Tislelizumab (Tevimbra®) monotherapy or in combination with chemotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

General information

Drug description [1]

The active substance of Tevimbra® is tislelizumab, a humanised immunoglobulin G4 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.

Indication [2]

- ❖ Tislelizumab (Tevimbra®) in combination with pemetrexed and platinum-containing chemotherapy is indicated 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.
- ❖ Tislelizumab (Tevimbra®) in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated 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.
- ❖ Tislelizumab (Tevimbra®) as monotherapy is indicated 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.

Incidence [3]

In Austria, in 2022, the age-standardised[1] incidence of carcinoma of the lung, trachea and bronchus was 68.0/100,000 in men and 45.8/100,000 in women.

Current treatment [4]

The treatment recommendation for non-molecular stratified drug therapy in advanced stages of NSCLC available from the Onkopedia website is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]	FDA [5]
Approval status for this indication: On May 30 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 as follows: ❖ Tevimbra® in combination with **pemetrexed and platinum-containing chemotherapy,** is indicated 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, platinum-based chemoradiation, or • metastatic NSCLC. ❖ Tevimbra® in combination with **carboplatin and either paclitaxel or nab-paclitaxel** is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer who have: • locally advanced NSCLC and are not candidates for surgical resection, platinum-based chemoradiation, or • metastatic NSCLC.	**Approval status for this indication**: not approved **Other indications**: ❖ Tevimbra® is indicated for the treatment of adult patients with unresectable or metastatic oesophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

[1] European Standard Population 2013.

❖ Tevimbra® as **monotherapy** is indicated 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.

Other indications:

❖ Tevimbra® as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic OSCC after prior platinum-based chemotherapy.

✓ **Medicine is under additional monitoring**

Manufacturer

Tevimbra® is manufactured by BeiGene.

Costs

Currently, there is no cost information available.

Warnings and precautions [1]

❖ **Traceability**
- In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

❖ **Patient Card**
- Patients treated with Tevimbra® must be given the Patient Card to be informed about the risks of immune-related adverse reactions during Tevimbra® therapy. The prescriber must discuss the risks of immune-related adverse reactions during Tevimbra® therapy with the patient.

❖ **Immune-related adverse reactions**
- Immune-related adverse reactions have been reported, including fatal cases, during treatment with tislelizumab. The majority of these events improved with interruption of tislelizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also been reported after the last dose of tislelizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.
- An adequate evaluation to confirm aetiology or exclude alternative aetiologies, including infection, should be ensured for suspected immune-related adverse reactions. Based on the severity of the adverse reaction, tislelizumab should be withheld and corticosteroids administered. Based on limited data from clinical studies, administration of other systemic immunosuppressants can be considered in patients whose immune-related adverse reactions are not controlled with corticosteroid use. Upon improvement to grade ≤1, corticosteroid taper should be initiated and continued over at least one month.
- Immune-related pneumonitis
  - Immune-related pneumonitis, including fatal cases, has been reported in patients receiving tislelizumab. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging, and infectious or disease-related aetiologies should be ruled out.
  - Patients with immune-related pneumonitis should be managed according to the treatment modifications as recommended in Product Information.
- Immune-related hepatitis
  - Immune-related hepatitis, including fatal cases, has been reported in patients treated with tislelizumab.
  - Patients should be monitored for signs and symptoms of hepatitis and changes in liver function. Liver function tests should be performed at baseline and periodically during treatment. Patients with immune-related hepatitis should be managed according to the treatment modifications as recommended in Product Information.
- Immune-related skin reactions
  - Immune-related skin rash or dermatitis has been reported in patients receiving tislelizumab. Patients should be monitored for suspected skin reactions, and other causes should be excluded. Based on the severity of the skin adverse reactions, tislelizumab should be withheld or permanently discontinued as recommended in Product Information.

- Cases of severe cutaneous adverse reactions (SCARs) including erythema multiforme, Stevens-Johnson Syndrome and Toxic epidermal necrolysis, some of them with fatal outcome, have been reported in patients receiving tislelizumab. Patients should be monitored for signs or symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash) and other causes should be excluded. For suspected SCAR, tislelizumab should be withheld and the patient should be referred to specialised care for assessment and treatment. If SCAR is confirmed, tislelizumab should be permanently discontinued.

- Immune-related colitis
  - Immune-related colitis, frequently associated with diarrhoea, has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of colitis. Infectious and disease-related aetiologies should be ruled out. Patients with immune-related colitis should be managed according to the treatment modifications as recommended in Product Information.
- Immune-related endocrinopathies
  - Immune-related endocrinopathies, including thyroid disorders, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, have been reported in patients treated with tislelizumab. These may require supportive treatment depending on the specific endocrine disorder. Long-term hormone replacement therapy (HRT) may be necessary in cases of immune-related endocrinopathies. Patients with immune-related endocrinopathies should be managed according to the treatment modifications as recommended in Product Information.

❖ **Thyroid disorders**
- Thyroid disorders, including thyroiditis, hypothyroidism and hyperthyroidism, have been reported in patients treated with tislelizumab. Patients should be monitored (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) for changes in thyroid function and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with HRT without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically.

❖ **Adrenal insufficiency**
- Adrenal insufficiency has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of adrenal insufficiency. Monitoring of adrenal function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated.

❖ **Hypophysitis**
- Hypophysitis has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of pituitary function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated

❖ **Type 1 diabetes mellitus**
- Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients treated with tislelizumab. Patients should be monitored for hyperglycaemia and other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes. In patients with severe hyperglycaemia or ketoacidosis (grade ≥3), tislelizumab should be withheld and anti-hyperglycaemic treatment should be administered. Treatment with tislelizumab may be resumed when metabolic control is achieved.

❖ **Immune-related nephritis with renal dysfunction**
- Immune-related nephritis with renal dysfunction has been reported in patients treated with tislelizumab. Patients should be monitored for changes in renal function (elevated serum creatinine), and other causes of renal dysfunction should be excluded. Patients with immune-related nephritis with renal dysfunction should be managed according to the treatment modifications as recommended in Product Information.

❖ **Other immune-related adverse reactions**
- Other clinically important immune-related adverse reactions were reported with tislelizumab: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis and Guillain-Barré syndrome
- Patients with other immune-related adverse reactions should be managed according to the treatment modifications as recommended in Product Information.

❖ **Solid organ transplant rejection**
- Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with tislelizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with tislelizumab versus the risk of possible organ rejection should be considered in these patients.

❖ **Infusion-related reactions**
- Severe infusion-related reactions (grade 3 or higher) have been reported in patients receiving tislelizumab as a single agent. Patients should be monitored for signs and symptoms of infusion-related reactions.
- Infusion-related reactions should be managed as recommended in Product Information.

- **Patients excluded from clinical studies**
  - Patients with any of the following conditions were excluded from clinical studies: baseline ECOG performance score greater than or equal to 2; active brain or leptomeningeal metastases; active autoimmune disease or history of autoimmune disease that may relapse; any condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressants within the 14 days prior to study treatment; active or untreated HIV; untreated hepatitis B or hepatitis C carriers; history of interstitial lung disease; administration of live vaccine within the 14 days prior to study treatment; infection requiring systemic therapy within the 14 days prior to study treatment; history of severe hypersensitivity to another monoclonal antibody. In the absence of data, tislelizumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
- **Patients on controlled sodium diet**
  - Each ml of this medicinal product contains 0.069 mmol (or 1.6 mg) sodium. This medicinal product contains 16 mg sodium per 10 ml vial, equivalent to 0.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Study characteristics: RATIONALE-304 (Tislelizumab in combination with pemetrexed and platinum-containing chemotherapy) [6, 7]

Trial name	*n*	Intervention[2] (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
RATIONALE-304, BGB-A317-304 NCT03663205	332 2:1	tislelizumab 200 mg + platinum-based chemotherapy[3] once every 3 weeks IV for 4-6 cycles during induction treatment, followed by maintenance tislelizumab + pemetrexed treatment	platinum-based chemotherapy[4] every 3 weeks for 4-6 cycles during induction treatment, followed by maintenance pemetrexed treatment	PFS by IRC	9.8 months	open-label, multicentre, randomised, phase 3 trial	-	BeiGene	RATIONALE-304 [6]

Inclusion criteria[5]	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=223 vs. n=111)
❖ Adult patients (aged 18–75 years) who were treatment-naive for histologically confirmed locally advanced (stage IIIB) or metastatic (stage IV) non-squamous-NSCLC, as classified by the seventh edition of the American Joint Committee on Cancer Cancer Staging Manual, and without known sensitising EGFR mutations or ALK rearrangements by tissue-based analyses. ❖ Patients not amenable to curative surgery or radiotherapy had measurable disease (RECIST version 1.1). ❖ ECOG PS ≤1. ❖ Patients with prior neoadjuvant or adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a disease-free interval of ≥6 months from the last dose of chemotherapy and/or radiotherapy prior to randomisation to be eligible.	❖ Uncontrolled or untreated brain metastasis. ❖ History of interstitial lung disease or non-infectious pneumonitis. ❖ Active or relapsed autoimmune disease. ❖ Prior treatment of any systemic immunosuppressive agents within 14 days prior to initiation of study treatment.	❖ Median age (range): 60 years (27–75) vs. 61 years (25–74) ❖ <65 years: 73.1% vs. 66.7% ❖ >65 years: 26.9% vs. 33.3% ❖ Male sex: 75.3% vs. 71.2% ❖ Smoking status: • Former: 51.6% vs. 47.7% • Current: 14.3% vs. 11.7% • Never: 34.1% vs. 40.5% ❖ ECOG performance status • 0: 24.2% vs. 21.6% • 1: 75.8% vs. 78.4% ❖ Disease stage at baseline • Stage IIIB: 17.9% vs. 18.9% • Stage IV: 82.1% vs. 81.1% ❖ Histologic type • Adenocarcinoma: 96.4% vs. 96.4%

[2] All patients received premedication with folic acid, vitamin B12, and glucocorticoids according to local clinical practice or local guidelines for use of chemotherapy. The choice of platinum-based drug was determined by the investigator before the initiation of study treatments. Patients in group C could cross over to receive tislelizumab monotherapy on (IRC)-confirmed disease progression.
[3] Carboplatin area under the curve 5 or cisplatin 75 mg/m2 in combination with pemetrexed 500 mg/m^2).
[4] Carboplatin area under the curve 5 or cisplatin 75 mg/m2 in combination with pemetrexed 500 mg/m^2).
[5] Trial protocol not available.

		• Mixed adenosquamous: 0.4% vs. 1.8% • Other: 3.1% vs. 1.8% ❖ PD-L1% expression in tumour cells • <1a: 43.0% vs. 43.2% • 1–49: 23.8% vs. 24.3% • >50: 33.2% vs. 32.4% ❖ EGFR sensitising mutation status • Negative: 79.8% vs. 98.2% • Positive/unknow: 2.2% vs. 1.8% ❖ ALK rearrangement status • Negative: 74.4% vs. 71.2% • Unknown: 25.6% vs. 28.8% ❖ Location of distant metastases • Bone: 33.6% vs. 36.9% • Liver: 9.0% vs. 15.3% • Brain: 4.9% vs. 6.3% ❖ Any previous anticancer drug therapy: 6.7% vs. 7.2% ❖ Type of previous anticancer drug therapy • Adjuvant: 73.3% vs. 87.5% • Neoadjuvant: 13.3% vs. 0.0% • Curative radio chemotherapy: 6.7% vs. 0.0% • Other: 13.3% vs. 12.5%

Efficacy (I vs. C), interim analysis data	**Safety** (I vs. C, n=222 vs. n=110)
<u>Interim analysis data (data cutoff January 23 2020); median follow-up 9.8 months:</u> **PFS_{IRC}** : significantly longer in I than in C; HR 0.645 (95% CI, 0.462–0.902); p=0.0044 **Median PFS_{IRC}**: 9.7 months (95% CI, 7.7–11.5) vs. 7.6 months (95% CI, 5.6–8.0) **Estimated proportion of patients who were alive and progression-free at 12 months**: 31.3% (95% CI, 21.7–41.4) vs. 16.7% (95% CI, 6.8–30.5) **PFS by investigator's assessment:** HR 0.561 (95% CI, 0.411–0.767); p=0.0001 **Median PFS estimates in patients with stage IIIB disease**: 9.0 months vs. 7.6 months; the risk of disease progression and death was reduced in I compared with C: HR 0.664 (95% CI, 0.319–1.379) **Median PFS in patients with stage IV disease**: 9.7 months vs. 7.5 months; HR 0.632 (95% CI, 0.436–0.917) **Median PFS in patients with negative ALK rearrangement status**: 9.7 months vs. 7.6 months; HR 0.636 (95% CI, 0.434–0.930) **Median PFS in patients with unknown ALK rearrangement status**: 9.0 months vs. 6.7 months; HR 0.669 (95% CI, 0.345–1.297) **ORR:** 57.4% (95% CI, 50.6–64.0) vs. 36.9% (95% CI, 28.0–46.6) **Median DoR_{IRC} among the 128 responders receiving tislelizumab combination therapy:** 8.5 months (95% CI, 6.80–10.58) **Median DoR_{IRC} in 41 patients who achieved a response with chemotherapy alone**: 6.0 months (95% CI, 4.99–NE) **Median OS:** not reached in either arm	**Serious TEAEs:** 33.3% vs. 20.9% **Discontinuation of any treatment component due to TEAEs**: 25.7% vs. 9.1% **TEAEs leading to permanent discontinuation of tislelizumab and dose modifications**: 11.3% vs. 59.9% **TRAEs leading to death**[6]: n=3 vs. n=1

[6] All TRAEs leading to death were due to pneumonitis.

Patient-reported outcomes [8]

- HRQoL was measured using the EORTC-QLQ-C30 items and the EORTC-QLQ–LC.
- Key patient-reported outcome endpoints include mean score change from baseline at weeks 12 (during chemotherapy) and 18 (following chemotherapy) in the QLQ-C30 Core's GHS/QoL and time to deterioration in GHS/QoL.
- 332 patients received at least one dose of the study drug and completed at least 1 HRQoL assessment.
- GHS/QoL score improved in arm I at week 18 (between-group LS mean difference, 5.7 (95% CI, 1.0–10.5; p = 0.018).
- Patients in arm I experienced greater reduction in coughing (−5.9; 95% CI, −11.6 to −0.1; p = 0.044), dyspnoea (−3.8; 95% CI, −7.8 to 0.1; p = 0.059), chest pain (−6.2; 95% CI, −10.8 to −1.6; p = 0.008), and peripheral neuropathy (−2.6; 95%CI, −5.5 to 0.2; p = 0.066).
- Median time to deterioration in GHS/QoL was not achieved for either arm.

ESMO-MCBS version 1.1 [9]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	>6 months	PFS: +2.1 months	HR 0.645 (0.462–0.902)	HR≤0.65 BUT gain <3 months	2	-	-	-	2
Adapted	NC	2B	>6 months	PFS: +2.1 months	HR 0.645 (0.462–0.902)	HR≤0.65 BUT gain <3 months	2	+12.4 TEAES	-	-1[7]	1

Risk of bias (RCT) [10]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	unclear unclear risk[8]	yes high risk[9]	unclear risk

Other aspects and conclusions

- In May 2024, the **CHMP adopted a positive opinion**, recommending a change to the terms of the marketing authorisation for Tevimbra®, in combination with pemetrexed and platinum-containing chemotherapy, indicated 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. This indication has not been **approved by the FDA.**
- **RATIONALE-304 (NCT03663205)** is an **open-label phase 3 trial** (NCT03663205) assessing tislelizumab + chemotherapy as first-line treatment for locally advanced or metastatic non-squamous NSCLC. Adult patients who were treatment-naive for histologically confirmed locally advanced (stage IIIB) or metastatic (stage IV) non-squamous NSCLC, without known sensitising EGFR mutations or ALK rearrangements by tissue-based analyses and an ECOG of ≤1, were eligible. Patients with uncontrolled or untreated brain metastasis, a history of interstitial lung disease or non-infectious pneumonitis, active or relapsed autoimmune disease and prior treatment of any systemic immunosuppressive agents were excluded.
- **PFS by IRC was the primary endpoint**. **Median PFS_{IRC} was 9.7 months** (95% CI, 7.7–11.5) **vs. 7.6 months** (95% CI, 5.6–8.0); HR 0.645 (95% CI, 0.462–0.902), **p=0.0044.**
- Evaluation of PROs showed an **improvement** in Global health status/QoL, and patients in I experienced a greater reduction in coughing, dyspnoea, chest pain and peripheral neuropathy. However, improvements were **not significant**.
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **2 and 1**, respectively.
- Since only interim analysis data is available and the **trial protocol is lacking**, the risk of bias was considered **unclear**. However, the risk is **increased** by the trial's open-label design and industry-funded background.
- Final analysis data for this indication is required.

[7] Downgrade 1 level due to +12.4% toxicities.

[8] Currently, only interim analysis data is available. Trial protocol is not available.

[9] The sponsor provided financial support for the manuscript, including writing and editorial assistance. The study protocol was developed by the sponsor, in collaboration with the study investigators. The sponsor was also involved in data collection, analysis, and interpretation of results. Statistical analyses were performed by statisticians at BeiGene Ltd. and the sponsor was involved in the writing of the report and the decision to submit the article for publication.

Study characteristics: RATIONALE-307 (Tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel) [11-13]										
Trial name	*n*	Intervention (I)	Intervention (I2)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
RATIONALE-307 NCT03594747	360 1:1:1	tislelizumab (200 mg, day 1) + paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC of 5, day 1)	tislelizumab (200mg, day 1) + nab-paclitaxel (100 mg/m^2, days 1, 8, and 15) and carboplatin (AUC of 5, day 1)	paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC of 5, day 1)	PFS assessed by IRC	8.6 months	open-label, randomised, multicentre, phase 3 trial	PD-L1	BeiGene, Ltd.	RATIONALE-307

Inclusion criteria[10]	Exclusion criteria	Patient characteristics at baseline (ITT-population, I vs. I2 vs. C, n=120 vs. n=119 vs. n=121)
❖ Age 18-75 years, male or female, and signed informed consent form. ❖ Advanced NSCLC diagnosed by pathological or clinical physicians. ❖ ECOG PS ≤ 1. ❖ Participants must have ≥ 1 measurable lesion as defined per RECIST v1.1. ❖ Treatment-naive for locally advanced or metastatic squamous NSCLC. ❖ Life expectancy ≥ 12 weeks. ❖ Adequate organ function. ❖ Male/Female is willing to use a highly effective method of birth control.	❖ Diagnosed with NSCLC but with EGFR-sensitizing mutation or ALK gene translocation. ❖ Received any approved systemic anticancer therapy. ❖ Received prior treatment with EGFR inhibitors or ALK inhibitors. ❖ Received prior therapies targeting PD-1 or PD-L1. ❖ History of interstitial lung disease. ❖ Clinically significant pericardial effusion. ❖ Severe infections, active leptomeningeal disease or uncontrolled, untreated brain metastasis. ❖ Any major surgical procedure before randomisation. ❖ HIV infection. ❖ Untreated HBV/HCV. ❖ Active autoimmune diseases or history of autoimmune diseases. ❖ History of allergic reactions to chemotherapy.	❖ Median age (range): 60 (41-74) vs. 63 (38-74) vs. 62 (34-74) years ❖ Age group: • <65: 67.5 vs. 56.3 vs. 70.2 years • ≥65: 32.5% vs. 43.7% vs. 29.8% ❖ Male sex: 89.2% vs. 94.1% vs. 91.7% ❖ Tobacco use: • Current/former: 80.0% vs. 89.9 vs. 81.0% • Never: 20.0% vs. 10.1% vs. 19.0% ❖ ECOG status: • 0: 25.8% vs. 18.5% vs. 26.4% • 1: 74.2% vs. 81.5% vs. 73.6% ❖ Solid tumour stage: • Stage IIIB: 31.7% vs. 33.6% vs. 36.4% ❖ Stage IV: 68.3% vs. 66.4% vs. 63.6% ❖ PD-L1 expression on tumour cells: • <1: 40.0% vs. 39.5% vs. 40.5% • 1-49: 25.0% vs. 25.2% vs. 25.6% • ≥50: 35.0% vs. 35.3 vs. 33.9% ❖ Confirmed distant metastatic site(s): • Bone: 20.0% vs. 13.4% vs. 17.4% • Liver: 12.5% vs. 12.6% vs. 11.6% • Brain: 1.7% vs. 2.5% vs. 0.8%

Efficacy (I vs. I2 vs. C), interim analysis data	**Safety** (I vs. I2 vs. C, n=120 vs. n=118 vs. n=117)
Data cutoff December 6 2019; median follow-up time 8.6 months At the time of data cutoff, 54 patients had **crossed over** from group C to tislelizumab monotherapy. **Median IRC-assessed PFS**: 7.6 months (95% CI, 6.0-9.8) vs. 7.6 months (95% CI, 5.8–11.0) vs. 5.5 months (95% CI, 4.2-5.7) **Stratified HRs:** 0.524 (95% CI, 0.370-0.742; p< .001) between arms I and C and 0.478 (95% CI, 0.336-0.679; p< .001) between arms I2 and C	**Patients with ≥1 TEAE:** 100.0% vs. 99.2% vs. 100.0% **Grade ≥3 TEAE:** 88.3% vs. 86.4% vs. 83.8% **Serious TEAE:** 36.7% vs. 38.1% vs. 24.8% **TEAE leading to death:** 3.3% vs. 4.2% vs. 4.3% **TEAEs leading to discontinuation**

[10] For detailed in- and exclusion criteria, please see trial protocol.

9-month PFS rate: 41.7% (95% CI, 30.9-52.1) vs. 47.2% (95% CI, 36.5-57.2) vs. 17.5% (95% CI, 9.8-26.9)
Median PFS estimates in patients with stage IIIB disease: 9.8 vs.11.0 vs. 5.6 months
Risk of disease progression and death: I vs. C (HR 0.402; 95% CI, 0.215-0.750); I2 vs. C (HR, 0.372; 95% CI, 0.202-0.686)
Median PFS estimates in patients with stage IV disease: 7.6 vs. 7.4 vs. 5.2 months
Risk of disease progression and death: I vs. C (HR 0.570; 95% CI, 0.376-0.862); I2 vs. C (HR 0.537; 95% CI, 0.350-0.824)
ORR: 73% (95% CI, 63.6%-80.3%) vs. 75% (95% CI, 66.0%-82.3%) vs. 50% (95% CI, 40.4%-58.8%)
Median IRC-assessed DoR: 8.2 months (95% CI, 5.0-NE) vs. 8.6 months (95% CI, 6.3-NE) vs. 4.2 months (95% CI, 2.8-4.9)
OS data: not mature

- **Any study treatment component:** 12.5% vs. 29.7% vs. 15.4%
  - **Tislelizumab:** 10.0% vs. 10.1% vs. NA
  - **Paclitaxel:** 7.5% vs. NA vs. 14.5%
  - **nab-paclitaxel:** NA vs. 23.7% vs. NA
  - **Carboplatin:** 7.5% vs. 22.9% vs. 14.5%

TRAEs grade≥3: 85.8% vs. 83.9% vs. 80.3%
TEAEs leading to death: 3.3% vs. 4.2% vs. 4.3%
TRAEs leading to death[11]: n= vs. n=2 vs. n=3

Patient-reported outcomes [14]

- HRQoL was measured using the EORTC-QLQ-C30 and the EORTC-QLQ-LC13.
- Mean score change from baseline at Weeks 6 and 12 in the QLQ-C30's GHS/QoL, fatigue, and physical functioning scores and QLQ-LC13 lung cancer-specific subscales were examined.
- Time to deterioration was estimated for the GHS/QoL score.
- A total of 355 squamous-NSCLC patients received at least one dose of the study drug and completed at least one HRQoL assessment.
- The GHS/QoL scores improved in I and I2 relative to C at weeks 6 and 12.
- Groups I and I2 also experienced a reduction in most lung cancer-specific symptoms relative to group C.
- The time to deterioration of GHS/QoL was not reached by any of the three groups.
- The addition of tislelizumab to platinum-based chemotherapy is associated with improvements in squamous-NSCLC patients' HRQoL, especially in GHS/QoL and in lung cancer-specific symptoms, including coughing, dyspnoea, and haemoptysis.

ESMO-MCBS version 1.1 [9]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	≤6 months	PFS: +2.1 months	0.524 (0.370-0.742)	HR ≤0.65 AND gain ≥1.5 months	3	-	-	-	3
Adapted	NC	2B	≤6 months	PFS: +2.1 months	0.524 (0.370-0.742)	HR ≤0.65 AND gain ≥1.5 months	3	Serious TEAEs: +11.9%	-	-1[12]	2

Risk of bias (RCT) [10]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	unclear unclear risk[13]	yes high risk[14]	unclear

Other aspects and conclusions

- In May 2024, the **CHMP adopted a positive opinion** recommending a change to the terms of the marketing authorisation for Tevimbra®, 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. This indication has not been **approved by the FDA**.
- **RATIONALE-307 (NCT03594747)** is an **open-label, randomised, multicentre, phase 3 trial** evaluating the efficacy and safety/tolerability of tislelizumab plus chemotherapy vs. chemotherapy alone as first-line treatment for patients with advanced squamous NSCLC. Adult patients with treatment-naive, histologically confirmed locally advanced (stage IIIB) or

[11] None of which were solely attributed to tislelizumab. These TRAEs were hydrocephalus (I, n = 1), hepatic failure (I2, n = 1), death (I2, n = 1 and C, n = 1), and septic shock (C, n = 2).
[12] Downgrade 1 level due to +11.9% TEAEs.
[13] Currently, only interim analysis data is available.
[14] The study protocol was developed by the sponsor in collaboration with the study investigators. The sponsor was also involved in data collection, analysis, and interpretation of results. Statistical analyses were performed by statisticians at BeiGene, Ltd.

metastatic (stage IV) squamous-NSCLC who were not amenable to curative surgery or radiotherapy and had an ECOG PS of ≤1 was eligible. Patients with known EGFR-sensitizing sequence variants or ALK fusions, a history of interstitial lung disease, or non-infectious pneumonitis were ineligible.

- **PFS by IRC was the primary endpoint**. Median IRC-assessed PFS was 7.6 months (95% CI, 6.0-9.8) vs. 7.6 months (95% CI, 5.8–11.0) vs. 5.5 months (95% CI, 4.2-5.7); stratified HRs: 0.524 (95% CI, 0.370-0.742; p< .001) between arms I and C and 0.478 (95% CI, 0.336-0.679; p< .001) between arms I2 and C.
- Although evaluation of PROs showed **improvements in HRQoL**, especially in GHS/QoL and in lung cancer-specific symptoms, including coughing, dyspnoea, and haemoptysis, the improvements were **not significant.**
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit **grade of 3 and 2**, respectively.
- The **risk of bias** was considered **unclear**; no final analysis data is available. However, the **risk is increased** by the open-label trial design and the extensive involvement of the sponsor.
- Final analysis data is required to determine the role of tislelizumab for this indication.

Study characteristics: RATIONALE-303 (Tislelizumab monotherapy) [15, 16]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
RATIONALE-303 NCT03358875	805 2:1	tislelizumab 200 mg IV every 3 weeks	docetaxel 75 mg/m^2 every 3 weeks.	OS in the ITT- and PD-L1 TC expression≥25-populations	16.0 months vs. 10.7 months	global, open-label, randomised, phase 3 clinical trial	PD-L1	BeiGene	Rationale-303 [15]

Inclusion criteria[15]	Exclusion criteria	Patient characteristics at baseline I vs. C, n=535 vs. n=270)
❖ Aged ≥ 18 with histologically confirmed disease, which is currently locally advanced or metastatic NSCLC of either squamous or non-squamous histology. ❖ Disease progression during or following treatment with at least one platinum-containing regimen. ❖ Patients who received prior neo-adjuvant or adjuvant chemotherapy but progressed within six months after the last dose are eligible, provided the target lesion(s) have not been previously treated with local therapy (radiation) or the target lesion(s) within the field of local therapy have subsequently progressed as defined per RECIST v1.1. ❖ Patients must be able to provide archival/fresh tumour tissues for biomarker analysis to assess PD-L1 expression and provide sufficient tissue, including tumour mutational burden, and gene expression profiling. ❖ ECOG PS ≤ 1. ❖ Adequate haematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 28 days prior to randomisation):	❖ Prior docetaxel treatment for metastatic disease or prior immune checkpoint inhibitor therapies targeting PD-1, PD-L1 or CTLA-4. ❖ Diagnosed with NSCLC that harbours EGFR sensitising, driver mutation, or ALK gene translocation. ❖ Patients with toxicities (as a result of prior anticancer therapy, including radiation) have not recovered to baseline or stabilised, except for AEs not constituting a likely safety risk. ❖ Received chemotherapy, immunotherapy, or investigational agent used to control cancer ≤ 28 days prior to randomisation. ❖ Received any herbal medicine used to control cancer within 14 days prior to randomisation. ❖ History of severe hypersensitivity reactions to other monoclonal antibodies. ❖ History of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc. ❖ Patients with significantly impaired pulmonary function or who require supplemental oxygen at baseline. ❖ Clinically significant pericardial effusion. ❖ Clinically uncontrolled pleural effusion or ascites that requires pleurocentesis or abdominal tapping for drainage within 2 weeks prior to randomisation.	❖ Median age (range): 61.0 (28–88) vs. 61.0 (32–81) years ❖ Patients aged <65 years: 68.0% vs. 66.7% ❖ Male sex: 77.8% vs. 76.3% ❖ Race: • Asian: 79.3% vs. 81.1% • White: 17.4% vs. 16.3% • Other: 3.4% vs. 2.6% ❖ Region: • People's Republic of China: 79.1% vs. 80.7% • Rest of world: 20.9% vs. 19.3% ❖ ECOG performance status: • 0: 21.7% vs. 18.5% • 1: 78.3% vs. 81.5% ❖ Smoking status: • Never: 30.3% vs. 30.4% • Current/former: 69.7% vs. 69.6% ❖ PD-L1 expression: • <25% TC: 57.6% vs. 57.0% • 25% TC: 42.4% vs. 43.0% ❖ Pathologic type: • Squamous: 46.4% vs. 45.2%

[15] For detailed in- and exclusion criteria, please see trial protocol.

• ANC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and haemoglobin ≥ 90 g/L. • eGFR > 30 mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration equation. • Total serum bilirubin ≤ 1.5 × ULN • ≤ 3 × ULN, if Gilbert's syndrome or if indirect bilirubin concentrations are suggestive of extrahepatic source of the elevation. • AST and ALT ≤ 3 × ULN (≤ 5 × ULN, if liver metastases) ❖ Females of childbearing potential must be willing to practice highly effective method of birth control for the duration of the study, and, for patients in I, for at least 120 days after the last dose of tislelizumab, and have a negative urine or serum pregnancy test within 7 days of randomisation. ❖ Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and, for patients in I, for at least 120 days after the last dose of tislelizumab. ❖ Expected life span > 12 weeks.	❖ Active Leptomeningeal disease or uncontrolled, untreated brain metastasis. ❖ Major surgical procedure requiring general anaesthesia, or significant traumatic injury ≤ 28 days prior to randomisation, or anticipation of need for major surgical procedure during the course of the study. ❖ Malignancy other than NSCLC. ❖ Severe chronic or active infections requiring systemic antibacterial, antifungal, antiviral therapy, or systemic oral/IV antibiotics within 14 days prior to randomisation. ❖ A known history of HIV infection. ❖ Patients with active/symptomatic carrier or chronic HBV whose HBV DNA ≥ 500 IU/mL (or ≥ 2500 copies/mL) should be excluded. ❖ Active autoimmune diseases or history of autoimmune diseases that may relapse should be excluded. ❖ Requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of randomisation. ❖ Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomisation. ❖ Cardiovascular criteria as defined in the trial protocol. ❖ Prior allogeneic stem cell transplantation or organ transplantation. ❖ Was administered a live vaccine ≤ 4 weeks before randomisation.	• Non-squamous: 53.6% vs. 54.8% ❖ Current line of therapy: • Second: 84.7% vs. 84.8% • Third: 15.3% vs. 15.2% ❖ Disease stage: • Locally advanced: 15.7% vs. 12.2% • Metastatic: 84.3% vs. 87.8% ❖ Confirmed distant metastatic site(s): • Bone: 31.0% vs. 29.3% • Liver: 13.6% vs. 12.2% • Brain: 7.3% vs. 6.7%

Efficacy (I vs. C)	**Safety** (I vs. C, n=534 vs. n=258)
Data cutoff for interim analysis: August 10 2020 **Median OS in ITT population:** 17.2 months (95% CI: 15.3–20.0) vs. 11.9 months (95% CI: 10.2–13.9); HR 0.64 (95% CI: 0.53–0.78); p < 0.0001 **Median OS in PD-L1 ≥25% population:** 19.1 months (95% CI: 16.8–25.8) vs. 11.9 months (95% CI: 8.9–14.0); HR 0.52 (95% CI: 0.38–0.71) **Data cutoff for the final analysis: July 15 2021** **ITT population:** **Median OS:** 16.9 months (95% CI: 15.2–19.1) vs. 11.9 months (95% CI: 9.6–13.5); HR 0.66 (95% CI: 0.56–0.79) **OS rates at 12 and 24 months:** 62.1% vs. 49.7% and 36.8% vs. 23.7% **PFS:** HR 0.63 (95% CI: 0.53–0.75); p < 0.0001 **ORR:** 22.6% (95% CI: 19.1–26.4) vs. 7.1% (95% CI: 4.3–10.8); p < 0.0001 **Median DoR:** 13.5 (95% CI: 8.5–19.6) vs. 6.0 (95% CI: 2.1–7.2) months **PD-L1 ≥25% population:** **Median OS:** 19.3 months (95% CI: 16.5–22.6) vs. 11.5 months (95% CI: 8.2–13.5); HR 0.53 (95% CI: 0.40–0.70); p < 0.0001 **OS rates at 12 and 24 months:** 67.4% and 47.8% vs. 42.3% and 22.3%	**Data cutoff July 15 2021:** **TEAE of any grade and any cause**: 96.8% vs. 98.4% **TEAEs of grade ≥3**: 42.1% vs. 74.8% **TRAEs of any grade**: 74.9% vs. 93.8% **TRAEs of grade ≥3:** 15.7% vs. 66.3% **TEAEs leading to death**: 6.4% vs. 4.7% **Treatment-related deaths**: 1.5% vs. 1.6% **Immune-mediated TEAEs of all grades**: 18.9% vs. NA

PFS: 0.37 (95% CI: 0.28–0.49), p <0.0001
ORR: 37.4% (95% CI: 31.3–44.1) vs. 6.9% (95% CI: 3.0–13.1); p < 0.0001
Median DoR: 11.9 (95% CI: 8.3–19.6) vs. 4.2 (95% CI: 0.6–6.1) months

PD-L1 ≤25% population:
Median OS in the PD-L1 ≤25% population: 15.2 months (95% CI: 13.2–17.6) vs. 12.3 months (95% CI: 9.3–14.3); HR 0.77 (95% CI: 0.62–0.96).
OS rates at 12 and 24 months in the PD-L1 ≤25% population: 58.3% vs. 51.1% and 32.8% vs. 24.7%

Efficacy in the biomarker-evaluable population, final analysis (data cutoff July 15 2021)

- In the biomarker analysis, the association of TMB and genetic alterations at baseline, including single target gene mutation or pathway mutations, with clinical outcomes was explored. Tissue TMB was correlated with PFS benefit for tislelizumab vs. docetaxel but was not correlated with OS benefit, except at the highest cutoff (≥14 mutations/megabase).
- Among tested single target gene mutation or pathway mutations, NOTCH1–4 mutation was correlated with improved PFS and OS benefits for tislelizumab.
- Tislelizumab treatment had a greater OS benefit for patients with NOTCH1–4 mutation than wild type, compared with the docetaxel arm.
- Median OS for patients with NOTCH1–4 mutations was 24.7 months (95% CI: 14.2–not estimable) vs. 7.7 months in the docetaxel arm (95% CI: 3.3–14.3); HR 0.22 (95% CI: 0.10–0.49); p = 0.0002).
- Median OS for patients with NOTCH wild type: 15.7 months (95% CI: 13.9–17.9) vs. 12.9 months (95% CI: 10.4–14.9); HR 0.75 (95% CI: 0.57–0.99); p=0.0390
- Median PFS in patients with NOTCH1–4 mutations: 14.1 months (95% CI: 6.2–NE) vs. 2.6 months (95% CI: 2.0–4.1); HR 0.17 (95% CI: 0.08–0.37); p < 0.0001
- Median PFS in patients with NOTCH wild type: 4.1 months (95% CI: 2.2–6.2) vs. 3.3 months in the docetaxel arm (95% CI: 2.1–4.1); HR 0.72 (95% CI: 0.55–0.95); p=0.0197)

Patient-reported outcomes [17]

- HRQoL was assessed with the EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-5D-5L instruments.
- A longitudinal analysis of covariance assessed the change from baseline to Week 12 and from baseline to Week 18.
- A time-to-deterioration analysis was also performed using the Kaplan–Meier method.
- The tislelizumab arm improved while the docetaxel arm worsened in the QLQ-C30 global health status/QoL scale score (difference LS mean change Week 18: 5.7; 95% CI, 2.38, 9.07, p=0.0008), fatigue (Week 12: -3.2; 95% CI, −5.95, −0.37, p<0.0266; Week 18: −4.9;95% CI, −8.26, −1.61, p=0.0037), and QLQ-LC13 symptom index score (Week 12: −5.5; 95% CI, −6.93, −4.04, p<0.0001); Week 18: −6.6; 95% CI, −8.25, −4.95, p<0.0001).
- The tislelizumab arm had improvements in coughing versus the docetaxel arm (Week 12: −4.7; 95% CI, −8.57, −0.78, p=0.0188); Week 18: −8.3; 95% CI, −13.02, −3.51, p=0.0007).
- The patients who received tislelizumab were less at risk for clinically meaningful worsening in the overall lung cancer symptom index scale (HR 0.24; 95% CI, 0.162, 0.356, p<0.0001), dyspnoea (HR 0.74, 95% CI, 0.567, 0.958, p=0.0109), coughing (HR: 0.74, 95% CI, 0.534, 1.019, p=0.0309), and peripheral neuropathy (HR 0.55, 95% CI, 0.370, 0.810, p=0.0011).

ESMO-MCBS version 1.1 [9]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +5.0 months	0.66 (0.56–0.79)	HR≤0.65 AND gain ≥3 months	4	-	significant improvement	+1[16]	5

[16] Upgrade 1 level due to significant improvement of QoL.

Adapted	NC	2A	≤12 months	OS: +5.0 months	0.66 (0.56–0.79)	HR >0.65-0.70 AND gain ≥1.5 months	2	-	significant improvement	+1[17]	3

Risk of bias (RCT) [10]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	yes low risk	yes high risk[18]	High risk

Other aspects and conclusions

- In February 2024, the **CHMP adopted a positive opinion**, recommending a change to the terms of the marketing authorisation for Tevimbra®, indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy. This indication has not been **approved by the FDA**.
- **RATIONALE-303 (NCT03358875)** is a **global, open-label, randomised, phase 3 trial** comparing tislelizumab vs. docetaxel in patients with previously treated advanced NSCLC. Adults with histologically confirmed, locally advanced or metastatic squamous or non-squamous NSCLC, regardless of level of tumour PD-L1 expression, who had progressive disease during or after at least one platinum-containing doublet regimen and had an ECOG PS of 0 or 1, were included. Patients with previous docetaxel treatment for metastatic disease or previous immune checkpoint inhibitor therapies targeting PD-1, PD-L1, or CTLA-4 and patients with known EGFR mutation or ALK gene translocation were ineligible.
- **OS in the ITT- and PD-L1 TC expression≥ 25 populations were co-primary endpoints**. Median OS in the ITT populations was 16.9 months (95% CI: 15.2–19.1) vs. 11.9 months (95% CI: 9.6–13.5); HR 0.66 (95% CI: 0.56–0.79). Median OS in the PD-L1 ≥25% population was 19.3 months (95% CI: 16.5–22.6) vs. 11.5 months (95% CI: 8.2–13.5); HR 0.53 (95% CI: 0.40–0.70); p < 0.0001.
- **PROs** were assessed, showing **significant improvement** for patients receiving tislelizumab.
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **5 and 3**, respectively.
- The **risk of bias** was considered **high** due to the open-label design and the broad involvement of the sponsor.

Ongoing trials [18]

NCT number/trial name	Description	Estimated study completion date
NCT04379635	A randomised, double-blind, placebo-controlled, phase 3 study to compare the efficacy and safety of neoadjuvant treatment with tislelizumab or placebo plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab or placebo in resectable stage II or IIIA NSCLC.	11/2025
NCT04746924	A phase 3, randomised, double-blind study of ociperlimab, in combination with tislelizumab, compared to pembrolizumab in patients with previously untreated, PD-L1-selected, and locally advanced, unresectable, or metastatic NSCLC.	10/2026
NCT05990127	A randomised, double-blind, phase III trial to compare the efficacy and safety of AK104 combined with chemotherapy to tislelizumab combined with chemotherapy as first-line treatment in PD-L1 TPS < 1% NSCLC.	11/2026

Available assessments

- No assessment was identified via NICE, CADTH, G-BA, ICER and NIHR.

First published: 06/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, AUC=area under the curve, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DNA=deoxyribonucleic acid, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance score, eGFR=estimated glomerular filtration rate, EGFR=epidermal growth factor receptors, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EPAR=European public assessment report, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GHS=global health score, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HR=hazard ratio, HRQoL=health-

[17] Upgrade 1 level due to significant improvement of QoL.

[18] Financial support for this study was provided by the sponsor. The sponsor had a role in the study design, data collection, data analysis, and data interpretation. Funding for medical writing support was provided by the sponsor. Third-party medical writing assistance was funded by the sponsor.

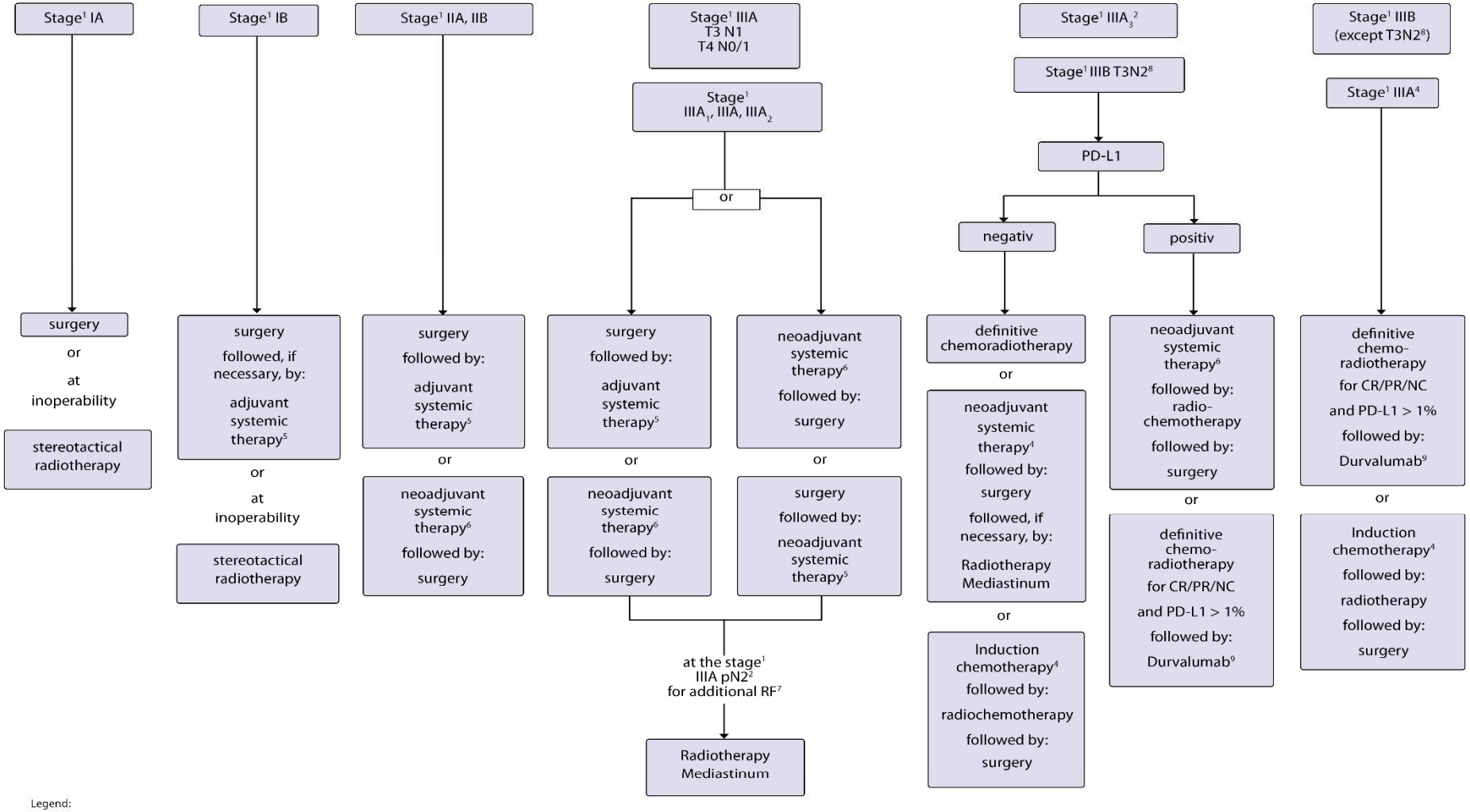
related quality of life, HRT=hormone replacement therapy I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IRC=independent review committee, ITT=intention-to-treat, IV=intravenous, LS= least square, MG=median gain, n=number of patients, NE=not estimable, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, OESCC=oesophageal squamous cell carcinoma, ORR=objective response rate, OS=overall survival, PD-1=programmed cell death protein-1, PD-L1=programmed death-ligand 1, PD-L2=Programmed cell death protein ligand -2, PE=primary endpoint, PFS=progression-free survival, PFS_{IRC}=PFS as assessed by the IRC, PM=preliminary grade, QLQ-LC13=Questionnaire Lung Cancer 13 items, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumours, SAE=serious adverse event, SCAR=severe cutaneous adverse reaction, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event, ULN=upper limit of normal, WHO=World Health Organization

References:

1. European Medicines Agency (EMA). Tevimbra: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/tevimbra-epar-product-information_en.pdf].
2. European Medicines Agency (EMA). Tevimbra - opinion on variation to marketing authorisation. [Available from: https://www.ema.europa.eu/en/medicines/human/variation/tevimbra].
3. Statistik Austria. Krebserkrankungen. Krebsinzidenz nach ausgewählten Lokalisationen und Geschlecht. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
4. Onkopedia, Griesinger F, et al. Onkopedia Guidelines. Lung Cancer, non small lung cancer (NSCLC). [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/lung-cancer-non-small-lung-cancer-nsclc/@@guideline/html/index.html#ID0EW5AG].
5. U.S. Food and Drug Administration (FDA). Tevimbra. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761232Orig1s000lbl.pdf].
6. Shun Lu, Jie Wang, Yan Yu ea. Tislelizumab Plus Chemotherapy as First-Line Treatment for Locally Advanced or Metastatic Non-squamous NSCLC (RATIONALE 304): A Randomised Phase 3 Trial. J Thorac Oncol 2021 Sep;16(9):1512-1522. DOI: 10.1016/j.jtho.2021.05.005 Epub 2021 May 23.
7. U.S. National Library of Medicine, ClinicalTrials.gov. A Study Evaluating the Efficacy and Safety of Tislelizumab Versus Chemotherapy in Advanced Non-Squamous NSCLC. [Available from: https://clinicaltrials.gov/study/NCT03663205#publications].
8. Lu S, et al. Examining the Impact of Tislelizumab Added to Chemotherapy on Health-Related Quality-of-Life Outcomes in Previously Untreated Patients With Non-squamous Non–Small Cell Lung Cancer. The Cancer Journal Volume 28, Number 2, March/April 2022.
9. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
10. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].
11. Supplement to: Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non–small-cell lung cancer: a phase 3 randomised clinical trial. JAMA Oncol. Published online April 1, 2021. doi:10.1001/jamaoncol.2021.0366.
12. Jie Wang, Shun Lu, Xinmin Yu, et al. Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non–Small-Cell Lung Cancer A Phase 3 Randomised Clinical Trial. JAMA Oncol 2021;7(5):709-717. DOI: 10.1001/jamaoncol.2021.0366
13. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of Tislelizumab in Combination With Chemotherapy Versus Chemotherapy in Advanced Lung Cancer. [Available from: https://clinicaltrials.gov/study/NCT03594747].
14. Wang J, et al. The effects of tislelizumab plus chemotherapy as first-line treatment on health-related quality of life of patients with advanced squamous non-small cell lung cancer: Results from a phase 3 randomised clinical trial. Cancer Treatment and Research Communications 30 (2022) 100501.
15. Caicun Zhou, Dingzhi Huang, Yun Fan ea. Tislelizumab Versus Docetaxel in Patients With Previously Treated Advanced NSCLC (RATIONALE-303): A Phase 3, Open-Label, Randomized Controlled Trial. Journal of Thoracic Oncology Vol 18 No 1: 93–105.

16. U.S. National Library of Medicine, ClinicalTrials.gov. Comparison of Efficacy and Safety of Anti-PD-1 Antibody BGB-A317 Versus Docetaxel as Treatment in the Second- or Third-line Setting in Participants With NSCLC. [Available from: https://www.clinicaltrials.gov/study/NCT03358875].
17. Huang D, et al. The effects of tislelizumab treatment on the health-related quality of life of patients with advanced non-small cell lung cancer. Cancer Med 2023 Aug;12(16):17403-17412.
18. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://www.clinicaltrials.gov/].

Appendix – Figure 1: Therapy algorithm for non-molecular stratified drug therapy in advanced stages of NSCLC



Legend:

curative intent therapy;

[1] *clinical stages;*
[2] *Individual therapy should be determined in an interdisciplinary tumor board involving all diagnostic and therapeutic disciplines;*
[3] *negative: PD-L1 <1%; positive ≥1%;*
[4] *surgery - umbrella term for all forms of tumor resection or ablation*
[5] *adjuvant systemic therapy after resection includes*
- *platinum-containing chemotherapy in stages IIA - IIIA and*
- *in case of EGFRmut (del 19, L858R) in stages IB - IIIA: osimertinib (for classification change from UICC 7th edition or according to UICC 8th edition see chapter 6.1.2.) and*
- *for PD-L1 expression on tumor cells ≥50% in stages IIA - IIIA in EGFR/ALK wild-type: atezolizumab;*
- *or a combination of these options*

[6] *platinum-containing combination chemotherapy + nivolumab; for divergent approvals in respective countries.*
[7] *Additional risk factors: multiple N2 infestations and capsular overgrowth;*
[8] *pT3 criterium based on extent of the tumor, infiltration of the chest wall or size between 5-7 cm*
[9] *see currently valid marketing authorization information; approval in Switzerland independent of PD-L1 status.*