HTA Austria
Austrian Institute for Health Technology Assessment GmbH

# Tislelizumab (Tevimbra®)

## with chemotherapy for the first-line treatment of HER-2-negative locally advanced unresectable or metastatic gastric/gastroesophageal junction adenocarcinoma

## General information [1]

| INN | ® | | ATC Code | Substance class | Type of indication [1] |
|---|---|---|---|---|---|
| Tislelizumab | Tevimbra® | Beone Medicines Ireland Limited (MAH) | L01FF09 | Antineoplastic agents | Type II variation (extension of indication) |

| Mechanism of action [2] | Dosing & administration [2] | Setting |
|---|---|---|
| Tislelizumab is a humanised immunoglobulin G4 (IgG4) variant monoclonal antibody against PD-1, binding to the extracellular domain of human PD-1. It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signalling and enhancing the functional activity in T-cells in in vitro cell-based assays. | The recommended dose of tislelizumab is 200 mg administered by intravenous (IV) infusion once every 3 weeks, in combination with chemotherapy. | ☒ Hospital<br>☐ Interface between hospital and outpatient sector<br>☐ Outpatient sector |

### Indication [2]

Tevimbra®, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor (HER)-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score[2] ≥ 5%.

| EMA approval status [1, 2, 4] | FDA approval status [5] |
|---|---|
| ☒ **Approved for this indication:**<br>✓ Positive CHMP opinion: 18.10.2024<br>✓ EC approved: 27.11.2024<br>☒ **Initial marketing authorisation issued:** 15.09.2023<br>☒ **Approved for other indications:** Tislelizumab is a cancer medicine used to treat:<br>❖ Non-small cell lung cancer (NSCLC)<br>❖ Small cell lung cancer (SCLC)<br>❖ Gastric or gastroesophageal junction adenocarcinoma<br>❖ Oesophageal squamous cell carcinoma (OSCC)<br>❖ Nasopharyngeal carcinoma (NPC) | ☒ **Approved for this indication:** Tevimbra® is indicated in combination with platinum and fluoropyrimidine-based chemotherapy in adults for the first-line treatment of unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours express PD-L1 (≥1).<br><br>☒ **Approved for other indications:** Tevimbra® is indicated:<br>❖ OSCC |

## Disease

| Description [6] | Prevalence & incidence [7] | Mortality [8] |
|---|---|---|
| **Gastric cancer** emerges in the proximal sections of the stomach (subcardial), in the middle third (fundus and corpus) and in the distal stomach (antrum). It is one of the more common malignant diseases. Men are affected twice as often as women.<br>The patient's prognosis is primarily determined by the stage, but also by histology, general condition and comorbidity. In metastatic stages, the treatment approach is palliative.<br>Risk factors are genetic (Lynch syndrome, Peutz-Jeghers syndrome, first-degree relatives with gastric cancer, male gender, blood group A) and/or acquired (Helicobacter pylori infection of the gastric mucosa, | Austria, 2023:<br>❖ 1,237 persons were newly diagnosed with gastric cancer.<br>❖ The age-standardised incidence rate for gastric cancer was 17.9/100,000 in men and 8.8/100,000 in women.<br>❖ 465 persons were newly diagnosed with oesophageal cancer.<br>❖ The age-standardised incidence rate for oesophageal cancer was 8.2/100,000 in men and 2.0/100,000 in women. | Austria, 2023:<br>❖ 705 patients died from gastric cancer.<br>❖ The age-standardised mortality rate for gastric cancer was 10.2/100,000 in men and 5.1/100,000 in women.<br>❖ 394 patients died from oesophageal cancer.<br>❖ The age-standardised mortality rate for oesophageal cancer was |

[1] New indication/extension to an existing indication/first-in-class.
[2] The TAP scoring system is measured as the percentages of the PD-L1-positive tumour cells plus immune cells are divided by the tumour area, which is occupied by all viable tumour cells and the tumour-associated stroma containing tumour-associated immune cells [3].

| | | |
|---|---|---|
| Epstein-Barr virus infection of the gastric mucosa, inhalative tobacco use, atrophic gastritis, partial gastrectomy, Ménétrier's disease).<br>Early gastric carcinomas are generally asymptomatic; in locally advanced or metastatic carcinomas, the following symptoms may be observed, including dysphagia, dyspepsia, recurrent vomiting, loss of appetite, early feeling of satiety, weight loss, signs of gastrointestinal bleeding, and epigastric pain.<br><br>**GEJ cancer** is a subtype of oesophageal cancer. Common risk factors are obesity and gastro-oesophageal acid reflux. Symptoms are similar to those of gastric cancer. | In patients with gastric cancer, approx. 50 % have a disease that extends beyond locoregional confines at the time of presentation [9]. GEJ cancers often present as advanced, unresectable, or metastatic disease. Approx. 80% of advanced gastric and GEJ cancers are HER2-negative [10]. In the RATIONALE-305 trial, 55% of patients had a TAP score ≥5% [11].<br><br>Taking these numbers into account, approx. 272 and 102 new patients with gastric and GEJ cancer, respectively, are expected in Austria per year[3]. | 7.4/100,000 in men and 1.5/100,000 in women. |

## Current treatment

The algorithms for first-line treatment of advanced gastric cancer and advanced adenocarcinoma of the oesophagus, as recommended by Onkopedia, are provided in the Appendix below [6, 12].

## Evidence

| Trial name<br>NCT number | Trial characteristics | Population size (n) | Intervention (I) | Control (C) | Follow-up | Treatment duration (I vs. C) |
|---|---|---|---|---|---|---|
| RATIONALE-305 [11]<br>NCT03777657 | randomised, double blind, placebo-controlled, phase 3 | 1,657 (1:1) | tislelizumab 200 mg IV<br>every 3 weeks in combination with chemotherapy[4] | placebo IV every 3 weeks in combination with chemotherapy[5] | 7.9 months at the interim analysis and 24.6 months at the final analysis | 5.9 vs. 5.7 months |

| Main efficacy outcomes (I vs. C) | Main safety outcomes (I vs. C) |
|---|---|
| **Efficacy in population with PD-L1 TAP score ≥5%, final analysis data**<br>Median OS: 16.4 months (95% CI 13.6 to 19.1) vs. 12.8 months (12.0 to 14.5); stratified hazard ratio (HR) 0.71 (95% CI 0.58 to 0.86)<br>Median PFS: 7.2 months (5.8 to 8.4) vs. 5.9 months (5.6 to 7.0); HR 0.68 (0.56 to 0.83)<br>**Efficacy in intention-to-treat population, final analysis data**<br>Median OS: 15.0 months (95% CI 13.6 to 16.5) vs. 12.9 months (12.1 to 14.1), stratified HR 0.80 (95% CI 0.70 to 0.92); P=0.001<br>OS rate at 18 months: 42% vs. 33%<br>OS rate at 24 months: 33% vs. 23%<br>Investigator assessed PFS: improved in the intervention group, HR 0.78 (0.67 to 0.90)<br>**Patients with a PD-L1 TAP score of <5%:**<br>Median OS: 14.1 months (95% CI 11.9 to 15.6) vs. 12.9 months (11.3 to 14.7); HR of 0.92 (95% CI 0.75 to 1.13) | **TRAEs:** 97% vs. 96%<br>**TRAEs ≥ grade 3** : 54% VS: 50%<br>**Serious TRAES** : 23% vs. 15%<br>**TRAEs leading to treatment discontinuation** : 16% vs. 8%<br>**TRAEs leading to death** : 1% vs. <1%<br>**Immune-mediated AEs ≥grade 3**: 8% vs. 2% |

**Patient-reported outcomes [13]**

- Health-related quality of life (HRQoL) was assessed by using EORTC QLQ-C30 and EORTC QLQ-STO22.
- A mixed model for repeated measures was used for PRO endpoints at treatment cycles 4 and 6, and time to deterioration was analysed.
- Patients in the tislelizumab arm had improved outcomes over those in the placebo arm in least-squares (LS) mean change from baseline to cycle 6 for QLQ-C30 global health status/quality of life (GHS/QoL) (LS mean difference, 2.52), physical functioning (2.46), fatigue (–3.01), and STO22 index score (–1.62) as well as maintenance of upper gastrointestinal symptoms (–1.74) and pain/discomfort (–1.88).
- Patients receiving tislelizumab plus chemotherapy had a lower risk for deterioration of GHS/QoL (HR 0.77), physical functioning (0.72), STO22 index score (0.64), pain/discomfort (0.74), and upper gastrointestinal symptoms (0.73).

**Limitations**

- No independent review committee assessment of tumour responses was conducted. As the investigators and site staff were blinded to group assignment and PDL1 expression, however, the potential for bias in investigator-assessed responses using standard criteria was expected to be minimal by the authors.

[3] Of note, these numbers are based on estimates; verification by clinical experts is required.
[4, 3] Investigator's choice of oxaliplatin and capecitabine, or cisplatin and 5-fluorouracil.

| ESMO-MCBS version 1.1 [14, 15] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Scale | Int. | Form | MG ST | MG | HR (95% CI) | Score calculation | PM | Toxicity | QoL | AJ | FM |
| Original [15] | NC | 2a | ≥12 months vs. ≤24 months | OS: +3.6 months | 0.71 (0.58-0.86) | HR≤0.70 AND gain ≥3-<5months | 3 | - | reviewed, but not qualified for an ESMO-MCBS credit | - | **3** |
| Adapted | NC | 2a | ≥12 months vs. ≤24 months | OS: +3.6 months | 0.71 (0.58-0.86) | HR≤0.70 AND gain ≥3-<5months | 3 | - | No significant improvements were observed throughout all cycles (limited to 2 cycles). | - | **3** |

| Risk of bias - RCT [16, 17] | | | | | |
|---|---|---|---|---|---|
| Adequate generation of randomisation sequence | Adequate allocation concealment | Blinding | Selective outcome reporting unlikely | Other aspects increasing the RoB | Risk of bias |
| yes<br>low risk | yes<br>low risk | yes<br>low risk | yes<br>low risk | yes[6]<br>high risk | **high risk** |

| Ongoing trials | | |
|---|---|---|
| NCT number | Description | Estimated completion date |
| NCT06871527 | Fruquintinib Combined With Tislelizumab and FOLFOX as First-Line Treatment For Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma: A Single-centre, Open-label, Phase Ib/II Clinical Study | 12/28 |
| NCT06206733 | A Phase III Study Evaluating the Efficacy and Safety of ASKB589 Combined With CAPOX and PD-1 Inhibitor as First-Line Treatment in Claudin18.2 Positive Patients With Unresectable Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma. | 12/28 |

| HTA reports | |
|---|---|
| Institution | Title |
| G-BA & IQWiG | Finished: No additional benefit has been proven [18, 19] |
| NIHR | Tislelizumab with chemotherapy for previously untreated unresectable or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma [20] |

## Costs

| Costs per patient per | | Costs for expected patient population per | | Additional costs categories | |
|---|---|---|---|---|---|
| Cycle | Year | Cycle | Year | Diagnostics | Monitoring |
| | | Based on an estimated number of 374 patients per year [7] | | | |
| €7,542.00<br><br>Tevimbra® concentrate for solution for infusion 100mg/10ml= € 3,771.00 (ex-factory price) | € 130,727.90 | € 2,820,708.00 | €48,892,234.60 | PD-1 status testing: should be assessed by a CE-marked IVD with the corresponding intended purpose. | ■ Regular testing of: liver function, kidney function tests, radiographic imaging tests<br>■ Regular blood tests to monitor blood sugar and hormone levels |

[6] The funder had a role in study design, data collection, data analysis, data interpretation and writing of the clinical study report, and provided medical writing support.

[7] A limitation of this cost estimation is the uncertainty regarding the actual number of patients eligible for the approved indication in Austria, as well as the lack of data on how many patients would receive alternative therapies.

| | | | | | |
|---|---|---|---|---|---|
| | | | | | ■ AEs and immune-mediated AEs<br>■ Haemophagocytic lymphohistiocytosis<br>■ Infusion-related reactions |
| | | | | Additional medication | |
| | | | | ■ Pre-medication: Corticosteroids<br>■ Chemotherapy | |

## Other aspects and conclusions

- In October 2024, the CHMP adopted a new indication for Tevimbra®, in combination with platinum and fluoropyrimidine-based chemotherapy, for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic G/GEJ adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%. This indication is also approved by the FDA.
- RATIONALE-305 (NCT03777657) is a randomised, double blind, placebo-controlled, phase 3 study, evaluating the efficacy and safety of tislelizumab added to chemotherapy as first-line (primary) treatment for advanced G/GEJ adenocarcinoma compared with placebo plus chemotherapy. Eligible patients were aged ≥18 years, had HER2-negative locally advanced, unresectable or metastatic disease and did not receive previous systemic therapy for advanced disease.
- The primary endpoint was OS, both in patients with a PD-L1 TAP score of ≥5% and in all randomised patients. Results showed a median OS of 16.4 months (95% CI 13.6 to 19.1) vs. 12.8 months (12.0 to 14.5); stratified hazard ratio (HR) 0.71 (95% CI 0.58 to 0.86).
- Analysis of HRQoL indicates an improvement; however, results were not consistent throughout all treatment cycles.
- RATIONALE-305 data is limited due to the lack of an independent review committee assessment of tumour responses.
- The original and adapted ESMO-MCBS were applied, resulting in a final adjusted magnitude of clinical benefit of 3 each.
- Due to the extensive involvement of the sponsor, the risk of bias was considered high.

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**Abbreviations**: AE=adverse event, AJ=adjustment, C=comparator, CDA-AMC=Canada´s Drug Agency – L´Agence des médicaments du Canada, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DoR=duration of response, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ES-SCLC=extensive-stage small-cell lung cancer, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, EU=European Union, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, G/GEJ=gastric, gastrooesophageal junction, Her=human epidermal growth factor receptor, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, IgG=immunoglobulin G, Int.=intention, ITT=intention-to-treat, IV=intravenous, LS=least square, MAH=marketing authorisation holder, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health Care Excellence, NSCLC=non-small-cell lung cancer, OS=overall survival, OSCC=oesophageal squamous cell carcinoma, PD-1=programmed cell death protein 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SoC=standard of care, ST=standard treatment, TAP=tumour area positivity, TRAE=treatment-related adverse event

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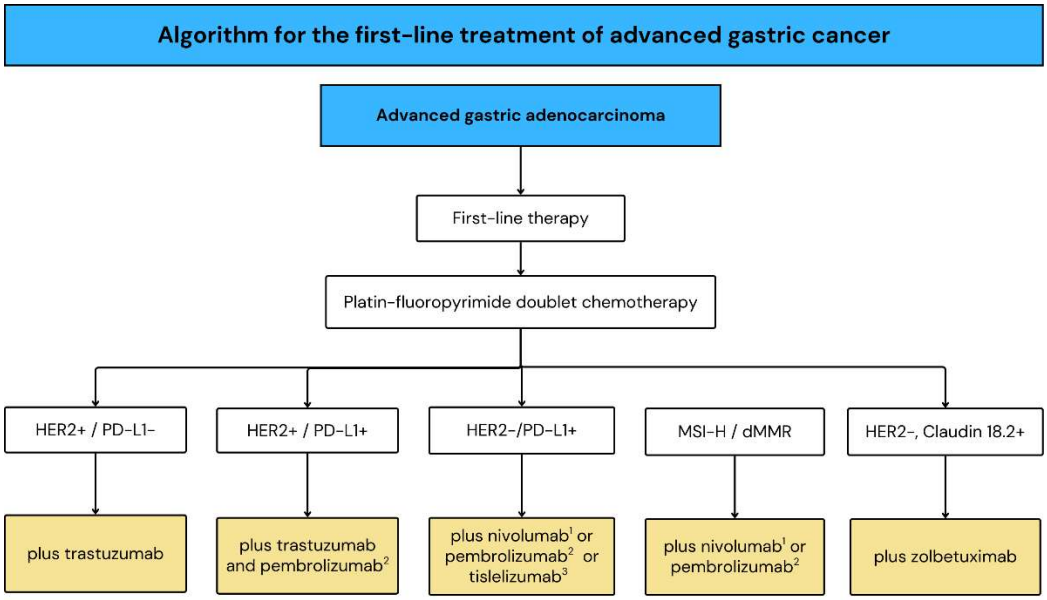
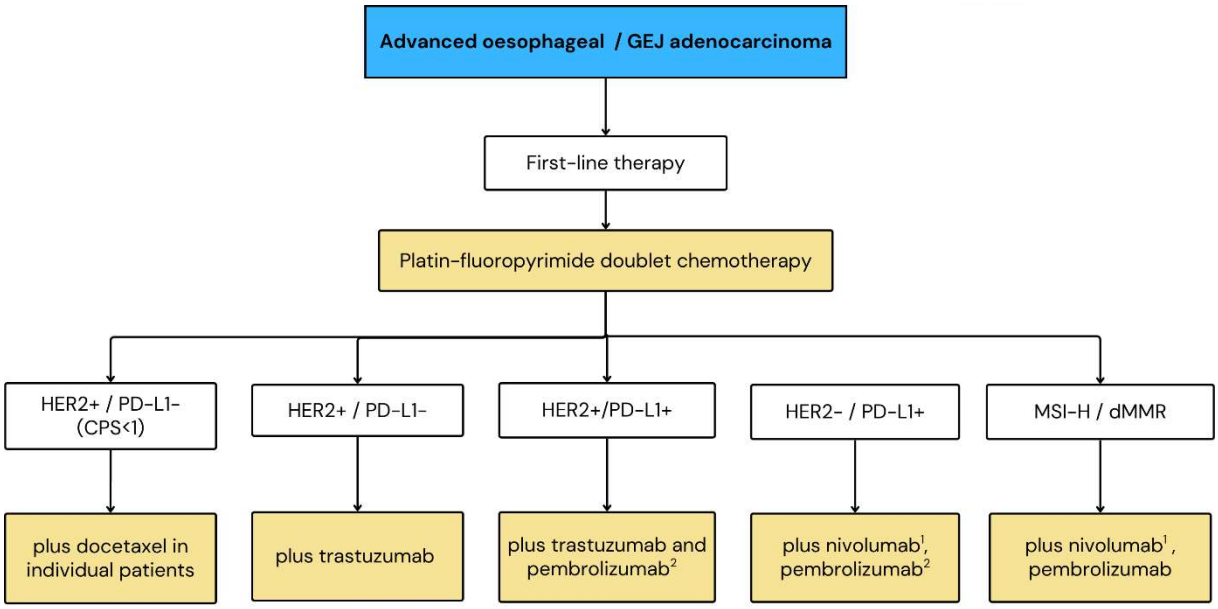
## Appendix [6, 12]:




*1 Nivolumab approved in Europe for PD-L1 CPS ≥ 5 according to Checkmate-649 study;*
*2 Pembrolizumab approved in Europe for adenocarcinoma of the esophagus in PD-L1 CPS ≥ 10 according to Keynote 590 study and for HER2 negative and HER2 positive adenocarcinoma of the stomach and esophago-gastric junction in PD-L1 CPS ≥ 1 according to Keynote 859 study and Keynote 811 study;*
*3 Tislelizumab approved in Europe for adenocarcinoma of the stomach and esophago-gastric junction with PD-L1 TAP ≥ 5%*
*Abbreviations: dMMR=deficient mismatch repair, HER= human epidermal growth factor, MSI-H=Microsatellite instability-high, PD-L1=programmed death protein ligand-1,*




*Therapy with non-curative intention*

*[1] Nivolumab is approved in Europe for PD-L1 CPS ≥ 5 based on results of the Checkmate-649 study;*
*[2] Pembrolizumab is approved in Europe for adenocarcinomas of the esophagus with PD-L1 CPS ≥ 10 based on the KEYNOTE -590 study and for HER2-negative and HER2-positive adenocarcinomas of the stomach and esophago-gastric junction with PD-L1 CPS ≥ 1 based on the KEYNOTE 859 study and KEYNOTE 811 study.*
*Abbreviations: dMMR=deficient mismatch repair, HER= human epidermal growth factor, MSI-H=Microsatellite instability-high, PD-L1=programmed death protein ligand-1*