HTA Austria
Austrian Institute for Health Technology Assessment GmbH

Tislelizumab (Tevimbra®)

in combination with gemcitabine and cisplatin for the first-line treatment of recurrent or metastatic nasopharyngeal carcinoma

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 infusion once every three weeks, in combination with chemotherapy.	☒ Hospital ☐ Interface between hospital and outpatient sector ☐ Outpatient sector

Indication [1]

Tislelizumab, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (NPC).

EMA approval status [1, 3]	FDA approval status [4]
☒ **Approved for this indication: On 23 May 2025, the CHMP** recommended an extension to the existing indication for Tevimbra® as mentioned above. ☒ **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)	☒ **Approved for this indication: no** ☒ **Approved for other indications: Tevimbra® is indicated for** ❖ Oesophageal cancer; ❖ Gastric Cancer

Disease

Description	Prevalence & incidence	Mortality
NPC is an epithelial neoplasm arising in the nasopharynx. The most common presenting symptoms are headache, diplopia, or facial numbness, caused by cranial nerve involvement, and a mass in the neck, due to cervical node metastases. Although nasopharyngeal carcinoma is rare in most parts of the world, it is endemic in southern China, Southeast Asia, North Africa, and the Arctic, where undifferentiated, nonkeratinizing squamous cell carcinoma is the predominant histology. The primary etiologic factors for endemic NPC are genetic susceptibility, early age exposure to chemical carcinogens, and Epstein-Barr virus (EBV) infection [5].	In 2022, the age-standardised incidence rate for NPC in Austria was 0.48/100,000 in men and 0.15/100,000 in women. A total of 48 patients were newly diagnosed with NPC [6].	In 2022, the age-standardised mortality rate for NPC in Austria was 0.16/100,000 in men and 0.05/100,000 in women. A total of 23 patients died from NPC [6].

Current treatment

The algorithm with ESMO´s treatment recommendations **[7]** is displayed in the Appendix below.

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

Evidence

Trial name NCT number	Trial characteristics	Population size (n)	Intervention (I)	Control (C)	Median follow-up	Treatment duration / cycles
RATIONALE-309 **[8]** NCT03924986	Multicentre, randomised, double-blind phase 3 trial	263 (1:1)	Tislelizumab 200 mg IV every 3 weeks (Q3W) + chemotherapy (Q3W for 4–6 cycles)	Placebo (Q3W) + chemotherapy (Q3W for 4–6 cycles)	10.0 months / 15.5[2] months	Median 35.9 weeks / median 11.0 cycles

Main efficacy outcomes (I vs C), interim analysis data

Median OS: not reached vs 23.0 months

Median IRC-assessed PFS :
9.2 vs 7.4 months; HR 0.52 (95% CI, 0.38-0.73); p < 0.0001

Median investigator-assessed PFS :
9.8 vs 7.6 months; HR 0.54 (95% CI, 0.38-0.76); p = not reported

Median IRC-assessed PFS at the updated data cutoff [3]:
9.6 vs 7.4 months; HR 0.50 (95% CI, 0.37-0.68); nominal p < 0.0001

Median PFS2 [4]**:** not reached vs 16.6 months; HR 0.39 (95% CI, 0.24-0.63); p = not reported

PFS2 rates at 12 months : 87.1% vs 70.0%

IRC-assessed ORR : 69.5% vs 55.3%
Confirmed CR: 16.0% vs 6.8%

Median DoR among responders : 8.5 vs 6.1 months

CROSSOVER:

49.2% of patients in the placebo-chemotherapy arm crossed over to receive tislelizumab monotherapy after disease progression.

Main safety outcomes (I vs C), interim analysis data

Patients with at least one TEAEs: 100.0% vs 99.2%
- Related to any component of study treatment: 100.0% vs 99.2%
- Related to tislelizumab/placebo: 74.8% vs 71.2%
- Related to any component of chemotherapy: 100.0% vs 99.2%

Grade ≥3 TEAEs: 80.9% vs 81.8%
- Related to any component of study treatment: 76.3% vs 81.8%
- Related to tislelizumab/placebo: 22.1% vs 23.5%
- Related to any component of chemotherapy: 76.3% vs 81.8%

Serious TEAEs: 27.5% vs 33.3%
- Grade ≥3 serious TEAEs: 22.9% vs 26.5%
- Related to any component of study treatment: 21.4% vs 28.8%
- Related to tislelizumab/placebo: 7.6% vs 12.1%
- Related to any component of chemotherapy: 19.1% vs 27.3%

TEAEs leading to permanent discontinuation of all treatments: 1.5% vs 2.3%
- TEAEs leading to permanent discontinuation of any component of study treatment: 13.0% vs 9.1%
- Leading to permanent discontinuation of tislelizumab/placebo: 5.3% vs 3.8%
- Leading to discontinuation of any chemotherapy: 9.2% vs 7.6%
  - Leading to permanent discontinuation of gemcitabine: 9.2% vs 7.6%
  - Leading to permanent discontinuation of cisplatin: 7.6% vs 6.8%

Infusion-related reaction: 4.6% vs 4.5%

Immune-mediated TEAEs: 18.3% vs NA
- Grade ≥3: 2.3% vs NA

TEAEs leading to death[5]: 3.8% vs. 1.5%
- Related to any component of study treatment: 1.5% vs 1.5%
- Related to tislelizumab/placebo: 0.8% vs 0.8%
- Related to any component of chemotherapy: 1.5% vs 1.5%

Patient-reported outcomes [9]

- No differences in change in selected scores on the QLQ-C30 from baseline to cycle 4 or 8 were observed for the ITT or liver metastases subgroup.
- No differences in selected QLQ-H&N35 scores were observed between the arms from baseline to cycle 4. In the ITT population and the liver metastases subgroup, a greater reduction from baseline to cycle 8 was observed in the tislelizumab + chemotherapy arm than the placebo + chemotherapy arm in QLQ-H&N35 pain score.
- At cycle 8 in the liver metastases subgroup, the tislelizumab + chemotherapy arm experienced greater improvement in the QLQ-H&N35 senses problems score than the placebo + chemotherapy arm.
- Differences in time to deterioration between arms were not observed.

Limitations

- The trial was conducted in Asia, where the predominant histology is undifferentiated non-keratinizing NPC. Whether or not tislelizumab + chemotherapy has comparable efficacy in keratinizing NPC needs to be further investigated.
- The number of patients who underwent biomarker evaluation was relatively small, and further validation is required.
- As the OS data are still immature, a longer follow-up is needed to assess whether the PFS advantage observed for tislelizumab + chemotherapy translates into long-term survival benefit.
- Patients in the tislelizumab + chemotherapy arm were permitted to continue tislelizumab monotherapy, and patients in the placebo + chemotherapy arm were permitted to crossover to tislelizumab monotherapy after disease progression (confirmed by IRC).

[2] *At the updated data cutoff.*
[3] *Primary study endpoint.*
[4] *PFS2 was defined as the time from randomisation to second or subsequent disease progression after initiation of new anticancer therapy or death from any cause, whichever occurred first.*
[5] *One patient (0.8%) in the tislelizumab-chemotherapy arm experienced a TEAE (myelodysplastic syndrome) leading to death considered related to tislelizumab.*

ESMO-MCBS version 1.1 [10, 11]											
Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	>6 months	PFS: +2.2 months	0.50 (0.37-0.68)	HR ≤0.65 BUT gain <3 months	2	-	No adjustment[6]	-	**2**
Adapted	NC	2b	>6 months	PFS: +2.2 months	0.50 (0.37-0.68)	HR ≤0.65 BUT gain <3 months	2	-	No adjustment[7]	-	**2**

Risk of bias - RCT [12, 13]						
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting unlikely	Other aspects increasing the RoB	**Risk of bias**
yes low risk	yes low risk	unclear[8] unclear risk	yes[9] high risk	unclear[10] unclear risk	yes[11] high risk	**unclear**

Ongoing trials [14]		
NCT number	Description	Estimated completion date
NCT06177301	A phase 3 clinical study of tislelizumab combined with GX (gemcitabine/capecitabine) regimen vs tislelizumab combined with GP (gemcitabine/cisplatin) regimen in the first-line treatment of recurrent or metastatic NPC.	12/2027

HTA reports	
Institution	Status
NIHR	Health Technology Briefing, published in October 2021 [15]
Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA)	Benefit assessment procedure is currently ongoing [16]
National Institute for Health and Care Excellence (NICE)	Awaiting development [17]

Costs

Costs per patient [18]		Costs for expected patient population [12] (n=48)		Additional costs categories	
Cycle	Year	Cycle	Year	Diagnostics	Monitoring
€ 7,542 *Tevimbra® concentrate for solution for IV 100 mg/10 ml: € 3,771 (ex-factory price)*	€ 130,728	€ 362,016	€ 6,274,939	not applicable Additional medication Chemotherapy: gemcitabine or cisplatin	■ AEs and immune-mediated AEs ■ Haemophagocytic lymphohistiocytosis ■ Infusion-related reactions

[6] *Reviewed, but not qualified for an ESMO-MCBS credit.*
[7] *No QoL adjustment, differences between treatment groups were considered too small.*
[8] *Potential for unblinding due to differential toxicity profiles (tislelizumab-specific immune-mediated AEs.*
[9] *There are some concerns due to differential treatment discontinuation: 51.9% tislelizumab vs 72% placebo.*
[10] *Currently, only interim analysis data is available.*
[11] *Industry-funded. At the investigator's discretion and with the sponsor's agreement, provided protocol-defined criteria were met, patients in the tislelizumab + chemotherapy arm were permitted to continue tislelizumab monotherapy, and patients in the placebo + chemotherapy arm were permitted to crossover to tislelizumab monotherapy after disease progression (confirmed by IRC: high crossover rate: 49.2%).*
[12] *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.*

Other aspects and conclusions

- In May 2025, the CHMP recommended an extension to the existing indication for tislelizumab (Tevimbra®), in combination with gemcitabine and cisplatin, indicated for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC. Tevimbra® is not yet approved by the FDA for this indication.
- The RATIONALE-309 (NCT03924986) is randomised, double-blind, phase 3 trial, evaluating the efficacy and safety of tislelizumab compared with placebo, in combination with gemcitabine and cisplatin, as first-line treatment for recurrent/metastatic NPC. Eligible patients were aged between 18 and 75 years, had histologically or cytologically confirmed NPC with recurrence or metastasis, an ECOG PS of ≤1 and must be treatment-naive for recurrent or metastatic NPC.
- The primary endpoint was IRC-assessed PFS in the ITT population. Median IRC-assessed PFS at the updated data cutoff was 9.6 vs 7.4 months; HR 0.50 (95% CI, 0.37-0.68); nominal $p < 0.0001$.
- Assessment of PROs showed only minor differences between the two treatment groups.
- Limitations of the RATIONALE-309 trial include the participation of only Asian patients, the short period of follow-up (OS data are still immature) and the possibility for crossover.
- The original and adapted EMSO-MCBS were applied, resulting in a final adjusted score of 2 out of 5 each, indicating no meaningful clinical benefit.
- The risk of bias was considered unclear, since there is currently only interim analysis data available. However, the risk is increased by the industry-funded background of the trial and the high crossover rate.

First published: Vienna, 11/2025

Abbreviations : AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, 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, DoR=duration of response, EBV=Ebstein-Barr Virus, 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, ICR=independent review committee, Int.=intention, ITT=Intention-to-treat, MAH=marketing authorisation holder, MG=median gain, n=number of patients, NICE=National Institute for Health Care Excellence, NPC=nasopharyngeal carcinoma, NSCLC=non- small-cell lung cancer, OESCC=oesophageal squamous cell carcinoma, OS=overall survival, PD-1=programmed cell death protein 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QLQ-C30=Quality of Life Questionnaire C30, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TAP=tumour area positivity, TEAE=treatment-related adverse event

References

[1] European Medicines Agency (EMA). Medicines. Tevimbra.: 2025 [cited 2025-08-12]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tevimbra.

[2] European Medicines Agency (EMA). Tevimbra: EPAR - Product Information.: 2025 [cited 2025-08-12]. Available from: https://www.ema.europa.eu/en/documents/product-information/tevimbra-epar-product-information_en.pdf.

[3] 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.

[4] 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.

[5] Pun Hui E, Chan ATC and UpToDate. Epidemiology, etiology, and diagnosis of nasopharyngeal carcinoma. 2024 [cited 2025-08-13]. Available from: https://www.uptodate.com/contents/epidemiology-etiology-and-diagnosis-of-nasopharyngeal-carcinoma?search=nasopharyngeal%20carcinoma&source=search_result&selectedTitle=1~73&usage_type=default&display_rank=1#H2.

[6] WHO and International Agency for Research on Cancer (IARC). Nasopharynx. 2022 [cited 2025-08-13]. Available from: https://gco.iarc.who.int/today/en/dataviz/maps-heatmap?cancers=4&types=1&sexes=2&palette=Blues&mode=population&zoom=5.

[7] ESMO. ESMO-EURACAN Clinical Practice Guideline update for nasopharyngealcarcinoma: adjuvant therapy and first-line treatment of recurrent/metastatic disease. Ann Oncol Vol 34, Issue 3 2023. 2023.

[8] Yang Y., Pan J., Wang H., Zhao Y., Qu S., Chen N., et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: A multicenter phase 3 trial (RATIONALE-309). Cancer Cell. 2023;41(6):1061-1072.e1064. DOI: 10.1016/j.ccell.2023.04.014.

[9] Yang Y., Pan J., Chen N., Guo Y., Huang X., Wu Y., et al. Effects of tislelizumab on health-related quality of life in patients with recurrent or metastatic nasopharyngeal cancer. Head Neck. 2024;46(9):2301-2314. Epub 20240426. DOI: 10.1002/hed.27785.

[10] 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.

[11] European Society for Medical Oncology (ESMO). ESMO-MCBS Scorecard. Tislelizumab. RATIONALE 309. [cited 2025-08-12]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=503.

[12] 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.

[13] 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.

[14] ClinicalTrials.gov. 2025 [cited 2025-08-12]. Available from: https://www.clinicaltrials.gov/.

[15] National Institute for Health and Care Research (NIHR). Tislelizumab in combination with chemotherapy for nasopharyngeal cancer – first line. 2021 [cited 2025-11-12]. Available from: https://io.nihr.ac.uk/wp-content/uploads/2022/01/27171-Tislelizumab-in-Combination-with-Chemotherapy-for-Nasopharyngeal-Cancer-V1.0-OCT2021-NON-CONF.pdf.

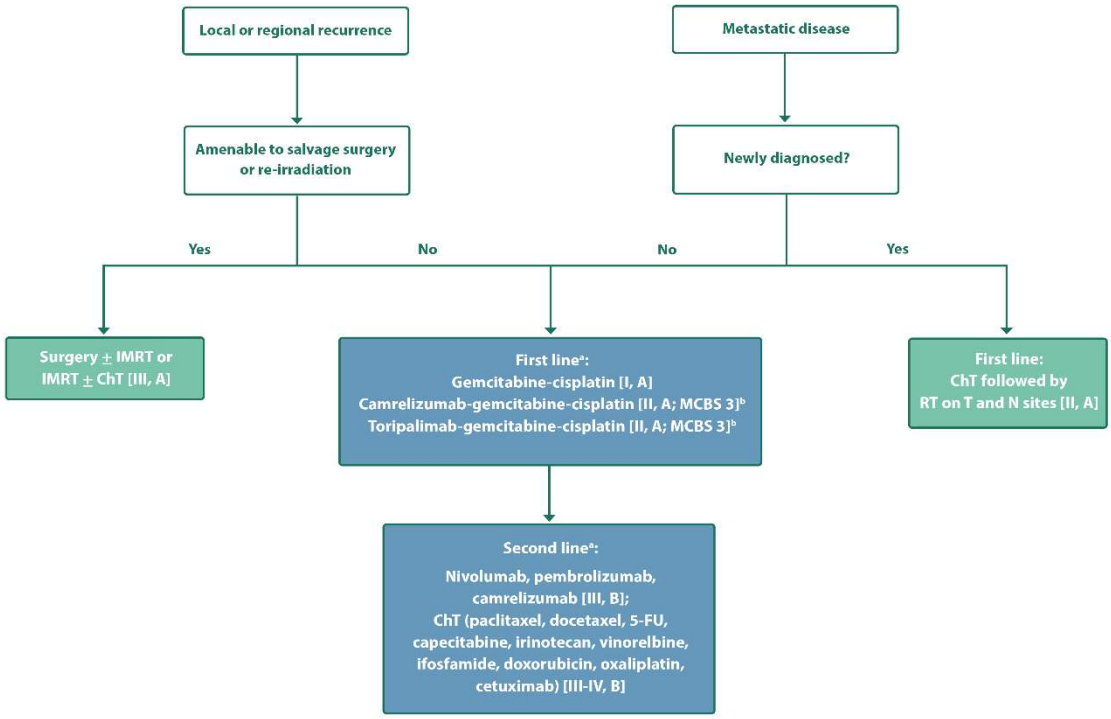
[16] Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Tislelizumab (Neues Anwendungsgebiet: rezidiviertes oder metastasiertes Nasopharynxkarzinom (NPC), Erstlinie, Kombination mit Gemcitabin and Cisplatin). [cited 2025-11-12]. Available from: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1254/.

[17] National Institute for Health and Care Excellence (NICE). Tislelizumab with chemotherapy for untreated recurrent or metastatic nasopharyngeal cancer [ID6304]. [cited 2025-11-12]. Available from: https://www.nice.org.uk/guidance/awaiting-development/gid-ta11100.

[18] Österreichischer Apothekerverlag. Warenverzeichnis. 2024 [cited 2025-08-12]. Available from: https://warenverzeichnis.apoverlag.at/.

Appendix: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up [7]:

Treatment algorithm for recurrent and/or metastatic NPC



5-FU, 5-fluorouracil; ChT, chemotherapy; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IMRT, intensity-modulated radiotherapy; MCBS, Magnitude of Clinical Benefit; N, node; NPC, nasopharyngeal carcinoma; RT, radiotherapy; T, tumour.
[a]Consider RT [III, B] or surgery [IV, C] on metastatic sites.
[b]ESMO-MCBS v1.1 was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH