HTA Austria
Austrian Institute for Health Technology Assessment GmbH

Tislelizumab (Tevimbra®)

with platinum-based chemotherapy for the first-line treatment of unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma

General information [1]

INN	®		ATC Code	Substance class	Type of indication
Tislelizumab	Tevimbra®	Beone Medicines Ireland Limited (MAH)	L01FF09	Antineoplastic agents	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.	Tislelizumab 200 mg is administered IV once every 3 weeks, in combination with chemotherapy	☒ Hospital ☐ Interface between hospital and outpatient sector ☐ Outpatient sector

Indication [2]

Tislelizumab, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OESCC) whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.

EMA approval status	FDA approval status [3]
☒ **Approved for this indication:** On 17 October 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Tevimbra®. The CHMP adopted a new indication to extend the use of Tevimbra® to patients with previously untreated OESCC as mentioned above [4]. ☒ **Approved for other indications: Tevimbra® is indicated** ✓ in combination with pemetrexed and platinum-containing chemotherapy, for the first-line treatment of adult patients with non-squamous NSCLC whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have: ▪ locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or ▪ metastatic NSCLC. ✓ in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of adult patients with squamous NSCLC who have: ▪ locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or ▪ metastatic NSCLC. ✓ as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving tislelizumab. ✓ in combination with etoposide and platinum chemotherapy, for the first-line treatment of adult patients with extensive-stage SCLC. ✓ 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 gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a TAP score ≥ 5%. ✓ as monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic OSCC after prior platinum-based chemotherapy. ✓ in combination with gemcitabine and cisplatin, for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma [2].	☒ **Approved for this indication:** Tevimbra® in combination with platinum-containing chemotherapy for the first-line treatment of adults with unresectable or metastatic OESCC whose tumours express PD-L1[1]. ☒ **Approved for other indications: Tevimbra® is indicated** ✓ as a single agent in adults with unresectable or metastatic OESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. ✓ in combination with platinum and fluoropyrimidine-based chemotherapy in adults for the first line treatment of unresectable or metastatic HER2-negative G/GEJ whose tumours express PD-L1 (≥1).

[1] Of note, no TAP score value is specified within the FDA approval.

Disease

Description	Prevalence & incidence	Mortality
OESCC is a type of oesophageal carcinoma that can affect any part of the oesophagus, but is usually located in the upper or middle third [5]. The average age of onset is between the ages of 60 and 70 years, and it occurs more frequently in males. Smoking and alcohol are major risk factors. Patients with advanced thoracic or cervical oesophageal carcinoma usually present with progressive dysphagia and weight loss. As OESCC is usually diagnosed at an advanced disease stage, the overall prognosis is poor, with an overall 5-year survival of between 10-20%. In patients treated with curative intent the cure rate currently approaches 40% [5, 6].	In Austria, in 2023, 465 people were newly diagnosed with oesophageal cancer. The age-standardised incidence rate[2] was 8.2/100,000 in men and 2.0/100,000 in women [7]. Assuming that OSCC accounts for 90% cases of OC [8], approx. 419 newly diagnosed patients with OSCC are expected per year.	The absolute number of deaths associated with oesophageal cancer in 2023 in Austria was 394, of which 317 occurred in men and 77 in women. The age-standardised mortality rate[3] was 7.4 per 100,000 men and 1.5 per 100,000 women [9].

Current treatment

For the **first-line treatment of OESCC in stage IV, the guideline recommends the following [10]:**

- The treatment is palliative, with non-curative intention.
- Platinum-based chemotherapy (Platinum / Fluoropyrimidine (5-Fluorouracil + Folinic Acid or Capecitabine)) remains the treatment of choice despite little evidence.
- For TPS < 1, a combination chemotherapy of cisplatin and 5-FU is considered standard. The addition of EGFR antibodies (panitumumab) does not improve the response.
- In adults with PD-L1-positive tumours, a combination of chemotherapy and checkpoint inhibitor or immunotherapy alone with dual checkpoint inhibition can be used followingly:
  - for tumours expressing PD-L1 with a CPS ≥10 (combined positive score), pembrolizumab in combination with chemotherapy,
  - for tumours with PD-L1 and TPS ≥1% (tumour proportion score, i.e. the ratio of PD-L1-positive stained tumour cells in relation to all vital tumour cells), recommendations include nivolumab in combination with chemotherapy or as a so-called double checkpoint blockade (nivolumab + ipilimumab)
- Checkpoint inhibitors are approved either in combination with chemotherapy (pembrolizumab, PD-L1 CPS ≥ 10, nivolumab PD-L1 TPS ≥ 1%) or as a so-called double checkpoint blockade (nivolumab + ipilimumab, PD-L1 TPS ≥ 1%) in the first line.
- The algorithm for the first-line treatment of OSCC in stage IV recommended by the guideline is shown in the Appendix [10].

Evidence [11, 12]

Trial name NCT number	Trial characteristics	Population size (n)	Intervention (I)	Control (C)	Follow-up (I vs. C)	Treatment duration/ cycles
RATIONALE-306 NCT03783442	multi-regional, randomized, placebo-controlled, double-blind phase III study	649 (1:1)	tislelizumab IV 200 mg once every 3 weeks + investigator-chosen chemotherapy doublet (platinum agent + fluoropyrimidine/ capecitabine/paclitaxel)	placebo IV 200 mg once every 3 weeks + investigator-chosen chemotherapy doublet (platinum agent + fluoropyrimidine/ capecitabine/paclitaxel)	16.3 months (IQR 8.6–21.8) vs. 9.8 months (IQR 5.8–19.0)	6.41 months vs. 4.90 months / 8.0 cycles vs. 7.0 cycles

Main efficacy outcomes (I vs. C)	Main safety outcomes (I vs. C)
Data cutoff: **28 February 2022; median follow-up: 16.3 months (tislelizumab goup) vs. 9.8 months (placebo group)** Primary endpoint: OS in the ITT Analysis Set (median): **significantly improved; 17.2 months (95% CI, 15.8–20.1) vs. 10.6 months (95% CI, 9.3–12.1), HR for death 0.66 (95% CI, 0.54–0.80); p<0.0001** Secondary endpoints:	**AEs of any grade:** 99.7% vs. 99.4% **AEs of grade 3 to 5:** 78.7% vs. 77.6% **Serious AEs:** 48.8% vs. 39.6% ❖ **related:** 29.3% vs. 19.3% **AEs leading to treatment discontinuation:** 32.1% vs. 22.4%

[2,3] European Standard Population 2013.

PFS by investigator (median): **significantly improved; 7.3 months (95% CI, 6.9-8.3) vs. 5.6 months (95% CI, 4.9-6.0), HR 0.62 (95% CI, 0.52-0.75), p<0.0001** ORR by investigator (unconfirmed): **significantly improved; 63.5% (95% CI, 58.0-68.7) vs. 42.4% (95% CI, 37.0-48.0), odds ratio 2.38 (95% CI, 1.73-3.27), p<0.0001** OS in PD-L1 Score ≥ 10% Subgroup (median): **significantly improved; 16.6 months (95% CI, 15.3-24.4) vs. 10.0 months (95% CI, 8.6-13.3), HR 0.62 (95% CI, 0.44-0.87), p=0.0029** DOR by Investigator (unconfirmed, median): **7.1 months (95% CI, 6.1-8.1) vs. 5.7 months (95% CI, 4.4-7.1)**	**TEAEs leading to treatment discontinuation:** 13.3% vs. 6.5% **AEs resulting in death:** 4.3% vs. 5.0%
Patient-reported outcomes	
HRQoL outcomes- assessed using the EORTC QLQ-C30, the EORTC QLQ-OES18, and EQ-5D-5L showed: ❖ no significant differences between treatment arms. ❖ adjusted completion rates from baseline through Cycle 6 and Cycle 8 were >90% for each questionnaire in both arms.	
Limitations	
❖ External validity: low proportions of patients aged ≥ 75 years (approximately 6%), female patients (approximately 13%), and non-Asian patients (approximately 25%); only half of patients was treated with the European Standard of Care ChT regimen (platinum with a fluoropyrimidine). ❖ Unknown PD-L1 expression status in 107 (16.5%) of participants.	

ESMO-MCBS version 1.1 [13, 14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +6.6. months	0.62 (0.44-0.87)	HR ≤0.65 AND gain ≥3 months	4	-	No significant improvement	-	**4**
Adapted	NC	2a	≤12 months	OS: +6.6. months	0.62 (0.44-0.87)	HR ≤0.65 AND gain ≥3 months	4	+10% TRAE	No significant improvement	-1[4]	**3**

Risk of bias - RCT [15, 16]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects increasing the RoB	Risk of bias
yes low risk	yes low risk	unclear unclear risk[5]	unclear unclear risk[6]	yes high risk[7]	**unclear**

[4] Adjustment due to toxicity.
[5] Double-blind study, with BIRC performing an independent review of all radiological images for the efficacy analysis, and to determine all instances of response and disease progression on the basis of the RECIST v1.1 criteria.
However, during the 4th amendment, BIRC-assessed PFS moved from a dual primary endpoint to an exploratory endpoint assessed by the investigator. Nevertheless, the consistency between investigator-assessed outcomes and BIRC-assessed outcomes (e.g., "Results overall consistent between INV and BIRC" mentioned in the Effects Table) provides some reassurance that investigator bias was minimal. Some unintentional unblinding might have arose due to distinctive safety profiles of I and C (particularly immune-mediated AEs).
[6] Protocol Amendment 4.0 (moving of endpoints) and 3.0 (sample size increase) raise some concerns about potential reporting bias, as they were made during the study conduct, but the justifications provided were deemed sufficient and changes transparently reported by EMA. It appears that all prespecified outcomes (after amendment) were reported, including subgroup analyses that show both positive and negative results. The consistency between different analyses and the transparent reporting of protocol changes suggest that reporting bias was likely minimized in this study. Follow-up data was provided as well (data cut-off dates of April 28, 2023, and November 24, 2023).
[7] From EPAR: The global protocol was amended a total of 4 times before the data cut-off date for the clinical study report. All patients were enrolled after the implementation of Protocol Amendment Version 1.0. In the ITT Analysis Set, a total of 143 patients (22.0%), including 69 patients (21.2%) in the T+C Arm and 74 patients (22.9%) in the P+C Arm, had ≥ 1 important protocol deviation. The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report. Medical writing support was provided by the funder.

Ongoing trials [17]		
NCT number	Description	Estimated completion date
NCT05919030 (RENMIN-236)	Chemoradiation vs. Chemotherapy in Combination with Tislelizumab As First Line Treatment for Advanced OESCC with Low PD-L1 Expression: Multicentre, Randomised, Phase 3 Trial	2027-07-01
HTA reports		
Institution	Status	Link
IQWiG	Processing completed. No additional benefit has been proven.	Nutzenbewertung

Costs

Costs per patient per		Costs for expected patient population per		Additional costs categories [2]
Cycle	Year	Cycle	Year	Diagnostics
Per cycle: € 7,542 given that ex-factory price is € 3,771 per 100mg/10ml [18]	€ 128,214 (assuming 17 3-week cycles in a year, not counting in the price of the ChT)	NA	NA	**PD-L1 testing:** should be assessed by a CE-marked IVD with the corresponding intended purpose.
				Regular monitoring throughout treatment
				❖ Liver function tests (baseline and periodically during treatment) ❖ Kidney function tests ❖ Radiographic imaging tests ❖ Regular blood tests to monitor blood sugar and hormone levels
				Monitoring for specific immune-related adverse reactions
				❖ Thyroid function monitoring (at start, periodically during treatment) ❖ Adrenal function and hormone levels monitoring ❖ Pituitary function and hormone levels monitoring ❖ Monitoring for hyperglycemia and diabetic ketoacidosis

Other aspects and conclusions

- In October 2024, CHMP adopted a new indication for Tevimbra®, in combination with platinum-based chemotherapy, indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5%. This was the eleventh indication approved by the EMA overall, and the second for OSCC.
- The indication discussed within this Fact Sheet is approved by the FDA, although there is no TAP score value specified within the approval.
- RATIONALE-306 (NCT03783442) is a randomised, double-blind, parallel-arm, placebo-controlled, phase 3 study, comparing tislelizumab plus chemotherapy vs. placebo plus chemotherapy as first-line treatment for advanced or metastatic OSCC.
- The primary endpoint was OS, which was superior with tislelizumab vs. placebo.
- Limitations of RATIONALE-306 are related to the external validity (low proportions of patients aged ≥ 75 years, female patients and non-Asian patients; only half of the patients were treated with the European Standard of Care ChT regimen) and the unknown PD-L1 expression status in 107 (16.5%) of participants.
- Evaluation of PROs showed no significant differences between treatment arms.
- The original and adapted ESMO-MCBS were applied, resulting in a clinical final magnitude of clinical benefit of 4 and 3, respectively.

- Due to concerns regarding the blinding and potential reporting bias, the RoB was considered unclear. However, it is improved by the number of protocol amendments and the industry-funded background of the trial.
- 2 ongoing trials, assessing the efficacy and safety of tislelizumab in patients with OSCC, were identified via ClinicalTrials.gov.

Vienna, July 2025

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CDA-AMC=Canada´s Drug Agency – L´Agence des médicamnets du Canada, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, 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, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IV=intravenous(ly), MG=median gain, n=number of patients, NICE=National Institute for Health Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

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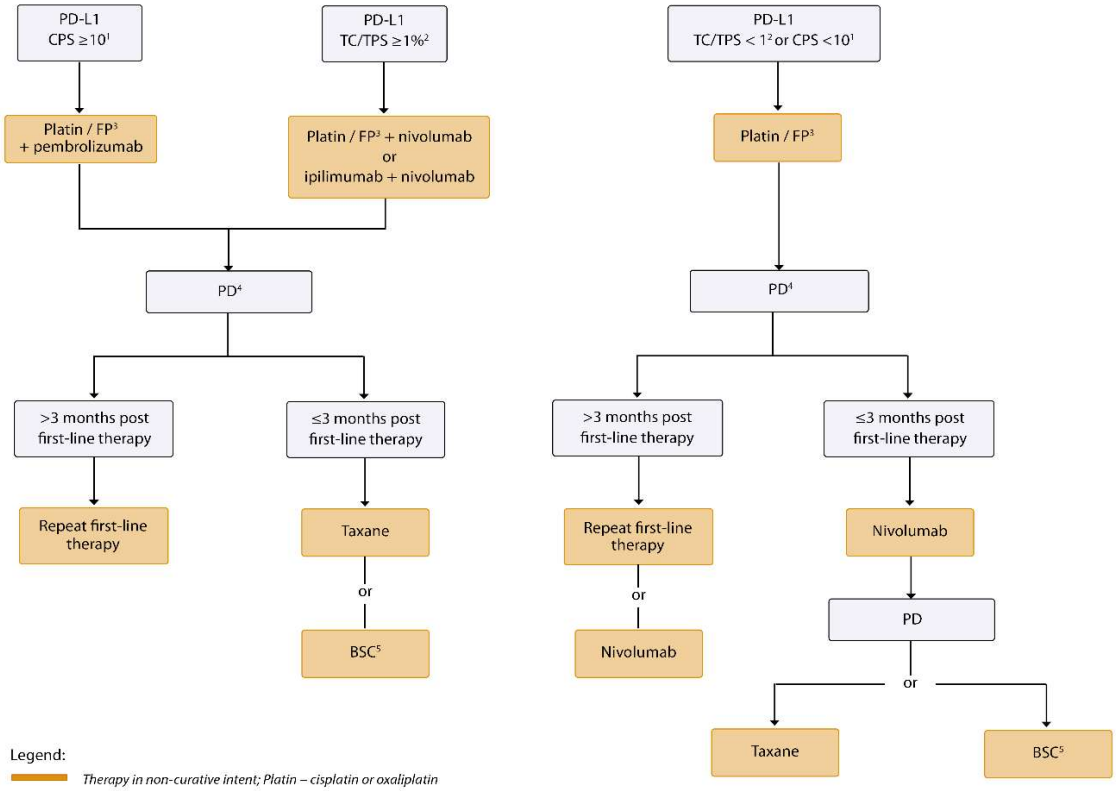
Appendix:

Algorithm for the treatment of stage IV esophageal squamous cell carcinoma



Legend:

Therapy in non-curative intent; Platin – cisplatin or oxaliplatin

[1] *CPS - Combined score of PD-L1 expression on tumor cells and immune cell infiltrate*
[2] *TC or TPS - number of PD-L1 positive tumor cells per 100 tumor cells*
[3] *FP - Fluoropyrimidine (5-fluorouracil + folinic acid, or capecitabine)*
[4] *PD - Progressive disease*
[5] *BSC - Best Supportive Care*