristics	Total number of patients (n=2)
Sex	
Female	2
Male	0
Median age	47.5
Indication	CC
Role	
Patient	2
Carer	0
Patient representative	0
Member of a patient organisation	
Yes	0
No	2
Patient already received tisotumab vedotin	
Yes	2
No	0

Abbreviations: CC ... cervical cancer, n ... number

Results from the questionnaires

Patientinneninput zu QoL und Erfahrungen mit Tisotumab vedotin:

The input of the patients highlighted two main areas: QoL and experiences with tisotumab vedotin. To synthesise the findings, outcomes were again structured using the domains of the WHOQOL framework [57]:

körperliche Domäne: z. B. Schwierigkeiten beim Urinieren, Fatigue

- **Physical domain:** Both patients reported symptoms related to CC and its treatment. One patient described fatigue and difficulties with urination. The other patient reported treatment-related side effects, including hair loss, loss of appetite, and diarrhoea. Changes in the perception of sexuality were also reported.

psychische Domäne: z. B. Gefühl der Nutzlosigkeit

- **Psychological domain:** CC was noted to impose a substantial burden on the mental health of patients and their families. Feelings of worthlessness were reported.

Unabhängigkeit: z. B. Angst ein „Pflegefall" zu werden

- **Level of independence domain:** Both patients lost employment due to their inability to work. One patient expressed a desire to avoid becoming dependent on her children or requiring assistance in her activities of daily living.

soziale Beziehungen: z. B. Arbeitsunfähigkeit

- **Social relationships:** Due to the inability to work, social relationships were reduced [61].

positive Erfahrungen mit Tisotumab vedotin nach Eingewöhnung

In addition, experiences with tisotumab vedotin were evaluated. Compared with other therapies, certain advantages were observed, including simplified administration and reduced or improved perceptions of side effects. One patient reported that several months were required to adjust, but with the appropriate dosage and supportive measures, such as nasal ointment and eye drops, a restricted but largely independent life could be maintained. Another patient expressed gratitude for receiving the treatment [61].

6.3 Further considerations

Disparitäten beim Screening und bei der Diagnosestellung zwischen Bevölkerungsgruppen

As outlined in Chapter 1.1, CC is largely preventable through HPV vaccinations and screening [59, 62]. However, disparities in access or uptake of these preventive measures may result in certain populations presenting with advanced disease and being more likely to require later-line treatments, such as tisotumab vedotin. However, there are disparities in screening and detection. The NICE scope highlights higher CC incidence and lower screening rates in deprived populations, as well as lower HPV vaccination uptake among deprived and non-white groups in the UK [63]. Health disparities associated with key demographic and socioeconomic factors were also described by Castellano et al. (2024) and Soares et al. (2024) [59, 64].

Austria lags far behind the HPV vaccination coverage rates of other countries. The HPV vaccination uptake by socioeconomic status is not reported, limiting the assessment of equity. With regard to equity in healthcare provision, Austria shows pronounced regional disparities in HPV vaccination coverage (approximately 28% in Salzburg vs around 80% in Vienna) as well as in the uptake of screening programmes, which may indirectly influence the incidence of cervical cancer and, consequently, (cost-intensive) future treatment needs [14, 22, 65, 66].

6.4 Registries and documentation of tisotumab vedotin use

österreichweites Register zum Krankheitsverlauf: KRT Österreich für Mammakarzinome und gynäkologische Tumore

anwendungsbegleitende Dokumentation zu Tisotumab vedotin: möglicherweise im KRT

Effective cancer registration in Austria relies on multiple national and regional systems, each serving distinct data-collection purposes. The National Cancer Registry primarily focuses on incidence, prevalence, and survival data and therefore does not collect information on treatment pathways, disease progression and treatment outcomes. The "Klinisches Tumorregister (KTR) Österreich" for breast cancer and gynaecological tumours, established in the early 2000s, includes participating sites across all federal states, aiming to collect, review and analyse data on breast, cervical, endometrial and ovarian cancers (results are available on request only [67]). Additional cancer registration initiatives exist at the regional level, such as the "Onkologisches Informationssystem and the Tumorzentrum Oberösterreich" [68]. In the context of this report, the KTR may provide an appropriate framework for documenting the use of tisotumab vedotin, enabling the collection of real-world data on its clinical use.

7 Development costs and public contributions

7.1 Own development costs, acquisitions and licences

Übersicht zu Entwicklungskosten

Genmab/Pfizer has not published the total amount of R&D expenses attributed to TIVDAK®. As this chapter is based entirely on publicly accessible information, the funding amounts relating to the development of tisotumab vedotin may be incomplete. Table 7-1 provides a brief summary of the key development points of tisotumab vedotin.

Table 7-1: TIVDAK® overview

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
Genmab	Genmab Seagen (a wholly-owned subsidiary of Pfizer) Pfizer	**Initial development 1999:** Licensing agreement between Genmab and Medarex **2011:** Licensing and collaboration agreement between Genmab and Seagen **2017:** Joint development programme launched by Genmab and Seagen	n.a.	n.a.

Abbreviations: n.a. ... not applicable

Basic research and clinical development

Entwicklungsgeschichte von Tisotumab vedotin

Tisotumab vedotin, marketed as TIVDAK®, is the result of a long-standing collaboration between Genmab, a Danish antibody specialist, and Seagen (fully acquired by Pfizer), a US-based pharmaceutical company. The drug's development draws on two distinct proprietary technologies: Genmab's tissue factor (TF) antibody and Pfizer's ADC platform, originally developed by Seagen prior to Pfizer's acquisition of that company in December 2023.

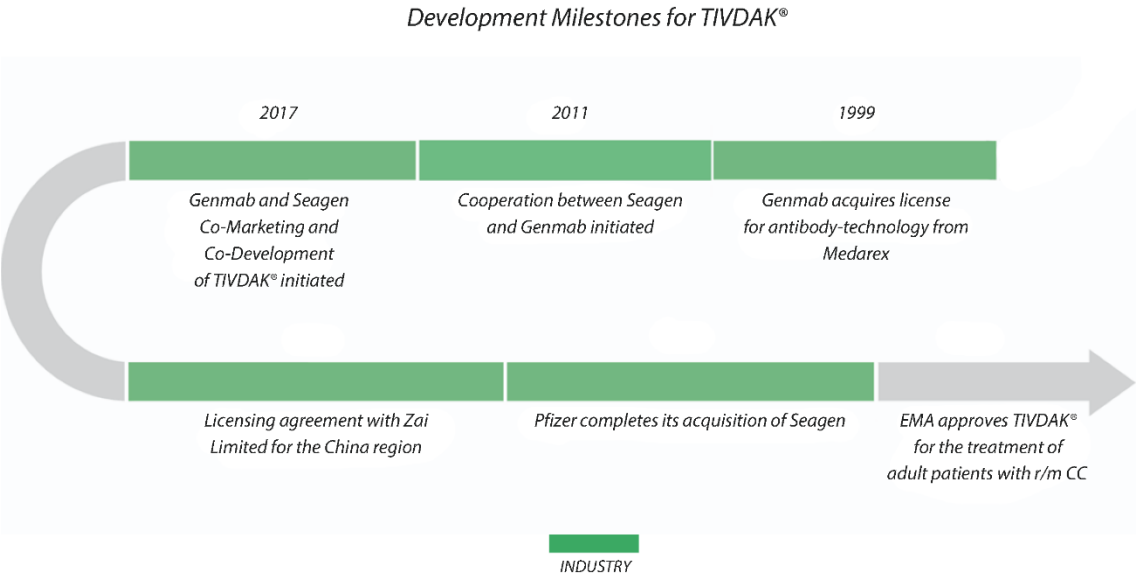


Figure 7-1: Development milestones for tisotumab vedotin

Clinical development was conducted by
Genmab (NCT02001623, NCT03245736, NCT03438396, NCT06952660, NCT03786081, NCT03657043, NCT02552121, NCT03485209, NCT04697628, NCT03913741),
Seagen (NCT02001623, NCT03245736, NCT03438396, NCT03786081, NCT03657043, NCT02552121, NCT03485209, NCT04697628, NCT03913741) and
Pfizer (NCT06952660).

Involved organisations in the clinical trials were the European Network of Gynaecological Oncological Trial Groups (NCT03438396, NCT03786081, NCT06459180), the Belgian Gynaecological Oncology Group (NCT03438396, NCT03786081) and the Gynaecologic Oncology Group (NCT03438396).

7.2 Public contributions to drug development

We were unable to find any public funding amounts associated with the development of tisotumab vedotin.

keine direkten öffentlichen Beiträge identifiziert

Company structure and financials

The collaboration between Genmab and Seagen traces back to October 2011, when Genmab and Seagen entered into a license and collaboration agreement granting Genmab rights to utilise Seagen's ADC technology in exchange for milestone payments and royalties, while also providing Seagen with an option to co-develop and co-commercialise the resulting compound. Seagen exercised this option in August 2017, formally launching the joint development programme. A joint commercialisation agreement followed in October 2020, establishing the commercial framework under which TIVDAK® would be brought to market [69].

Kooperation seit 2011: Lizenzvertrag mit Seagen (Pfizer), Option ausgeübt 2017, kommerzieller Rahmen 2020

50:50-Gewinnaufteilung in USA, Europa, China und Japan; Pfizer-Royalties in übrigen Märkten

Under the terms in effect prior to 2025, Pfizer led commercial operations in the US, Europe, and China, while Genmab co-promoted in the US and led commercial activities in Japan. Profits and costs were split equally (50:50) across the US, Europe, China, and Japan. In all other markets, Pfizer holds sole commercialisation responsibility and pays Genmab royalties ranging from the mid-teens to the mid-twenties as a percentage of aggregate net sales [30, 69].

ab Jänner 2025: Genmab übernimmt Vermarktung für Zweitlinien-Anwendung außerhalb USA/China; Pfizer bleibt alleiniger Hersteller

Effective 1 January 2025, the two companies amended their agreements, restructuring the commercial arrangement. Genmab assumed sole responsibility for the development and commercialisation of TIVDAK® in second line plus r/m CC across Europe and all regions globally, excluding the US and China. Under the revised structure, Genmab will record sales for Europe, Japan, and rest-of-world markets and will pay Pfizer royalties in the low teens on net sales in those territories. Pfizer remains solely responsible for the manufacturing of tisotumab vedotin [30].

Zai Lab-Abkommen: $ 30 Mio. Vorauszahlung, Meilensteine und Royalties für China-Region

A separate geographic partnership was announced in September 2022, when Pfizer and Zai Lab Limited entered into an exclusive collaboration and license agreement covering mainland China, Hong Kong, Macau, and Taiwan. Under this agreement, Pfizer received a $30-million upfront payment, with additional development, regulatory, and commercial milestone payments, as well as tiered royalties on net sales, all of which are shared equally with Genmab per their bilateral agreement [69].

Medarex-Lizenz von 1999: keine künftigen Meilenstein- oder Royalty-Zahlungen für Tisotumab vedotin

The underlying antibody technology used to generate the tisotumab component of tisotumab vedotin was developed using technology licensed from Medarex (now a wholly owned subsidiary of Bristol-Myers Squibb) under a 1999 agreement. Notably, tisotumab vedotin is not subject to future milestone or royalty payment obligations to Medarex under that agreement, distinguishing it from several other Genmab pipeline assets [30].

Patents

Tisotumab vedotin in den USA bis 2033 patentgeschützt

Tisotumab vedotin has a US basic product patent expiration year of 2033 [69].

8 Landscape overview

8.1 Ongoing studies on tisotumab vedotin

5 laufende klinische Studien, die Tisotumab vedotin evaluieren, davon 3 aktiv und 2 rekrutierend

Five ongoing clinical studies evaluating tisotumab vedotin were identified via ClinicalTrials.gov (see Chapter 8 in the Appendix for further details). These include three active but not recruiting:

- The innovaTV 205 study (NCT03786081), a phase 1/2 trial assessing tisotumab vedotin monotherapy and in combination with bevacizumab, pembrolizumab, or carboplatin in subjects with recurrent or stage IVB CC (estimated completion 31 March 2026).
- The innovaTV 207 study (NCT03485209), a phase 2 trial studying tisotumab vedotin to find out whether it is an effective treatment alone or with other anticancer drugs for certain solid tumours and what side effects may occur (estimated completion 31 March 2027)
- The innovaTV 301 study (NCT04697628), a phase 3 trial evaluating whether tisotumab vedotin works better than chemotherapy to treat r/m CC (estimated completion 7 May 2026).

Additionally, two studies are recruiting:

- The MK-2870-020 study (NCT06459180), a phase 3 trial to test the efficacy and safety of MK-2870 versus treatment of the physician's choice (among other tisotumab vedotin) as second-line treatment for participants with r/m CC (estimated completion 15 June 2028).
- The C5721005 study (NCT06952660), a phase 4 trial to learn about possible side effects of tisotumab vedotin, especially any side effect related to the eye (estimated completion 13 December 2028).

8.2 Treatments in development

20 Therapien in Entwicklung für r/m CC

Using the IHSI database [37], a total of 20 therapies were identified as under development for r/m CC in adults.

früheste Therapie mit ähnlicher Indikation im April 2026 erwartet

For r/m CC treatments in adults the expected EC decisions are as follows: trastuzumab deruxtecan (April 2026), lifileucel (April 2027), catequentinib (May 2027), peltopepimut-S (August 2029), adrixetinib (October 2029), neratinib (January 2030), Adrx-0706 (February 2030), Crb-701 (February 2030), sacituzumab tirumotecan (February 2030), Scg142 (November 2030), onvapegleukin alfa (July 2031), raludotatug deruxtecan (August 2031), ifinatamab deruxtecan (June 2032), Ro7502175 (July 2033), Imgn151 (July 2033). Ei-201, tipapkinogene sovacivec, prolgolimab, tiragolumab and balstilimab have no expected EC decision date.

meist vorkommende Wirkstoffgruppen sind: 7 ADCs, 3 ICIs, 3 Impfstoffen, 3 Kinaseinhibitoren

The identified therapies were grouped by drug class: seven ADCs (Imgn 151, sacituzumab tirumotecan, Crb-701, Adrx-0706, trastuzumab deruxtecan, raludotatug deruxtecan, ifinatamab deruxtecan), three ICIs (balstilimab + zalifrelimab, tiragolumab + atezolizumab , prolgolimab), three cancer vaccines (peltopepimut-s, tipapkinogene sovacivec, ei-201), three small molecule kinase inhibitors (catequentinib, adrixetinib, neratinib), one

cytokine-based therapy (onvapegleukin alfa) and one bispecific/other biologics (Ro7502175).

For details on the indication, active ingredient, NCT number, phase of clinical development, treatment line, developer company, drug class and estimated EC decision see Table 8-1 below.

Table 8-1: Landscape overview for r/m CC (sorted by treatment line)

Indication	Active ingredient	NCT Number	Phase	Treatment line	Developer	Drug class	Estimated EC decision
Prolgolimab							
Prolgolimab in combination with platinum-based chemotherapy with and without bevacizumab for first-line treatment of advanced CC in adults and the elderly	prolgolimab	NCT03912415	3	first line	Biocad	Immune Checkpoint Inhibitors (ICIs)	n.a.
Ei-201							
Ei-201 monotherapy for first-line or later treatment of incurable r/m HPV16-positive oropharyngeal cancer in adults and the elderly	Ei-201	2021-004277-31 (only EudraCT Number available)	1/2	first line or later	etherna	Cancer Vaccines	n.a.
Tipapkinogene Sovacivec							
Tipapkinogene sovacivec in combination with avelumab for first-line or later treatment of metastatic or refractory/recurrent HPV16-positive cancer in adults and the elderly	tipapkinogene sovacivec	NCT03260023	1/2	first line or later	Transgene	Cancer Vaccines	n.a.
Raludotatug deruxtecan							
Raludotatug deruxtecan monotherapy for treatment of locally advanced or metastatic solid tumour in adults and the elderly	raludotatug deruxtecan	NCT06660654	2	Above ≥1line of therapy (no more than 3)	Daiichi Sankyo	Antibody-Drug Conjugates (ADCs)	August 2031
Ifinatamab deruxtecan							
Ifinatamab deruxtecan monotherapy for the treatment of r/m solid tumour in adults and the elderly	ifinatamab deruxtecan	NCT06330064	2	Above ≥1 line of therapy (no more than 3)	Daiichi Sankyo	Antibody-Drug Conjugates (ADCs)	June 2032
Peltopepimut- S							
Peltopepimut- S in combination with cemiplimab for second-line treatment of r/m HPV16-positive, squamous cell CC in adults and the elderly who have experienced disease progression after first-line chemotherapy	peltopepimut- S	NCT04646005	2	second line	ISA Pharmaceuticals	Cancer Vaccines	August 2029
Balstilimab							
Balstilimab in combination with zalifrelimab for second-line treatment of metastatic, locally advanced, and/or unresectable CC in adults and elderly who have relapsed after a platinum-based treatment	balstilimab	NCT03894215	2	second line	Agenus	Immune Checkpoint Inhibitors (ICIs)	n.a.
Tiragolumab							
Tiragolumab in combination with atezolizumab for second-line or later treatment of r/m PD-L1-positive CC in adults and elderly following progression on or after prior systemic chemotherapy	tiragolumab	NCT04300647	2	second line or later	Hoffmann-La Roche	Immune Checkpoint Inhibitors (ICIs)	n.a.
Adrx-0706							
Adrx-0706 monotherapy for second-line or later treatment of advanced CC in adults and the elderly	Adrx-0706	NCT06036121	1	second line or later	Adcentrx Therapeutics	Antibody-Drug Conjugates (ADCs)	February 2030
Trastuzumab deruxtecan							
Trastuzumab deruxtecan monotherapy for second-line or later treatment of locally advanced or metastatic unresectable, HER2-expressing solid tumour in adults and the elderly	trastuzumab deruxtecan	NCT04482309	2	second line or later	Daiichi Sankyo	Antibody-Drug Conjugates (ADCs)	April 2026

Indication	Active ingredient	NCT Number	Phase	Treatment line	Developer	Drug class	Estimated EC decision
Lifileucel							
Lifileucel monotherapy for second-line or later treatment of r/m, or persistent CC in adults and the elderly after a non-myeloablative lymphodepletion preparative regimen	lifileucel	NCT03108495	2	second line or later	Iovance Biotherapeutics	Cell therapies	April 2027
Scg142							
Scg142 monotherapy for second-line or later treatment of advanced or metastatic HPV16- or HPV52-positive squamous cell carcinoma in adults and elderly	Scg142	NCT06505551	1/2	second line or later	SCG Cell Therapy	Cell Therapies	November 2030
Adrixetinib							
Adrixetinib in combination with pembrolizumab for the treatment of advanced CC, gastric cancer, oesophageal cancer, hepatocellular carcinoma, and gastroesophageal junction cancer in adults and the elderly	adrixetinib	NCT05438420	1/2	second line or later	Qurient	Small Molecule Kinase Inhibitors	October 2029
Onvapegleukin alfa							
Onvapegleukin alfa in combination with pembrolizumab, TransCon TLR7/8 agonist, or other anticancer therapies or as monotherapy for treatment of locally advanced or metastatic solid tumour in adults and elderly	onvapegleukin alfa	NCT05081609	1/2	second line or later	Ascendis Pharma	Cytokine-Based Therapy	July 2031
Neratinib (HER2 mutation)							
Neratinib monotherapy for the treatment of advanced HER2-mutated solid tumour in adults and the elderly	neratinib	NCT06519110	2	Above ≤2 lines	Convalife Pharmaceuticals	Small Molecule Kinase Inhibitors	January 2030
Crb-701							
Crb-701 monotherapy for third-line treatment of r/m CC in adults and the elderly who have failed platinum-containing chemotherapy and PD-1/L1 inhibitor therapy	Crb-701	NCT07230626	3	third line	Corbus Pharmaceuticals	Antibody-Drug Conjugates (ADCs)	February 2030
Catequentinib							
Catequentinib in combination with background chemotherapy for third-line or later treatment of r/m CC, endometrial cancer, fallopian tube cancer, ovarian cancer, primary peritoneal carcinosarcoma in adults and the elderly	catequentinib	NCT02584478	3	third line or later	Advenchen Laboratories	Small Molecule Kinase Inhibitors	May 2027
Sacituzumab tirumotecan							
Sacituzumab tirumotecan monotherapy for third-line treatment of r/m CC in adults and elderly previously treated with platinum doublet chemotherapy and anti-PD-1/anti-PD-L1 therapy	sacituzumab tirumotecan	NCT06459180	3	third line treatment	MSD	Antibody-Drug Conjugates (ADCs)	February 2030
Imgn151							
Imgn151 monotherapy for the treatment of recurrent CC, endometrial cancer, fallopian tube cancer, ovarian cancer, and primary peritoneal carcinosarcoma in adults and the elderly	Imgn151	NCT05527184	1	no more than 5 prior lines of therapy, with no more than 2 prior therapies since development of platinum resistance	AbbVie	Antibody-Drug Conjugates (ADCs)	July 2033
Ro7502175							
Ro7502175 in combination with atezolizumab or pembrolizumab or as monotherapy for the treatment of locally advanced or metastatic solid tumour in adults and the elderly	Ro7502175	NCT05581004	1	n.a.	Hoffmann-La Roche	Bispecific/Other Biologics	July 2033

Abbreviations: ADC … antibody drug conjugate, EC … European Commission, HER2 … human epidermal growth factor 2, HPV … human papilloma virus, ICI … immune checkpoint inhibitor, n.a. … not available/applicable, PD-L1 … programmed cell death-ligand 1, r/m CC … recurrent or metastatic cervical cancer

9 Discussion

Einordnung der Evidenz zu Wirksamkeit, Sicherheit und Versorgungskontext

This HTA evaluates the available evidence on tisotumab vedotin in adult patients with r/m CC who have progressed on or after prior systemic therapy. In addition to clinical effectiveness and safety, the assessment considers economic, organisational, and ethical aspects relevant to the potential use of this intervention within the Austrian healthcare system. The following discussion summarises the main findings of the assessment and interprets their implications for clinical practice and healthcare decision-making.

Clinical evidence and uncertainties

Pivotalstudie innovaTV 301 zeigt moderaten Überlebensvorteil von Tisotumab vedotin

The pivotal and only phase 3 RCT in this indication, innovaTV 301, demonstrated a statistically significant improvement in OS for tisotumab vedotin compared with ICC (HR 0.70; 95% CI 0.54-0.89). Median OS was prolonged by two months (11.5 vs 9.5 months). The relative reduction in the risk of death was consistent across most predefined subgroups, although the trial was not powered for definitive subgroup conclusions. In the later DCO, the HR was 0.79; however, this updated OS analysis was descriptive and not alpha-controlled and should therefore be interpreted as supportive rather than confirmatory evidence [9, 38].

begrenzte Effekte bei PFS und ORR sowie Unsicherheiten der Evidenzbasis

In contrast, the improvement in PFS was limited (median difference of approximately 1.3 month), and the ORR was higher with tisotumab vedotin but remained relatively low. The higher ORR was primarily driven by partial responses, while complete responses were rare in both treatment arms. Patient-reported outcomes did not provide conclusive evidence of an improvement in health-related QoL compared with ICC [9, 38]. The OS benefit was observed at a DCO with approximately 52% event maturity [9, 38], indicating moderate maturity of the survival data. Given the open-label design, the RoB was judged to have some concerns, which introduces additional uncertainty regarding the interpretation of the observed OS effect [42-44].

spezifisches Sicherheitsprofil mit erhöhter okulärer Toxizität

In innovaTV 301, the overall frequency of TEAEs was high in both treatment arms. Grade ≥3 TEAEs and TESAEs occurred less frequently with tisotumab vedotin than with ICC. The safety profiles differ primarily in the type of AEs observed: ocular toxicity occurred more frequently under tisotumab vedotin and requires specific preventive and monitoring measures. In the clinical trial setting, most ocular adverse reactions were low grade and considered manageable with protocol-mandated risk mitigation strategies; permanent discontinuations due to ocular toxicity were infrequent [9, 38]. According to the clinical experts consulted for this assessment, these AEs are currently perceived as less problematic in routine practice than at the time of initial introduction, as treatment teams have gained practical experience with the required prophylactic measures, monitoring procedures and management strategies [22]. Available post-marketing data from the USA, where tisotumab vedotin was introduced earlier, have not identified new safety signals and are therefore consistent with the known safety profile, thereby supporting the observations reported from the Austrian clinical experts [27].

Unsicherheiten zum Langzeitverlauf und zum Toxizitätsprofil

Nevertheless, some uncertainties remain regarding the long-term course and reversibility of ocular adverse reactions, particularly beyond the observation period of the pivotal trial, as well as regarding the consistent implementation of risk-mitigation measures across routine care settings. According to

the EPAR, long-term safety data for tisotumab vedotin are not available at present, and final safety data from the pivotal study are to be provided post-authorisation. Compared with commonly used cytotoxic regimens in this treatment line, tisotumab vedotin is associated with a different pattern of toxicity rather than a clearly reduced overall toxicity burden [9, 38].

eingeschränkte Übertragbarkeit auf Patientinnen mit reduziertem Allgemeinzustand

Further, the study population of innovaTV 301 comprised patients with ECOG performance status 0-1 and predefined prior treatment exposure. Patients with relevant ocular comorbidities or significant uncontrolled medical conditions were excluded [9, 38]. In routine care, however, patients with r/m CC may present with greater comorbidity or reduced functional status, which may influence both tolerability and treatment outcomes. The transferability of efficacy and safety results to patients with poorer performance status, therefore, remains uncertain.

begrenzte Evidenz bei ICI-vortherapierten Patientinnen

Another aspect relevant for the interpretation of the results concerns prior exposure to ICIs. In innovaTV 301, approximately 28% of patients had received prior anti-PD-(L)1 therapy [40]. Since the conduct of the trial, however, the treatment landscape for r/m CC has evolved, and ICIs are now commonly used in earlier treatment lines. According to Austrian clinical experts, most patients in routine practice are expected to have received prior immunotherapy before reaching the treatment line evaluated in the trial [22]. Subgroup analyses of innovaTV 301 suggested a generally consistent treatment effect irrespective of prior ICI exposure. Currently, there is no evidence that prior PD-(L)1 inhibitor treatment substantially affects the effectiveness of tisotumab vedotin. However, the relatively small number of patients in the ICI-pretreated subgroup limits the precision of these estimates [9, 38]. Consequently, some uncertainties remain regarding the magnitude of benefit in populations with more extensive prior exposure to ICIs.

Vergleichstherapie entspricht mit gewissen Limitationen der österreichischen Versorgungspraxis

A further aspect that may affect the interpretation of the results concerns the comparator regimen used in innovaTV 301. The control arm consisted of ICC, including gemcitabine, pemetrexed, topotecan, vinorelbine, or irinotecan. Among the 239 treated patients in the ICC arm, gemcitabine (45.6%) and pemetrexed (33.5%) were the most frequently administered agents, whereas topotecan was used in only 7.9% of patients [40]. According to Austrian clinical experts, treatment patterns in routine practice may partially differ, with topotecan reportedly used more frequently in this setting. While all comparator treatments included in the trial are guideline-consistent options for this patient population, differences in the distribution of chemotherapy agents may influence the direct applicability of the trial results to specific national treatment patterns [22]. Further considerations regarding the transferability of the results relate to the patient characteristics in innovaTV 301. Most patients were treated in later therapy lines, and both squamous cell carcinoma and adenocarcinoma histologies were included. Prior bevacizumab exposure was reported in a relevant proportion of patients and was used as a stratification factor. The study population comprised both patients with recurrent and metastatic disease; however, detailed stage-specific analyses were limited [9].

While subgroup analyses did not indicate major differences in treatment effect across these characteristics, the study was not powered to detect such differences. In routine clinical practice, variations in prior treatment sequences, histological subtypes, and disease presentation may influence treatment decisions and outcomes. These factors should therefore be considered when interpreting the applicability of the results to the Austrian healthcare setting.

Economic aspects

Unterschiede der ICER-Schätzungen durch Preisannahmen und Modellierung

The available economic evidence suggests that the cost-effectiveness of tisotumab vedotin is highly dependent on the assumed drug price. The analysis conducted for Spain estimated an ICER of €35,600 per QALY gained under the assumption that the price of tisotumab vedotin equals that of cemiplimab [45], whereas the US analysis reported an ICER of $839,108 per QALY gained using Medicare-based price estimates [46]. These differences can largely be explained by variations in key modelling assumptions between the studies, particularly the assumed drug acquisition costs. Overall, both analyses indicate that the cost-effectiveness of tisotumab vedotin is highly sensitive to the assumed drug price, suggesting that price adjustments would be required for cost-effectiveness under commonly applied thresholds.

Kosten-Effektivität stark vom Preis abhängig; begrenzte Übertragbarkeit auf den österreichischen Kontext

Sensitivity analyses in both studies demonstrated that the ICER increases substantially with higher drug acquisition costs, indicating that the economic value of tisotumab vedotin is primarily price-driven. However, both studies have methodological limitations, including the absence of trial-based utility data, simplified modelling of adverse events, and reliance on price assumptions rather than real market prices. In addition, differences in healthcare systems and treatment pathways limit the transferability of these results to the Austrian healthcare context.

geschätzter Budgetimpact von ca. € 1,63 Mio. pro Jahr bei 45 Patientinnen

As no BIA was submitted by the MAH for Austria, a self-conducted BIA was performed based on literature-derived parameters complemented by expert opinions. The introduction of tisotumab vedotin is estimated to approximately triple treatment costs in this therapy line. Assuming approximately 45 eligible patients per year and complete substitution of currently used chemotherapy regimens by tisotumab vedotin, the estimated additional expenditure amounts to approximately €1.63 million per year, totalling €4.89 million over a 3-year period.

Schätzung mit Unsicherheiten bei Patientinnenzahl und Kostendaten

However, the reliability of these estimates is limited by several structural uncertainties. The analysis relied on literature-based epidemiological data and expert judgement to estimate the eligible population, as routine Austrian data for this treatment line are lacking. Given the small size of the target population, the actual number of eligible patients may therefore deviate from the assumed average of 45 per year. In addition, the analysis was conducted from a healthcare payer perspective and included only direct medical costs. Further methodological limitations of the BIA are described in Chapter 5.2.

International HTA evaluations of tisotumab vedotin

begrenzte internationale HTA-Evidenz und unterschiedliche methodische Interpretation

At the time of writing this report, only a limited number of international HTAs of tisotumab vedotin have been published. These evaluations illustrate that the interpretation of the available evidence may differ depending on the methodological framework and the definition of the relevant patient population.

IQWiG/G-BA-Bewertung (Deutschland): Zusatznutzen nicht belegt wegen abweichender Vergleichstherapie und Subgruppenanalyse

In Germany, the early benefit assessment conducted by the IQWiG and the subsequent decision by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) concluded that an additional benefit of tisotumab vedotin could not be established. In the German assessment, the patient population was stratified by prior PD-(L)1 therapy, leading to different comparators for the respective subgroups. For patients without prior immunotherapy, cemiplimab was defined as the appropriate comparator; however, no comparative data were available for this subgroup. For patients previously treated with PD-(L)1 inhibitors, chemotherapy was defined as the comparator. Although

the innovaTV 301 trial compared tisotumab vedotin with investigator's choice chemotherapy, the submitted analyses did not correspond to the subgroup definitions applied in the German assessment. Consequently, the available evidence was considered insufficient to demonstrate an additional benefit [49, 70].

HAS-Bewertung (Frankreich): geringer Zusatznutzen (ASMR IV) gegenüber Monochemotherapie

In France, the Haute Autorité de Santé (HAS) issued a favourable reimbursement opinion for tisotumab vedotin and assigned an important medical benefit. Compared with monochemotherapy, the therapy was considered to provide a minor additional clinical benefit (l'amélioration de service médical rendu, ASMR IV). This judgement was based on the statistically significant improvements in OS and PFS observed in the innovaTV 301 study. However, HAS also highlighted several limitations, including the absence of conclusive QoL results, limited transposability to current clinical practice due to the low proportion of patients previously treated with PD-(L)1 inhibitors, and a higher incidence of specific toxicities such as conjunctivitis and peripheral sensory neuropathy [71].

NICE-Bewertung (UK): vorläufige Nicht-Empfehlung wegen unsicherer Kosteneffektivität

In the UK, tisotumab vedotin is currently undergoing appraisal by NICE. In the draft guidance issued during the consultation phase, the therapy was not recommended for routine use in the NHS. While the appraisal committee acknowledged the observed survival benefit, substantial uncertainty remained in the economic evaluation. In particular, the long-term survival extrapolation based on immature trial data, assumptions about the duration of the treatment effect, and uncertainties about subsequent therapies were identified as key drivers of the model results. As a consequence, the ICER for tisotumab vedotin was estimated to exceed the range typically considered cost-effective by NICE [72]. Final guidance has not yet been published.

Organisational aspects and patient perspectives

tagesklinische Anwendung, jedoch mit zusätzlichem Koordinationsbedarf

From an organisational perspective, tisotumab vedotin can be administered in a hospital daycare setting within existing oncology structures. According to the consulted Austrian clinical experts, the associated resource use is considered manageable. Preventive ocular measures and ophthalmologic assessments prior to treatment initiation are required but were regarded as feasible in routine care [22]. Nevertheless, consistent implementation of these measures and coordination between oncology and ophthalmology services remain necessary to ensure safe use. Treatment decisions are typically embedded in interdisciplinary tumour board processes. The 3-week administration interval may represent a practical advantage compared with some chemotherapy regimens.

Patientinneninput weist auf hohe Krankheitslast hin, jedoch sehr eingeschränkte Evidenz (n=2)

Patient input was collected through structured questionnaires completed by two patients with r/m CC who received tisotumab vedotin as part of their therapy. Due to the very small number of respondents, the findings are highly limited and not generalisable. Nevertheless, the responses indicate a substantial burden of disease affecting several domains of QoL, including physical symptoms, psychological distress, loss of independence, and reduced social participation. Experiences with tisotumab vedotin were described as manageable after an initial adjustment period and with appropriate supportive measures.

Other aspects

industriegetriebene Forschung und Entwicklung von Tisotumab vedotin

Tisotumab vedotin was developed through a collaboration between Genmab and Seagen (now part of Pfizer), combining Genmab's TF-targeting antibody with Seagen's ADC technology platform. The development was primarily industry-led, and public funding contributions to the early development of this therapy are not readily identifiable in the published literature [30, 69].

laufende Studien; Phase-4-Studie zur okulären Sicherheit

Tisotumab vedotin is currently being investigated in five ongoing clinical trials across phases 1/2 to 4, with estimated completion dates between 2026 and 2028. One phase 4 study (NCT06952660) specifically evaluates ocular AEs in patients with r/m CC, reflecting the clinical relevance of ocular toxicity associated with this ADC. Other studies are assessing the efficacy and safety of tisotumab vedotin as monotherapy or in combination with other anticancer therapies across different solid tumours [37].

sieben Therapien in Entwicklung, die direkte Mitkonkurrierende sind

Among approximately 20 therapies currently in development for r/m CC, seven belong to the same drug class as tisotumab vedotin, namely ADCs, including IMGN-151, sacituzumab tirumotecan, CRB-701, ADRX-0706, trastuzumab deruxtecan, raludotatug deruxtecan, and ifinatamab deruxtecan. As ADCs represent an expanding therapeutic class in oncology, the future availability of additional agents with potentially improved efficacy or safety profiles could influence the positioning of tisotumab vedotin within the treatment landscape. In particular, differences in safety profiles, such as the occurrence of ocular AEs, may become clinically relevant when comparing agents within this class. Several of these ADCs are currently in late-stage clinical development, with regulatory submissions anticipated over the coming years [37].

Conclusion

nachweisbarer Überlebensvorteil bei begrenzter Evidenzbasis

The available evidence from the pivotal innovaTV 301 trial suggests that tisotumab vedotin is associated with an overall survival benefit compared with ICC in patients with r/m CC after prior systemic therapy. However, the primary OS result is based on an interim analysis with approximately 52% event maturity, and the later OS update is descriptive and not alpha-controlled. Therefore, the magnitude and robustness of the treatment effect remain uncertain.

Unsicherheiten hinsichtlich des patientinnenrelevanten Zusatznutzens

The safety profile is characterised by specific adverse events, particularly ocular toxicities, which require targeted risk mitigation and monitoring but are considered manageable. Evidence on health-related QoL is inconsistent and does not allow for a conclusive assessment of patient-relevant benefit. The transferability of the results to the Austrian healthcare setting is limited due to differences between the trial population and patients treated in routine clinical practice. In the absence of real-world evidence, the effectiveness of tisotumab vedotin in routine care remains uncertain.

ökonomische Einstufung von Tisotumab vedotin für den österreichischen Kontext limitiert

From an economic perspective, the available evidence suggests that the cost-effectiveness of tisotumab vedotin is strongly influenced by assumptions about drug prices. For Austria, the absence of manufacturer-submitted economic analyses and the lack of an Austrian list price limit the interpretability of cost-effectiveness estimates. A self-conducted BIA with the assumption of a price for parallel import of €2,481 suggests additional expenditures of approximately €1.63 million per year, assuming around 45 eligible patients annually who all switch from chemotherapy to tisotumab vedotin treatment, although this estimate is subject to uncertainty.

Evidenzlage mit relevanten Unsicherheiten für Österreich

Taken together, tisotumab vedotin represents a targeted treatment option in a disease stage with limited therapeutic alternatives and poor prognosis. While the available evidence suggests a survival benefit of uncertain magnitude compared with chemotherapy, relevant uncertainties remain due to the robustness of the OS results. In addition, relevant uncertainties persist regarding long-term safety and the economic implications within the Austrian healthcare context.

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List of abbreviations

ADC	antibody-drug-conjugate
AE	adverse event
anti–PD-(L)1	programmed death (ligand) 1
AGO	Arbeitsgemeinschaft für Gynäkologische Onkologie
ATC	Anatomical Therapeutic Chemical classification system
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BIA	budget impact analysis
BSC	best supportive care
CC	cervical cancer
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
DCE	discrete choice experiment
DCO	data cut-off
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
EPAR	European Public Assessment Report
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire
ESGO	European Society of Gynaecological Oncology
ESMO-MCBS	European Society for Medical Oncology-Magnitude of Clinical Benefit Scale
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
FDA	US Food and Drug Agency
FIGO	Federation of Gynaecology and Obstetrics
FSFI	Female Sexual Function Index
HCP	health care providers
HPV	human papillomavirus
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICC	investigator's choice chemotherapy
ICD	International Classification of Diseases
ICI	immune checkpoint inhibitor
ICER	incremental cost effectiveness ratio
IHSI	International Horizon Scanning Initiative
INN	international non-proprietary name
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITT	intention-to-treat
IV	intravenous
KTR	Klinisches Tumorregister
MAH	marketing authorisation holder
MMAE	Monomethyl Auristatin E
NCCN	National Comprehensive Cancer Network
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PPRI	Pricing and Reimburse
PRIME	priority medicines
PRO	patient-reported outcomes
QALY	quality-adjusted life years
QoL	quality of life
PPRI	Pricing and Reimbursement Initiative
RECIST	Response Evaluation Criteria In Solid Tumors
ROB	risk of bias
r/m	recurrent or metastatic
RCT	randomised controlled trial
SoC	standard of care
TEAE	treatment-emergent adverse event
TE SAE	treatment-emergent serious adverse event
TF	tissue factor
TNM	tumour nodes metastases

TTR ..... time to response

WHOQOL ..... World Health Organization Quality of Life

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH