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

General information [1]

Drug description

The active substance of Tizveni® is tislelizumab, an antineoplastic agent. Tislelizumab is a humanised IgG4 variant monoclonal antibody that potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Indication

- ❖ Tislelizumab (Tizveni®) 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.
- ❖ Tiselizumab (Tizveni®) 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 (Tizveni®) 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 [2]

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 [3]

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 [1]	FDA
Approval status for this indication: On 22 February 2024, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tizveni®, intended for the treatment of locally advanced or metastatic NSCLC either in monotherapy or in combination with chemotherapy.	**Approval status for this indication**: not approved

The full indication is:
❖ Tizveni® 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.
❖ Tizveni® 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 or platinum-based chemoradiation, or
  • metastatic NSCLC.
❖ Tizveni® 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: none
	Other indications: not approved

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[1] European Standard Population 2013.

Manufacturer
Tizveni® is manufactured by BeiGene.

Costs
Currently, there is no cost information available.

Posology
Currently, there is no EMA EPAR available.

Warnings and precautions
Currently, there is no EMA EPAR available.

Study characteristics: RATIONALE-304 (Tizveni® in combination with pemetrexed and platinum-containing chemotherapy) [4, 5]

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, multicenter, randomized, phase 3 trial	-	BeiGene	RATIONALE-304 [4]

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 sensitizing EGFR mutations or ALK rearrangements by tissue-based analyses. - Patients who were 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 randomization to be eligible.	- Uncontrolled or untreated brain metastasis. - History of interstitial lung disease or noninfectious 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/m2).

[4] Carboplatin area under the curve 5 or cisplatin 75 mg/m2 in combination with pemetrexed 500 mg/m2).

[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 sensitizing 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 radiochemotherapy: 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)

Efficacy (I vs. C), interim analysis data

Interim analysis data (data cutoff 23 January 2020); median follow-up 9.8 months:

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

Safety (I vs. C, n=222 vs. n=110)

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

Patient-reported outcomes [6]

- ❖ 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.

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

- ❖ 332 patients received at least 1 dose of 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 [7]

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) [8]

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 February 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Tizveni®, 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 is **not 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 nonsquamous NSCLC. Adult patients who were treatment-naive for histologically confirmed locally advanced (stage IIIB) or metastatic (stage IV) nonsquamous NSCLC, without known sensitizing 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 noninfectious 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 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 there is only **interim analysis data** available and the **trial protocol is lacking**, the risk of bias was considered **unclear**. However, the risk is **increased** by the open-label design and the industry-funded background of the trial.
- ❖ Final analysis data for this indication is required.

Study characteristics: RATIONALE-307 (Tizveni® in combination with carboplatin and either paclitaxel or nab-paclitaxel) [9-11]

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/m², day 1) and carboplatin (AUC of 5, day 1)	tislelizumab (200mg, day 1) + nab-paclitaxel (100 mg/m², days 1, 8, and 15) and carboplatin (AUC of 5, day 1)	paclitaxel (175 mg/m², day 1) and carboplatin (AUC of 5, day 1)	PFS assessed by IRC	8.6 months	open-label, randomized, multicentre, phase 3 trial	PD-L1	BeiGene, Ltd.	RATIONALE-307

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[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.

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 randomization.
	❖ 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)

<u>Data cutoff 6 December 2019;</u> 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
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
	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
	  • **Any study treatment component:** 12.5% vs. 29.7% vs. 15.4%
	    o **Tislelizumab:** 10.0% vs. 10.1% vs. NA
	    o **Paclitaxel:** 7.5% vs. NA vs. 14.5%
	    o **nab-paclitaxel:** NA vs. 23.7% vs. NA
	    o **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

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

[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).

Patient-reported outcomes [12]

- ❖ 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 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.
- ❖ 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 [7]

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) [8]

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 February 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Tizveni®, 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 is **not approved by the FDA**.
- ❖ **RATIONALE-307 (NCT03594747)** is an **open-label, randomized, multicentre, phase 3 trial** evaluating 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 metastatic (stage IV) squamous-NSCLC who were not amenable to curative surgery or radiotherapy and had an ECOG PS of ≤1 were eligible. Patients with known EGFR-sensitizing sequence variants or ALK fusions, a history of interstitial lung disease, or noninfectious 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 (Tizveni® monotherapy) [13, 14]

Trial name	n	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)

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[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.

RATIONALE-303 NCT03358875	805 2:1	tislelizumab 200 mg IV every 3 weeks	docetaxel 75 mg/m² every 3 weeks.	OS in the ITT- and PD-L1 TC expression≥25-populations	16.0 months vs. 10.7 months	global, open-label, randomized, phase 3 clinical trial	PD-L1	BeiGene	Rationale-303 [13]

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 6 months after 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, provided 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 randomization):
  • ANC ≥ 1.5 × 10⁹/L, platelets ≥ 100 × 10⁹/L, and haemoglobin ≥ 90 g/L.
  • eGFR > 30 mL/min/1.73m² 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
	❖ 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 sensitizing or driver mutation or ALK gene translocation.
	❖ Patients with toxicities (as a result of prior anticancer therapy including radiation) which have not recovered to baseline or stabilized, except for AEs not constituting a likely safety risk.
	❖ Received chemotherapy, immunotherapy, or investigational agent, used to control cancer ≤ 28 days prior to randomization.
	❖ Received any herbal medicine used to control cancer within 14 days prior to randomization.
	❖ 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 randomization.
	❖ Active Leptomeningeal disease or uncontrolled, untreated brain metastasis.
	❖ Major surgical procedure requiring general anaesthesia, or significant traumatic injury ≤ 28 days prior to randomization, 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 randomization.
	❖ 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 randomization.
		❖ 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%
		  • Nonsquamous: 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%

have a negative urine or serum pregnancy test within 7 days of randomization. ❖ 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.	❖ 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 randomization. ❖ Cardiovascular criteria as defined in the trial protocol. ❖ Prior allogeneic stem cell transplantation or organ transplantation. ❖ Was administered a live vaccine ≤ 4 weeks before randomization.	

Efficacy (I vs. C)	Safety (I vs. C, n=534 vs. n=258)
Data cutoff for interim analysis: 10 August 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: 15 July 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% **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 15 July 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	**Data cutoff 15 July 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

- 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 [15]

- 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 [7]

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
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) [8]

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 the granting of a marketing authorisation for Tizveni®, indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy. This indication is **not approved by the FDA**.
- **RATIONALE-303 (NCT03358875)** is a **global, open-label, randomized, phase 3 trial**, comparing tislelizumab vs. docetaxel in patients with previously treated advanced NSCLC. Adults with histologically confirmed, locally advanced or metastatic squamous or nonsquamous 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 who had received 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 [16]

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

[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.

NCT number/trial name	Description	Estimated study completion date
NCT04379635	A randomized, 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, randomized, 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 randomized, 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: 03/2024

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-related quality of life, 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, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, 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, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event, ULN=upper limit of normal
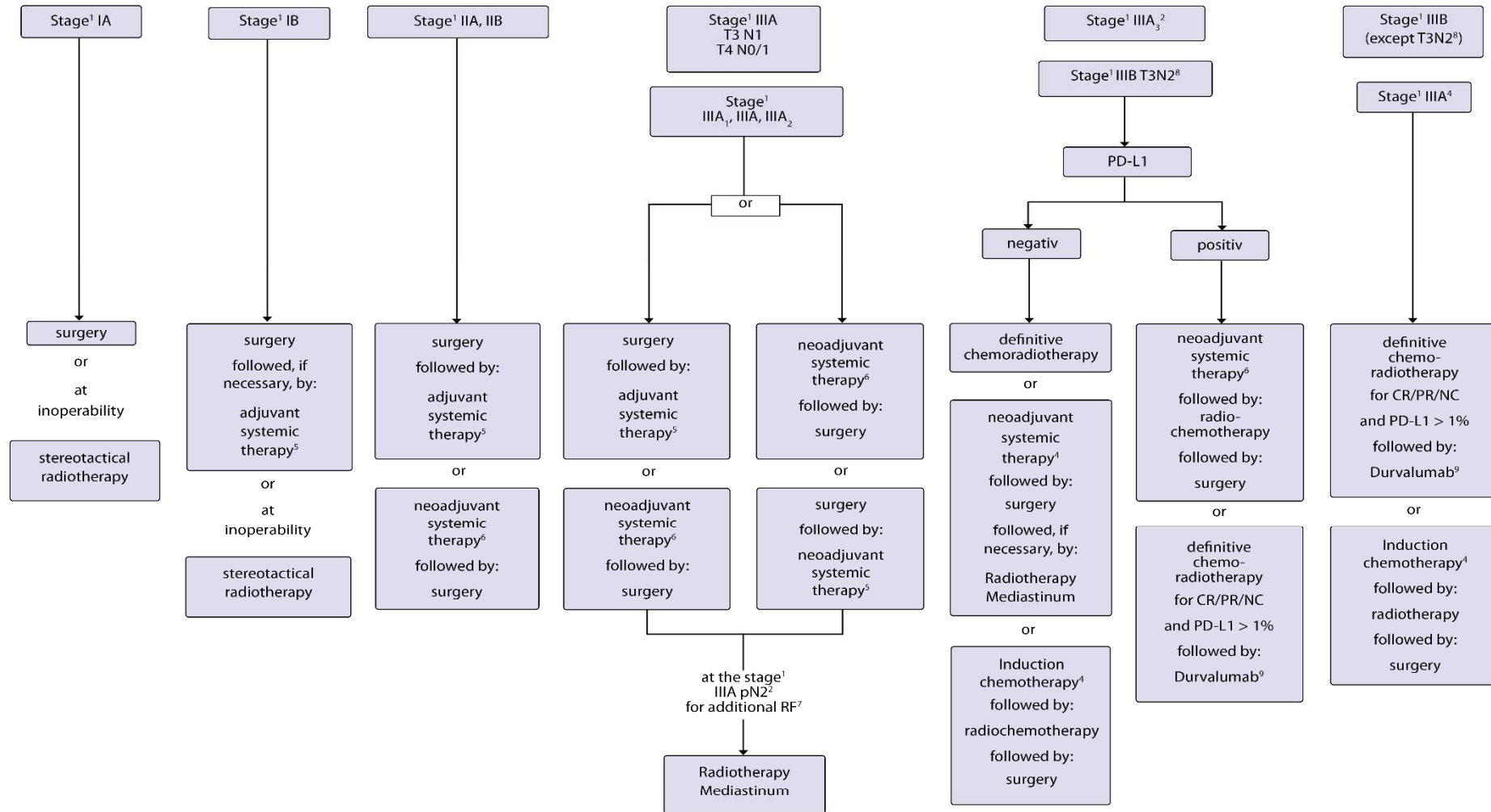
References:

1. European Medicines Agency (EMA). Medicines. Tizveni. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tizveni].
2. Statistik Austria. Krebserkrankungen. Krebsinzidenz nach ausgewählten Lokalisationen und Geschlecht. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
3. 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].
4. Shun Lu, Jie Wang, Yan Yu ea. Tislelizumab Plus Chemotherapy as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC (RATIONALE 304): A Randomized Phase 3 Trial. J Thorac Oncol 2021 Sep;16(9):1512-1522 doi: 101016/jjtho202105005 Epub 2021 May 23.
5. 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].
6. Lu S, et al. Examining the Impact of Tislelizumab Added to Chemotherapy on Health-Related Quality-of-Life Outcomes in Previously Untreated Patients With Nonsquamous Non–Small Cell Lung Cancer. The Cancer Journal Volume 28, Number 2, March/April 2022.
7. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.
8. 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].
9. 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 randomized clinical trial. JAMA Oncol. Published online April 1, 2021. doi:10.1001/jamaoncol.2021.0366.

10. 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 Randomized Clinical Trial. JAMA Oncol 2021;7(5):709-717 doi:101001/jamaoncol20210366.

11. 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].

12. 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 randomized clinical trial. Cancer Treatment and Research Communications 30 (2022) 100501.

13. 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.

14. 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].

15. 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.

16. 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

Stage[1] IA

Stage[1] IB

Stage[1] IIA, IIB

Stage[1] IIIA
T3 N1
T4 N0/1

Stage[1] IIIA$_3$[2]

Stage[1] IIIB
(except T3N2[8])

Stage[1]
IIIA$_1$, IIIA, IIIA$_2$

Stage[1] IIIB T3N2[8]

Stage[1] IIIA[4]

PD-L1

or

negativ

positiv

surgery

or

at
inoperability

stereotactical
radiotherapy

surgery

followed, if
necessary, by:

adjuvant
systemic
therapy[5]

or

at
inoperability

stereotactical
radiotherapy

surgery
followed by:

adjuvant
systemic
therapy[5]

or

neoadjuvant
systemic
therapy[6]

followed by:

surgery

surgery
followed by:

adjuvant
systemic
therapy[5]

or

neoadjuvant
systemic
therapy[6]

followed by:

surgery

neoadjuvant
systemic
therapy[6]

followed by:

surgery

or

surgery
followed by:

neoadjuvant
systemic
therapy[5]

at the stage[1]
IIIA pN2[2]
for additional RF[7]

Radiotherapy
Mediastinum

definitive
chemoradiotherapy

or

neoadjuvant
systemic
therapy[4]

followed by:

surgery

followed, if
necessary, by:

Radiotherapy
Mediastinum

or

Induction
chemotherapy[4]

followed by:

radiochemotherapy

followed by:

surgery

neoadjuvant
systemic
therapy[6]

followed by:
radio-
chemotherapy

followed by:

surgery

or

definitive
chemo-
radiotherapy

for CR/PR/NC

and PD-L1 > 1%

followed by:

Durvalumab[9]

definitive
chemo-
radiotherapy

for CR/PR/NC

and PD-L1 > 1%

followed by:

Durvalumab[9]

or

Induction
chemotherapy[4]

followed by:

radiotherapy

followed by:

surgery

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.*