HTA Austria
Austrian Institute for Health Technology Assessment GmbH

Tislelizumab (Tevimbra®)

with etoposide and platinum chemotherapy for the first-line treatment of extensive-stage small-cell lung cancer

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 intravenous (IV) infusion once every 3 weeks, in combination with chemotherapy.	☒ Hospital ☐ Interface between hospital and outpatient sector ☐ Outpatient sector

Indication [3]

Tevimbra®, in combination with etoposide and platinum chemotherapy, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

EMA approval status	FDA approval status [3]
☒ **Approved for this indication:** On 2 March 2025, the CHMP recommended an extension of indication for Tevimbra® for the indication mentioned above [4, 5]. ☒ **Initial marketing authorisation issued** : 15.09.2023 ☒ **Approved for other indications:** Tislelizumab is a cancer medicine used to treat: ❖ Non-small cell lung cancer (NSCLC) ❖ Small cell lung cancer (SCLC) ❖ Gastric or gastroesophageal junction adenocarcinoma ❖ Oesophageal squamous cell carcinoma (OSCC) ❖ Nasopharyngeal carcinoma (NPC) [6].	☒ **Approved for this indication: no** ☒ **Approved for other indications:** Tislelizumab is indicated for ❖ OSCC ❖ Gastric cancer

Description [6, 7]	Prevalence & incidence	Mortality [7, 8]
Small cell lung cancer (SCLC) is a neuroendocrine tumour of the lung which is distinguished biologically, histologically and clinically from NSCLC by its rapid doubling time, high growth fraction, and the early development of metastases. Patients with SCLC are typically divided into those with limited-stage (LS) versus extensive-stage (ES) disease. While LS-SCLC is limited to the ipsilateral hemithorax and regional lymph nodes, ES-SCLC is disease that has spread beyond this and may include distant metastases, malignant pericardial or pleural effusions, and/or contralateral supraclavicular and contralateral hilar lymph node involvement. Typical are the development in the central airways and the often short history of tumour-related symptoms such as dyspnoea, cough or signs of upper airway obstruction. A special feature of SCLC is the more frequent occurrence of paraneoplastic syndromes, most frequently with endocrine symptoms.	❖ In Austria, in 2023, 5,232 persons were newly diagnosed with cancer of the lung, bronchi and trachea [9]. ❖ The age-standardised incidence rate was 66.9/100,000 in men and 45.7/100,000 in women [9]. ❖ SCLC accounts for around 12-15% of lung cancers; 60-70% of patients with SCLC are in the extensive disease stage when they are first diagnosed [10]. ❖ Taking this into account, some approx. 550 patients with newly diagnosed ES-SCLC can be expected per year in Austria.	❖ Poor prognosis: Patients with SCLC rarely survive more than a couple of months without treatment. ❖ The median overall survival (OS) is approximately 10 months, with a 2-year survival rate of less than 15%

[1] New indication/extension to an existing indication/first-in-class.

Current treatment [10]

- As mentioned above, 60-70% of patients with SCLC are in the extensive disease stage when they are first diagnosed.
- The standard of care (SoC) is systemic chemotherapy and immunotherapy.
- In addition to improving symptom control and thus quality of life (QoL), it leads to a significant increase in survival.
- With chemo-immunotherapy, the median survival of patients with extensive disease is approx. 12 months, the 2-year survival rate is 20-25% and the 3-year survival rate is 15-20%.
- The addition of immunotherapy has thus tripled the 3-year survival rates of patients compared to chemotherapy alone.
- The algorithm for the first-line treatment of SCLC stage IV is presented in the Appendix.

Evidence

Trial name NCT number	Trial characteristics	Population size (n)	Intervention (I)	Control (C)	Follow-up	Median treatment duration (I. vs. C)
RATIONALE-312 [11] NCT04005716	multicentre, double-blind, placebo-controlled, randomised, phase 3	457 1:1	tislelizumab 200 mg for 4 cycles with etoposide plus carboplatin or cisplatin IV every 3 weeks, followed by tislelizumab 200 mg as maintenance	placebo for 4 cycles with etoposide plus carboplatin or cisplatin IV every 3 weeks, followed by placebo as maintenance	median 14.2 months	19.4 vs. 19.1 weeks

Main efficacy outcomes (I vs. C)	Main safety outcomes (I vs. C)
OS in the ITT population : stratified HR =0.75 (95% CI, 0.61–0.93); p=0.0040 **Median OS**: 15.5 months (95% CI, 13.5–17.1) vs. 13.5 months (95% CI, 12.1–14.9) **Estimated 1-, 2-, and 3-year OS rates** : 63% vs. 58%, 33% vs. 22%, and 25% vs.9% **Median PFS**: 4.7 months (95% CI, 4.3–5.5) vs. 4.3 months (95% CI,4.2–4.4) **Estimated 6- and 12-month PFS rates** : 35% vs. 18% and 21% vs. 5% **Confirmed ORR**: 68% (95% CI, 62–74) vs. 62% (95% CI: 55–68) **Median DoR**: 4.3 months (95% CI, 4.1–5.6) vs. 3.7 months (95% CI, 3.0–4.1) Patients who received **subsequent systemic anticancer therapies** after discontinuation of study drugs: 60% vs. 74% Improved PFS after the next line of treatment after discontinuation of study drugs was observed in the tislelizumab arm (PFS2): stratified HR=0.71 (95% CI, 0.57–0.89) **Median PFS2**: 13.1 months vs. 11.0 months	**TRAEs:** >99% vs. >99% **TRAES grade ≥3**: 86% vs. 86% **TRAEs leading to the discontinuation of therapy** : 11% vs. 2% **Serious TRAEs:** 31% vs. 18% **TRAE leading to death in tislelizumab arm** : 4% including five events assessed by investigator as related to both tislelizumab and chemotherapy, two assessed as only related to tislelizumab and one assessed as only related to chemotherapy) **TRAE leading to death in the placebo arm** : 0 **Immune-mediated AEs of any grade** : 38% vs. 18% **Immune-mediated AEs ≥ grade 3** : 11% vs. <1%

Patient-reported outcomes (abstract and accompanying poster data)

According to the study authors, the effect of treatment on health-related quality of life was assessed as a secondary end point and will be reported separately. Currently, only the abstract and accompanying poster are available, which show that patients in both arms improved on most patient-reported outcomes, including global health status/QoL and disease-specific symptoms (coughing, chest pain, haemoptysis and dyspnoea) at Cycle 6. A clinical meaningful benefit in general health status/QoL was observed in the tislelizumab arm at Cycle 6, with a least squares mean difference of 4.20 (95% CI, 0.76-7.64) [12].

Limitations

- All enrolled patients were from China and chemotherapy was selected as the control arm because immunotherapy had not been approved for ES-SCLC in China before the initiation of the study.
- Only a few patients with brain metastases at baseline were enrolled (1%).
- The correlation between PD-L1 expression and efficacy was not included.
- In the RATIONALE-312 study, the proportion of patients who were never-smokers (24.5%) was higher than global estimates (SCLC primarily occurs in smokers). However, according to Cheng et al., this is consistent with the higher observed prevalence of patients with SCLC in Asia.

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL[2]	AJ	FM
Original **[13]**	NC	2a	<12 months	OS: +2.0 months	0.75 (0.61–0.93)	HR<0.65-0.70 AND gain ≥1.5 months	2	-	NA	-	**2**
Adapted **[14]**	NC	2a	<12 months	OS: +2.0 months	0.75 (0.61–0.93)	HR<0.65-0.70 AND gain ≥1.5 months	2	+13% serious TRAEs	NA	-1[3]	**1**

[2] The information is only available from the abstract and poster.
[3] Toxicity adjustment.

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	unclear unclear risk	yes low risk	yes low risk	yes[4] high risk	**unclear risk**

Ongoing trials		
NCT number	Description	Estimated completion date
NCT06536868	Tislelizumab Plus Chemotherapy and Concurrent Thoracic Radiotherapy as First-line Therapy for ES-SCLC [17]	12/2026
NCT06897579	A Randomized Controlled, Open-label, Multicenter Clinical Trial Evaluating the Efficacy and Safety of Carboplatin/Cisplatin + Etoposide + Bemarituzumab Followed by Bemarituzumab Combined With Anlotinib Versus Carboplatin/Cisplatin + Etoposide + Tislelizumab Followed by Tislelizumab as First-line Treatment for ES-SCLC [17]	04/2027

HTA reports	
Institution	Status
Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA)	Benefit assessment procedure is currently ongoing [18].

Costs

Costs per patient per		Costs for expected patient population per		Additional costs categories [19]	
Cycle	Year	Cycle	Year	Diagnostics	Monitoring
		Based on an estimated number of 550 patients per year[5]			
€7,542.00 Tevimbra® concentrate for solution for infusion 100mg/10ml= € 3,771.00 (ex-factory price) **[20]**	€ 130,727.90	€ 414,810.00	€ 71,900,345.00	PD-1 status testing Additional medication ■ Etoposide: e.g. Vepesid® €489,60 for 10 capsules ■ Platinum-based chemotherapy	■ AEs and immune-mediated AEs ■ Haemophagocytic lymphohistiocytosis ■ Infusion-related reactions

Other aspects and conclusions

- On 27 March 2025, the **CHMP recommended** an extension of indication for Tevimbra® in combination with etoposide and platinum chemotherapy, indicated for the first-line treatment of adult patients with ES-SCLC. There is no FDA approval for this indication.
- **RATIONALE-312 (NCT04005716)** is a phase 3 study aiming to evaluate the efficacy and safety of tislelizumab plus chemotherapy as first-line treatment for patients with ES-SCLC. Patients were eligible if they were ≥18 years of age, had an ECOG of ≤1, a life expectancy of at least 12 weeks, adequate organ function and had not received previous systemic treatment for ES-SCLC.
- The primary end point of RATIONALE-312 was **OS**; results showed a statistically significant benefit in patients receiving tislelizumab: stratified HR was 0.75 (95% CI,0.61–0.93); one-sided p = 0.0040. Median OS was improved by 2.0 months: 15.5 months in patients receiving tislelizumab versus 13.5 months in the control group.
- According to the study authors, the effect of treatment on health-related quality of life was assessed as a secondary end point and will be reported separately (currently, only the abstract and accompanying poster are available).
- **Limitations** of the trial include the choice of chemotherapy as a comparator, the low number of patients with brain metastases, the relatively high rate of non-smokers, and the exclusion of the correlation between PD-L1 expression and efficacy.
- The original and adapted **ESMO-MCBS** were applied, resulting in a final magnitude of clinical benefit **score 2 and 1**, respectively.
- The **risk of bias** was considered **unclear** but is increased by the industry-funded background of the trial.
- The **costs** for one year of tislelizumab therapy are approx. € 130,000 per patient; in addition, costs for diagnostics, chemotherapy and monitoring occur.

First published: Vienna, 11/2025

[4] Industry-funded.
[5] 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.

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, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, IgG=immunoglobulin G, Int.=intention, ITT=intention-to-treat, IV=intravenous, LS=limited stage, 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, 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

References:

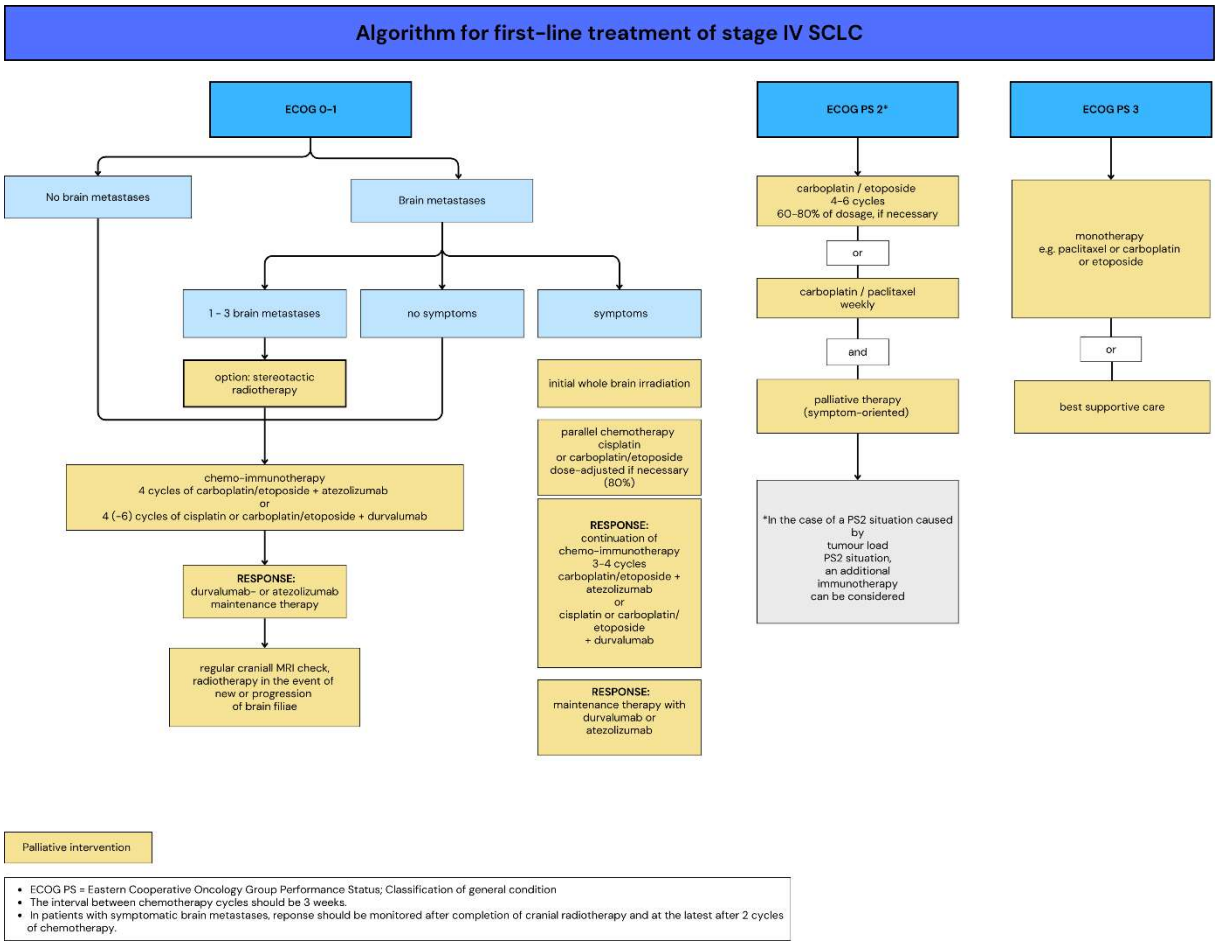
[1] European Medicines Agency (EMA). Medicines. Tevimbra.: 2025 [cited 2025-08-05]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tevimbra.
[2] European Medicines Agency (EMA). Tevimbra: EPAR - Product Information.: 2025 [cited 2025-08-05]. Available from: https://www.ema.europa.eu/en/documents/product-information/tevimbra-epar-product-information_en.pdf.
[3] U.S. Food & Drug Administration (FDA). Tevimbra. Label Information. 2025 [cited 2025-08-05]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761232s004lbl.pdf.
[4] European Medicines Agency (EMA). Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 24-27 March 2025. 2025 [cited 2025-08-05]. Available from: https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-24-27-march-2025.
[5] European Medicines Agency (EMA). CHMP Summary of opinion (post authorisation). Tevimbra.: 2025 [cited 2025-08-05]. Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-tevimbra-ii-16_en.pdf.
[6] European Medicines Agency (EMA). [cited 04.08.2025]. Available from: https://www.ema.europa.eu/en/homepage.
[7] Cheng Y., Fan Y., Zhao Y., Huang D., Li X., Zhang P., et al. Tislelizumab Plus Platinum and Etoposide Versus Placebo Plus Platinum and Etoposide as First-Line Treatment for Extensive-Stage SCLC (RATIONALE-312): A Multicenter, Double-Blind, Placebo-Controlled, Randomized, Phase 3 Clinical Trial. J Thorac Oncol. 2024;19(7):1073-1085. Epub 20240307. DOI: 10.1016/j.jtho.2024.03.008.
[8] Lilenbaum R, Schild S and UpToDate. Extensive-stage small cell lung cancer: Initial management. 2025 [cited 2025-08-05]. Available from: https://www.uptodate.com/contents/extensive-stage-small-cell-lung-cancer-initial-management?search=extensive%20stage%20small%20cell%20lung%20cancer&source=search_result&selectedTitle=1~18&usage_type=default&display_rank=1#H33.
[9] Statistik Austria. Krebserkrankungen. Krebsinzidenz nach ausgewählten Lokalisationen und Geschlecht. . 2024 [cited 2025-08-13]. Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen.
[10] Wolf M, Bleckmann A, Eberhardt W, et al. and Onkopedia. Onkopedia Leitlinien. Lungenkarzinom, kleinzellig (SCLC). 2023 [cited 2025-08-05]. Available from: https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-kleinzellig-sclc/@@guideline/html/index.html#ID0ERRAG.
[11] Cheng Y., Fan Y., Zhao Y., Huang D., Li X., Zhang P., et al. Tislelizumab Plus Platinum and Etoposide Versus Placebo Plus Platinum and Etoposide as First-Line Treatment for Extensive-Stage SCLC (RATIONALE-312): A Multicenter, Double-Blind, Placebo-Controlled, Randomized, Phase 3 Clinical Trial. Journal of Thoracic Oncology. 2024;19(7):1073-1085. DOI: 10.1016/j.jtho.2024.03.008.
[12] Cheng Y. Q., Tai; Chen, Chenqi (Yolanda); Barnes, Gisoo; Barnes, Bryant. Tislelizumab Plus Platinum and Etoposide Versus Placebo Plus Platinum and Etoposide

as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer: Patient-Reported

Outcomes in the RATIONALE-312 Trial. 30th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 13-16, 2025; Montreal, QC, Canada2025.
[13] ESMO. ESMO-MCBS Scorecard. Tislelizumab. RATIONALE 312. [cited 2025-08-12]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=491.

[14] Cherny NI D. U., Bogaerts J., and al. e. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.
[15] Higgins J. P. T., Altman D. G., Gøtzsche P. C., Jüni P., Moher D., Oxman A. D., et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. DOI: 10.1136/bmj.d5928.
[16] Member State Coordination Group on HTA (HTA CG). Guidance on Validity of Clinical Studies. 2024. Available from: https://health.ec.europa.eu/document/download/9f9dbfe4-078b-4959-9a07-df9167258772_en?filename=hta_clinical-studies-validity_guidance_en.pdf.
[17] ClinicalTrials.gov. [cited 2025-08-13]. Available from: https://www.clinicaltrials.gov/.
[18] Gemeinsamer Bundesausschuss (G-BA). [cited 04.08.2025]. Available from: https://www.g-ba.de/.
[19] European Medicines Agency (EMA). Tevimbra: EPAR - Product Information. [cited 2025-08-12]. Available from: https://www.ema.europa.eu/en/documents/product-information/tevimbra-epar-product-information_en.pdf.
[20] Apoverlag. Warenverzeichnis. 2024 [cited 13.11.2024]. Available from: https://warenverzeichnis.apoverlag.at/.

Appendix [10]:


Algorithm for first-line treatment of stage IV SCLC
ECOG 0-1
No brain metastases
Brain metastases
1 - 3 brain metastases
no symptoms
symptoms
option: stereotactic radiotherapy
initial whole brain irradiation
chemo-immunotherapy
4 cycles of carboplatin/etoposide + atezolizumab
or
4 (-6) cycles of cisplatin or carboplatin/etoposide + durvalumab
parallel chemotherapy
cisplatin
or carboplatin/etoposide
dose-adjusted if necessary
(80%)
RESPONSE:
durvalumab- or atezolizumab
maintenance therapy
RESPONSE:
continuation of
chemo-immunotherapy
3-4 cycles
carboplatin/etoposide +
atezolizumab
or
cisplatin or carboplatin/
etoposide
+ durvalumab
regular craniall MRI check,
radiotherapy in the event of
new or progression
of brain filiae
RESPONSE:
maintenance therapy with
durvalumab or
atezolizumab
ECOG PS 2*
carboplatin / etoposide
4-6 cycles
60-80% of dosage, if necessary
or
carboplatin / paclitaxel
weekly
and
palliative therapy
(symptom-oriented)
*In the case of a PS2 situation caused
by
tumour load
PS2 situation,
an additional
immunotherapy
can be considered
ECOG PS 3
monotherapy
e.g. paclitaxel or carboplatin
or etoposide
or
best supportive care
Palliative intervention
• ECOG PS = Eastern Cooperative Oncology Group Performance Status; Classification of general condition
• The interval between chemotherapy cycles should be 3 weeks.
• In patients with symptomatic brain metastases, reponse should be monitored after completion of cranial radiotherapy and at the latest after 2 cycles of chemotherapy.