Tislelizumab
(NSCLC, second line)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
BRAF	rapidly accelerated fibrosarcoma – isoform B
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EORTC QLQ-LC13	EORTC QLQ-Lung Cancer 13
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS G12C	Kirsten rat sarcoma viral oncogene homologue submutation G12C
MedDRA	Medical Dictionary for Regulatory Activities
METex14	mesenchymal-epithelial transition
MMRM	mixed-effects model with repeated measures
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RCT	randomized controlled trial
RET	rearranged during transfection
ROS1	proto-oncogene tyrosine-protein kinase 1
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TAP	Tumour Area Positivity
TPS	Tumour Proportion Score
VAS	visual analogue scale

Abbreviation	Meaning
VEGF	vascular endothelial growth factor

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tislelizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 20 December 2024.

Research question

The aim of this report is to assess the added benefit of tislelizumab as monotherapy in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior platinum-based therapy. Patients with epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC should also have received targeted therapies before receiving tislelizumab.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of tislelizumab

Therapeutic indication	**ACT**[a]
Adult patients with locally advanced or metastatic NSCLC after prior treatment with platinum-based chemotherapy; in addition, patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving tislelizumab[b]	▪ docetaxel (only for patients with PD-L1-negative tumours) or ▪ pemetrexed (only for patients with PD-L1-negative tumours and except in mainly squamous histology) or ▪ nivolumab or ▪ pembrolizumab (only for patients with PD-L1 expressing tumours, [TPS ≥ 1%]) or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib (only for patients with PD-L1-negative tumours and adenocarcinoma histology)

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, it is assumed that for the given therapeutic indication patients have no medical indication for definitive local therapy. In addition, it is assumed that no (other) molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon 20, HER2, KRAS G12C, METex14, RET or ROS1) is an option for the patients at the time of treatment with tislelizumab.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene homologue; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: proto-oncogene tyrosine-protein kinase 1; TPS: Tumour Proportion Score

The company followed the G-BA's specification of the ACT, which includes various options based on programmed cell death ligand 1 (PD-L1) status and histology.

Overall, it should be noted that the approved therapeutic indication for tislelizumab includes patients in second or later lines of treatment – after platinum-based chemotherapy. According to the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer valid at the time of this benefit assessment, a chemoimmunotherapeutic regimen that already includes an immune checkpoint inhibitor regardless of PD-L1 status should be offered in first-line treatment, particularly in the metastatic setting. It can therefore be assumed that the group of patients for whom treatment with an immune checkpoint inhibitor is still an option in second-line treatment will play an increasingly smaller role in the German health care context.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit.

Study pool and study design

The RATIONALE 303 study is used for the benefit assessment of tislelizumab. This study is a completed, open-label, multicentre RCT comparing tislelizumab versus docetaxel. The study included adult patients with locally advanced or metastatic NSCLC with disease progression following treatment with at least one platinum-containing regimen. However, patients should not have received more than 2 prior lines of systemic chemotherapy for advanced or metastatic disease. Furthermore, patients had to be in good general condition as measured by an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Both patients with squamous and patients with non-squamous histology were enrolled. Patients with known EGFR mutation or ALK translocation were excluded from study participation. Patients with non-squamous histology and unknown EGFR mutation status were required to be tested for EGFR mutations prior to enrolment. All patients included in the study were also required to have their PD-L1 expression status tested at enrolment. Study inclusion was independent from PD-L1 expression status, however.

Overall, 805 patients were included in the study and randomized in a 2:1 ratio either to treatment with tislelizumab (N = 535) or to docetaxel (N = 270). Tislelizumab treatment in the intervention arm was administered in 3-week cycles, largely in line with the specifications of the Summary of Product Characteristics (SPC). According to the planning of the study, treatment with tislelizumab was continued until disease progression, unacceptable toxicity, or withdrawal of informed consent, but could be continued beyond radiologically confirmed progression under certain conditions after approval by the sponsor. Docetaxel treatment in the comparator arm was also administered in 3-week cycles and was largely in line with the

specifications of the SPC. According to the planning of the study, docetaxel treatment was planned until disease progression, unacceptable toxicity or withdrawal of consent, without optional continuation after progression.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were outcomes in the categories of morbidity, health-related quality of life, and side effects.

This benefit assessment uses the results from the 3rd data cut-off of 18 January 2024.

Relevant subpopulation for the benefit assessment

The RATIONALE 303 study included patients irrespective of their PD-L1 expression status. However, according to the ACT specified by the G-BA, the comparator used in the study, docetaxel, is a suitable treatment option only for patients with PD-L1-negative tumours. Thus, only the RATIONALE 303 subpopulation of patients with a negative PD-L1 expression status is relevant for this benefit assessment. In Module 4 D of the dossier, the company presented analyses of a subpopulation of the study with PD-L1 expression ≤ 1%. This subpopulation analysed by the company, which comprises 214 of the patients randomized for tislelizumab and 103 for docetaxel, is used for this assessment.

However, based on the relevant subpopulation of the RATIONALE 303 study, conclusions on added benefit can only be applied to patients with PD-L1-negative tumours (PD-L1 expression status < 1%). No suitable data are available from the RATIONALE 303 study for patients with PD-L1-positive tumours (PD-L1 expression status ≥ 1%), however.

Subsequent therapies

The guideline recommendations available at the time of the assessment do not contain any clear treatment recommendations for patients in third-line treatment of locally advanced or metastatic NSCLC who have not yet received treatment with immune checkpoint inhibitors. The available recommendations relate to patients who have previously received immune checkpoint inhibitors (either in first- or second-line treatment). Depending on histology, general condition according to ECOG and contraindications, possible therapies include docetaxel, pemetrexed and combination therapies of docetaxel with nintedanib or ramucirumab, amongst others. It is not clear from the available recommendations whether treatment with immune checkpoint inhibitors is still recommended in the third line if treatment with this mechanism of action has not yet been carried out. Irrespective of this, immune checkpoint inhibitors in subsequent therapy in the comparator arm of the study were only used in individual patients. In contrast, different treatment options were administered to a relevant extent in both the intervention arm and the comparator arm of the study, in particular the protein kinase inhibitor catequentinib or catequentinib hydrochloride (also known as anlotinib). This is a vascular endothelial growth factor (VEGF) receptor inhibitor that

inhibits angiogenesis in a similar way to ramucirumab and nintedanib, but is not approved for the treatment of NSCLC in Europe (unlike in China).

Overall, there is uncertainty because the subsequent therapies administered in the study do not reflect the German health care context. In the given data situation, this has a potential influence on the results for the outcome of overall survival, as this outcome was observed until the end of the study also under subsequent therapy. The described deficiencies in the subsequent therapies used are therefore taken into account in the assessment of the outcome-specific risk of bias for overall survival.

Risk of bias

The risk of bias across outcomes is rated as low for the RATIONALE 303 study. There is a high risk of bias for the results of the outcome of overall survival due to the deficiencies in the subsequent therapies used.

No suitable data are available for the outcomes of symptoms, health status, health-related quality of life and immune-related adverse events (AEs), so that there is no assessment of the risk of bias of the results for these outcomes.

For all outcomes in the side effects category (except discontinuation due to AEs), the risk of bias of the results is rated high due to incomplete observations for potentially informative reasons. For the results of non-serious/non-severe AEs, the risk of bias is additionally increased due to lack of blinding in the presence of subjective outcome recording. The risk of bias of the results for the outcome of discontinuation due to AEs is rated as high because of lack of blinding in the presence of subjective decision on treatment discontinuation.

For the results of the specific AEs of alopecia (AE), blood and lymphatic system disorders (severe AEs) and investigations (severe AEs), a high certainty of results can be assumed despite a high risk of bias due to the size of the effects and the early occurrence of the events over time.

On the basis of the available information, no more than indications, e.g. of an added benefit, can be determined for the outcomes of alopecia (AEs), blood and lymphatic system disorders (severe AEs) and investigations (severe AEs), and no more than hints for the outcome of overall survival and the other outcomes in the side effects category due to the high risk of bias.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13) and health status (EQ-5D VAS)

No suitable data are available for the outcomes of symptoms (assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 [EORTC QLQ-C30] and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 [EORTC QLQ-LC13]) and health status (assessed using the EQ-5D visual analogue scale [EQ-5D VAS]). In each case, there is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30)

No suitable data are available for the outcome of health-related quality of life (recorded using EORTC QLQ-C30). There is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of serious AEs (SAEs) or discontinuation due to AEs. Hence there is no hint of greater or lesser harm from tislelizumab in comparison with docetaxel for either of them; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of tislelizumab in comparison with docetaxel was found for the outcome of severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). There is a hint of lesser harm from tislelizumab in comparison with docetaxel.

Immune-related AEs

No suitable data are available for the outcome of immune-related AEs. There is no hint of greater or lesser harm from tislelizumab in comparison with docetaxel; greater or lesser harm is therefore not proven.

Other specific AEs

Gastrointestinal disorders (AEs), asthenia (AEs) and insomnia (AEs)

A statistically significant difference in favour of tislelizumab in comparison with docetaxel was found for each of the outcomes of gastrointestinal disorders (AEs), asthenia (AEs) and insomnia (AEs). For each of these outcomes, there is a hint of lesser harm from tislelizumab in comparison with docetaxel.

Alopecia (AEs)

A statistically significant difference in favour of tislelizumab compared with docetaxel was shown for the outcome of alopecia (AE). There is an indication of lesser harm from tislelizumab in comparison with docetaxel.

Respiratory, thoracic and mediastinal disorders (SAEs)

A statistically significant difference to the disadvantage of tislelizumab in comparison with docetaxel was shown for the outcome of respiratory, thoracic and mediastinal disorders (SAEs). There is a hint of greater harm from tislelizumab in comparison with docetaxel.

Blood and lymphatic system disorders (severe AEs) (including: neutropenia [severe AEs], leukopenia [severe AEs], febrile neutropenia [severe AEs]) and investigations (severe AEs) (including: neutrophil count decreased [severe AEs], white blood cell count decreased [severe AEs])

A statistically significant difference in favour of tislelizumab compared with docetaxel was shown for the outcomes of blood and lymphatic system disorders (severe AEs) and investigations (severe AEs), as well as the Preferred Terms (PTs) (severe AEs) neutropenia, leukopenia, febrile neutropenia, neutrophil count decreased, and white blood cell count decreased, which are included in these System Organ Classes (SOCs). There is an indication of lesser harm from tislelizumab compared with docetaxel for each of the outcomes of blood and lymphatic system disorders (severe AEs) and investigations (severe AEs).

Infections and infestations (severe AEs) and metabolism and nutrition disorders (severe AEs)

A statistically significant difference in favour of tislelizumab in comparison with docetaxel was shown for each of the outcomes of infections and infestations (severe AEs) and metabolism and nutrition disorders (severe AEs). For each of these outcomes, there is a hint of lesser harm from tislelizumab in comparison with docetaxel.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug tislelizumab in comparison with the ACT are assessed as follows:

Overall, there are several positive and one negative effect of tislelizumab compared with docetaxel for outcomes in the side effects category. There are advantages particularly in terms of severe AEs, in some cases to a major extent. However, there are no suitable data for outcomes in the categories of morbidity and health-related quality of life. Furthermore, there is a lack of suitable data on immune-related AEs. However, no disadvantages are expected to an extent that would completely challenge the positive effects in severe AEs, though the extent of the added benefit cannot be quantified due to the lack of data on other outcomes.

In summary, there is a hint of a non-quantifiable added benefit of tislelizumab compared with the ACT for adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy, with PD-L1-negative tumours (PD-L1 expression < 1%).

No data are available to assess the added benefit of tislelizumab in comparison with the ACT specified by the G-BA for adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy with PD-L1-positive tumours (PD-L1 expression ≥ 1%). An added benefit of tislelizumab in comparison with the ACT is not proven for patients with PD-L1-positive tumours (PD-L1 expression ≥ 1%).

Table 3 shows a summary of probability and extent of the added benefit of tislelizumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Tislelizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic NSCLC after prior treatment with platinum-based chemotherapy; in addition, patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving tislelizumab[b]	▪ docetaxel (only for patients with PD-L1-negative tumours) or ▪ pemetrexed (only for patients with PD-L1-negative tumours and except in mainly squamous histology) or ▪ nivolumab or ▪ pembrolizumab (only for patients with PD-L1 expressing tumours, [TPS ≥ 1%]) or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib (only for patients with PD-L1-negative tumours and adenocarcinoma histology)	▪ Patients with PD-L1-negative tumours[c]: hint of non-quantifiable added benefit[d] ▪ Patients with PD-L1-positive tumours[e]: added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In accordance with the G-BA, it is assumed that for the given therapeutic indication patients have no medical indication for definitive local therapy. In addition, it is assumed that no (other) molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon 20, HER2, KRAS G12C, METex14, RET or ROS1) is an option for the patients at the time of treatment with tislelizumab.
c. PD-L1 expression < 1%.
d. The RATIONALE 303 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. In addition, the study only included patients in the second or third line of treatment and patients who had not received targeted therapies against EGFR-mutant or ALK-positive NSCLC. Therefore, it also remains unclear whether the observed effects are transferable to patients in the fourth or later lines of treatment and patients who have already received targeted therapies against EGFR-mutant or ALK-positive NSCLC.
e. PD-L1 expression ≥ 1%.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene homologue; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: proto-oncogene tyrosine-protein kinase 1; TPS: Tumour Proportion Score

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of tislelizumab as monotherapy in comparison with the ACT in 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.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of tislelizumab

Therapeutic indication	**ACT**[a]
Adult patients with locally advanced or metastatic NSCLC after prior treatment with platinum-based chemotherapy; in addition, patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving tislelizumab[b]	▪ docetaxel (only for patients with PD-L1-negative tumours) or ▪ pemetrexed (only for patients with PD-L1-negative tumours and except in mainly squamous histology) or ▪ nivolumab or ▪ pembrolizumab (only for patients with PD-L1 expressing tumours, [TPS ≥ 1%]) or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib (only for patients with PD-L1-negative tumours and adenocarcinoma histology)
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, it is assumed that for the given therapeutic indication patients have no medical indication for definitive local therapy. In addition, it is assumed that no (other) molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon 20, HER2, KRAS G12C, METex14, RET or ROS1) is an option for the patients at the time of treatment with tislelizumab. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene homologue; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: proto-oncogene tyrosine-protein kinase 1; TPS: Tumour Proportion Score	

The company followed the G-BA's specification of the ACT, which includes various options based on PD-L1 status and histology.

Overall, it should be noted that the approved therapeutic indication for tislelizumab includes patients in second or later lines of treatment – after platinum-based chemotherapy. According to the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer [3] valid at the time of this benefit assessment, a chemoimmunotherapeutic regimen that already

includes an immune checkpoint inhibitor regardless of PD-L1 status should be offered in first-line treatment, particularly in the metastatic setting. It can therefore be assumed that the group of patients for whom treatment with an immune checkpoint inhibitor is still an option in second-line treatment will play an increasingly smaller role in the German health care context.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on tislelizumab (status: 21 October 2024)
- Bibliographical literature search on tislelizumab (last search on 21 October 2024)
- Search of trial registries/trial results databases for studies on tislelizumab (last search on 21 October 2024)
- Search on the G-BA website for tislelizumab (last search on 21 October 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on tislelizumab (last search on 16 January 2025); for search strategies, see I Appendix A of the full dossier assessment

The review did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: tislelizumab vs. docetaxel

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no)	Registry entries[b] (yes/no)	Publication (yes/no)
BGB-A317-303 (RATIONALE 303[c])	Yes	Yes	No	Yes [4-8]	Yes [9,10]	Yes [8,11,12]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
CSR: clinical study report; RCT: randomized controlled trial

The RATIONALE 303 study is used for the benefit assessment. The study pool is consistent with that selected by the company. The study is described in the following section.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: tislelizumab vs. docetaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RATIONALE 303	RCT, open-label, parallel	Adult patients with ▪ locally advanced or metastatic NSCLC[b] ▪ prior platinum-containing therapy[c] ▪ ECOG PS ≤ 1	Tislelizumab (N = 535) Docetaxel (N = 270) relevant subpopulation thereof[d]: ▪ tislelizumab (n = 214) ▪ docetaxel (n = 103)	Screening: ≤ 28 days Treatment: until disease progression[e], unacceptable toxicity or withdrawal of consent Observation[f]: outcome-specific, at most until death, lost to follow-up, withdrawal of consent, or end of study	109 centres in Brazil, Bulgaria, China, Lithuania, Mexico, New Zealand, Poland, Russia, Slovak Republic, Turkey 11/2017–1/2024 Data cut-offs: ▪ 10 August 2020[g] ▪ 15 July 2021[h] ▪ 18 January 2024[i]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: tislelizumab vs. docetaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Both patients with squamous and with non-squamous histology were enrolled. Patients with known EGFR mutation or ALK translocation were excluded from study participation. Patients with unknown EGFR mutation status and non-squamous histology were required to be tested for EGFR mutations prior to enrolment. According to the information provided by the company in Module 4 D of the dossier, no testing was required for patients with unknown EGFR mutation status and squamous histology or for patients with unknown ALK translocation status due to the rare occurrence.
c. According to the inclusion criteria, there had to be disease progression during or following treatment with at least one platinum-containing regimen. However, no more than 2 prior lines of systemic chemotherapy for advanced or metastatic disease were allowed.
d. The subpopulation relevant for this benefit assessment comprises patients with PD-L1 expression < 1% (hereinafter referred to as PD-L1-negative patients).
e. Treatment with tislelizumab could be continued beyond radiologically confirmed disease progression if the investigator was of the opinion that the patient was benefitting from the treatment, and there was no worsening of symptoms or unacceptable toxicity.
f. Outcome-specific information is provided in Table 8.
g. Interim analysis of overall survival after 441 events (originally planned after approx. 318 events according to study protocol version Amendment 1.0 [dated 14 February 2018]). With protocol version Amendment 3.0 (dated 9 March 2020), the interim analysis was planned after 426 events.
h. Final analysis of overall survival after 571 events (originally planned after approx. 474 events according to study protocol version Amendment 1.0 [dated 14 February 2018]); with protocol version Amendment 3.0 (dated 9 March 2020), the final analysis was planned after 560 events).
i. Analysis after the end of the study; according to the planning of the study, the study ended when the last patient had died/became lost to follow-up or withdrew consent, or when the sponsor decided to terminate the study.

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomized patients; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: tislelizumab vs. docetaxel

Study	Intervention	Comparison
RATIONALE 303	Tislelizumab 200 mg IV every 3 weeks	Docetaxel 75 mg/m^2 BSA IV, every 3 weeks
	Dose adjustment: ▪ no dose adjustment allowed; interruption allowed for up to 12 weeks in case of toxicity	▪ dose reduction to 75% of the initial dose depending on the grade of toxicity
	Pretreatment Required: ▪ ≥ 1 prior platinum-containing regimen (≤ 2 prior lines of systemic chemotherapy for advanced/metastatic disease[a]) Not allowed: ▪ prior treatment of metastatic disease with docetaxel ▪ prior treatment with immune checkpoint inhibitors targeting PD-1, PD-L1 and CTLA-4 ▪ allogeneic stem cell transplantation or organ transplantation ▪ major surgical procedure requiring general anaesthesia ≤ 28 days prior to randomization **Concomitant treatment** Allowed: ▪ anti-emetics and antidiarrhoeals ▪ erythropoiesis-stimulating agents and haematopoietic growth factors ▪ bisphosphonates for non-malignant indications ▪ bisphosphonates and RANK-L inhibitors for bone metastases from the point of randomization and at a stable dose ▪ focally ablative therapy and palliative radiation therapy for other non-target lesions Not allowed: ▪ chemotherapy, immunotherapy (e.g. interleukin, interferon, thymoxin), ≤ 28 days (or ≤ 5 half-lives, whichever was shorter) prior to randomization ▪ immunosuppressants or systemic corticosteroids (> 10 mg daily prednisone equivalent) ≤ 14 days prior to randomization, except for drug-induced AE or for short-term (≤ 7 days) prophylaxis ▪ any other antineoplastic treatment and other investigational products	

a. Patients who received prior adjuvant/neoadjuvant chemotherapy could also be included provided they had progressed within 6 months after last dose and they had not been previously treated with targeted local radiotherapy (or progressed as defined per RECIST v1.1 under local therapy).

AE: adverse event; BSA: body surface area; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; NSCLC: non-small cell lung cancer; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RANK-L: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Study design

The RATIONALE 303 study is a completed, multicentre, open-label RCT comparing tislelizumab versus docetaxel. The study included adult patients with locally advanced or metastatic NSCLC with disease progression following treatment with at least one platinum-containing regimen. However, patients should not have received more than 2 prior lines of systemic chemotherapy for advanced or metastatic disease. Furthermore, patients had to be in good general condition as measured by an ECOG PS of 0 or 1. Both patients with squamous and with non-squamous histology were enrolled. Patients with known EGFR mutation or ALK translocation were excluded from study participation. Patients with non-squamous histology and unknown EGFR mutation status were required to be tested for EGFR mutations prior to enrolment. All patients included in the study were also required to have their PD-L1 expression status tested at enrolment, using the VENTANA PD-L1 (SP263) Assay. Study inclusion was independent from PD-L1 expression status, however.

Overall, 805 patients were included in the study and randomized in a 2:1 ratio either to treatment with tislelizumab (N = 535) or to docetaxel (N = 270). Randomization was stratified by histology (squamous cell carcinoma versus non-squamous cell carcinoma), line of treatment (second versus third line), and PD-L1 expression (≥ 25% versus < 25%).

Tislelizumab treatment in the intervention arm was administered in 3-week cycles, largely in line with the specifications of the SPC [13]. According to the planning of the study, treatment with tislelizumab was to continue until disease progression, unacceptable toxicity, or withdrawal of consent, but could be continued beyond radiologically confirmed disease progression if the investigator was of the opinion that the patient was benefitting from the treatment, and there was no worsening of symptoms or unacceptable toxicity. Docetaxel treatment in the comparator arm was also administered in 3-week cycles and was largely in line with the specifications of the SPC [14]. According to the planning of the study, docetaxel treatment was planned until disease progression, unacceptable toxicity or withdrawal of consent, without optional continuation after progression. The study protocol did not provide for any switching of patients from the comparator arm into the intervention arm due to disease progression.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were outcomes in the categories of morbidity, health-related quality of life, and side effects.

Relevant subpopulation for the benefit assessment

The RATIONALE 303 study included patients irrespective of their PD-L1 expression status. However, according to the ACT specified by the G-BA, the comparator used in the study, docetaxel, is a suitable treatment option only for patients with PD-L1-negative tumours. Thus, only the RATIONALE 303 subpopulation of patients with a negative PD-L1 expression status is

relevant for this benefit assessment. In Module 4 D of the dossier, the company presented analyses of a subpopulation of the study with PD-L1 expression ≤ 1%. Although the company did not provide any information on which analysis method the percentage refers to (i.e. Tumour Proportion Score [TPS] or Tumour Area Positivity [TAP], for example), it is assumed for this assessment that patients with a negative PD-L1 expression status were sufficiently reliably differentiated on the basis of the 1% threshold value used. The subpopulation analysed by the company is therefore used for the assessment. This includes 214 of the patients randomized for tislelizumab, and 103 for docetaxel.

However, based on the relevant subpopulation of the RATIONALE 303 study, conclusions on added benefit can only be applied to patients with PD-L1-negative tumours (PD-L1 expression status < 1%). No suitable data are available from the RATIONALE 303 study for patients with PD-L1-positive tumours (PD-L1 expression status ≥ 1%), however.

Data cut-offs

RATIONALE 303 is a completed study. Three data cut-offs are available:

- 1st data cut-off (10 August 2020): interim analysis on overall survival, conducted after 441 events
- 2nd data cut-off (15 July 2021): final analysis on overall survival, conducted after 571 events
- 3rd data cut-off (18 January 2024): analysis at the end of the study

This benefit assessment uses the results from the 3rd data cut-off of 18 January 2024. This concurs with the company's approach.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: tislelizumab vs. docetaxel

Study **Outcome category** **Outcome**	**Planned follow-up observation**
RATIONALE 303	
Mortality	
Overall survival	until death, lost to follow-up, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	until the last dose of the study medication
Health status (EQ-5D VAS)	until the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	until the last dose of the study medication
Side effects	
All outcomes of the side effects category (except immune-related AEs)	up to 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment, whichever was first[a]
Immune-related AEs	until 90 days after the last dose of the study medication

a. In addition, SAEs suspected by the investigator to be related to the study medication were observed until death, lost to follow-up, or withdrawal of consent, whichever was first.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The RATIONALE 303 study only surveyed overall survival until the end of the study. The observation periods for the outcomes of the categories of morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days or 90 days for side effects). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Patient characteristics

Table 9 shows the patient characteristics in the subpopulation of the included study.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: tislelizumab vs. docetaxel (multipage table)

Study **Characteristic** **Category**	**Tislelizumab** **N = 214**	**Docetaxel** **N = 103**
RATIONALE 303		
Age [years], mean (SD)	61 (9)	61 (9)
Sex [F/M], %	22/78	26/74
Family origin, n (%)		
Native American or Alaska Native	7 (3)	1 (1)
Asian	168 (79)	88 (85)
Caucasian	38 (18)	13 (13)
Other	1 (< 1)[a]	1 (1)[a]
Region, n (%)		
China	167 (78)	88 (85)
Rest of the world[b]	47 (22)	15 (15)
Smoking status, n (%)		
Current	18 (8.4)	6 (5.8)
Former	136 (63.6)	60 (58.3)
Never	60 (28.0)	37 (35.9)
ECOG PS, n (%)		
0	50 (23.4)	19 (18.4)
1	164 (76.6)	84 (81.6)
Histology, n (%)		
Squamous cell carcinoma	89 (41.6)	41 (39.8)
Non-squamous cell carcinoma	125 (58.4)	62 (60.2)
EGFR mutation status, n (%)		
Wild type	143 (66.8)	75 (72.8)
Mutant	0 (0)	0 (0)
Unknown	71 (33.2)	28 (27.2)
ALK translocation, n (%)		
Wild type	108 (50.5)	48 (46.6)
Translocated	0 (0)	0 (0)
Unknown	106 (49.5)	55 (53.4)
Line of treatment, n (%)		
Second line	180 (84.1)	88 (85.4)
Third line	34 (15.9)	15 (14.6)

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: tislelizumab vs. docetaxel (multipage table)

Study **Characteristic** **Category**	**Tislelizumab** **N = 214**	**Docetaxel** **N = 103**
Disease stage at study start, n (%)		
Locally advanced	33 (15.4)	8 (8.7)
Metastatic	181 (84.6)	95 (92.2)
Brain metastases, n (%)		
Yes	13 (6.1)	9 (8.7)
No	201 (93.9)	94 (91.3)
Liver metastases, n (%)		
Yes	27 (12.6)	16 (15.5)
No	187 (87.4)	87 (84.5)
Time since diagnosis [years], mean (SD)	1.3 (1.2)	1.3 (1.0)
Time since diagnosis of metastatic disease [months], mean (SD)	12 (8)	12 (10)
Type of prior systemic therapy[c]		
Chemotherapy	214 (100)	103 (100)
Protein kinase inhibitors	3 (1.4)	3 (2.9)
Immunotherapy	0 (0)	0 (0)
Other	59 (27.6)	22 (21.4)
Treatment discontinuation, n (%)[d]	213 (99.5)	98 (95.1)
Study discontinuation, n (%)[e]	214 (100)	103 (100)

a. Institute's calculation.
b. The following countries were included: Brazil, Bulgaria, Lithuania, Mexico, New Zealand, Poland, Russia, Slovak Republic, Turkey.
c. Patients may have received more than one type of prior therapy.
d. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): radiological disease progression (46.3% vs. 65%), loss of clinical benefit (24.8% vs. 0%), AEs (10.7% vs. 12.6%), withdrawal of consent (6.1% vs. 11.7%). An additional 1 vs. 5 patients never started treatment.
e. Study discontinuations resulting from the termination of the study by the sponsor are included in these data. Overall, all randomized patients discontinued the study for this reason. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): study discontinuation by sponsor (13.6% vs. 13.6%), withdrawal of consent (1.4% vs. 5.8%). The data additionally include patients who died during the course of the study (intervention arm: 77.6% vs. control arm: 79.6%).

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The baseline demographic and clinical patient characteristics in both treatment arms were largely comparable. The patients' mean age was about 61 years, most of them were male

(approx. 77%) and of Asian family origin (approx. 81%). In addition to patients from China, the study mainly included patients from Eastern European countries. However, patients from Germany or Western European countries were not included. As described in Chapter I 2, it is assumed for the German health care context that the group of patients for whom treatment with an immune checkpoint inhibitor is still an option in second-line treatment will play an increasingly smaller role.

The majority of patients were former smokers (approx. 62%). About 59% of the relevant subpopulation had non-squamous NSCLC histology, and the majority had metastatic disease (approx. 87%). The study included mostly patients in the second line of treatment (85%), as well as a small proportion of patients in the third line of treatment. Patients in further lines of treatment were not included.

In accordance with the inclusion criteria of the study, patients with known EGFR mutation or ALK translocation were also not included. Around two-thirds of the patients had an EGFR wild type and almost half had an ALK wild type. Accordingly, one-third of the patients had an unknown mutation status, and half of the patients had an unknown translocation status.

In accordance with the given therapeutic indication, patients with EGFR-mutant or ALK-positive NSCLC should have received targeted therapies before receiving tislelizumab. The population of the RATIONALE 303 study is assumed to include only a very small number of patients with EGFR-mutant or ALK-positive NSCLC. This is due to the fact that patients with known EGFR mutation or ALK translocation could not be enrolled, and that patients with non-squamous histology and unknown EGFR mutation status were required to be tested for EGFR mutations prior to enrolment. In addition, EGFR mutations are assumed to be rare in patients with squamous histology. The same applies to ALK translocations regardless of histology and to other mutation types for which the G-BA assumes that no (other) molecularly stratified therapy is an option for the patients at the time of treatment with tislelizumab. This concerns targeted therapies against ALK, rapidly accelerated fibrosarcoma – isoform B (BRAF), EGFR, exon 20, human epidermal growth factor receptor 2 (HER2), Kirsten rat sarcoma viral oncogene homologue submutation G12C (KRAS G12C), mesenchymal-epithelial transition (METex14), rearranged during transfection (RET) or proto-oncogene tyrosine-protein kinase 1 (ROS1).

The RATIONALE 303 study is a completed study for which an end-of study analysis is available with the 3rd data cut-off. The patient flow data presented by the company show that, by the time of the 3rd data cut-off, all patients who had started treatment had either completed or discontinued this treatment. Common reasons for treatment discontinuation were radiological disease progression (46.3% versus 65%), loss of clinical benefit (24.8% versus 0%), AEs (10.7% versus 12.6%) or withdrawal of consent (6.1% versus 11.7%), with some notable differences in the reasons for discontinuation between the study arms.

Since the study has been completed, all patients have discontinued the study. In 13.6% of patients per study arm, however, discontinuation was due to the fact that the study was terminated by the sponsor after no more patients received the study medication. The data on study discontinuation additionally include patients who died during the course of the study (intervention arm: 77.6% versus control arm: 79.6%). In addition, the most common reason for study discontinuation in a small proportion of patients was withdrawal of consent (1.4% versus 5.8%).

Information on the course of the study

Table 10 shows patients' median and mean treatment durations and the median and mean observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: tislelizumab vs. docetaxel

Study **Duration of the study phase** **Outcome category/outcome**	**Tislelizumab** **N = 214**	**Docetaxel** **N = 103**
RATIONALE 303		
Treatment duration [weeks]		
Median [Q1; Q3]	17.7 [9.0; 42.9]	9.3 [6.1; 18.3]
Mean (SD)	42.0 (58.0)	21.2 (33.9)
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	45.9 [44.4; 46.5]	40.9 [39.0; 49.6]
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)		
Median [Q1; Q3]	3.7 [1.9; 9.9]	2.1 [0.8; 4.2]
Mean (SD)	9.5 (13.4)	4.5 (7.9)
Health status (EQ-5D VAS)		
Median [Q1; Q3]	2.3 [0.03; 7.7]	1.4 [0.03; 3.3]
Mean (SD)	7.3 (11.8)	3.3 (6.8)
Health-related quality of life (EORTC QLQ-C30)		
Median [Q1; Q3]	3.7 [1.9; 9.9]	2.1 [0.8; 4.2]
Mean (SD)	9.5 (13.4)	4.5 (7.9)
Side effects		
AEs, SAEs, severe AEs		
Median [Q1; Q3]	4.2 [2.3; 10.2]	2.4 [1.7; 4.5]
Mean (SD)	9.9 (13.3)	5.1 (7.8)
Immune-related AEs		
Median [Q1; Q3]	6.4 [4.3; 12.2]	4.4 [3.6; 6.5]
Mean (SD)	11.5 (13.1)	6.9 (7.8)

a. Calculated using the inverse Kaplan-Meier method: Deceased patients are censored at the time of death, non-deceased patients are counted as event at the time of the end of observation.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; N: number of randomized patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation, VAS: visual analogue scale

The median treatment duration was notably longer in the intervention arm than in the comparator arm (17.7 weeks for tislelizumab versus 9.3 weeks for docetaxel). The mean treatment duration was also notably longer in the intervention arm than in the comparator arm, with additional large differences between the median and mean treatment duration in

both treatment arms. This is mainly due to the fact that some patients with long treatment durations were included in the calculation of the mean values.

While the median observation period for overall survival was similar between the 2 treatment arms (46 months for tislelizumab and 41 months for docetaxel), the observation periods of the other outcomes were linked to the end of treatment and were therefore very notably shorter overall than the observation period of the overall survival outcome (for most outcomes around 4 months in the intervention arm and 2 months in the comparator arm). In addition, notable differences were shown between the treatment arms with shorter observation periods in the comparator arm. This results from the fact that outcomes on symptoms, health-related quality of life and health status were recorded until the end of treatment (or discontinuation of treatment) and the observation for outcomes in the side effects category was linked to the end of treatment (plus 30 or 90 days) (see Table 8). For these outcomes, conclusions can therefore be drawn only for the period under treatment or up to 30 or 90 days after the end of treatment. As described above, this period of a few months in the given data situation is very much shortened compared with several years of observation for overall survival.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies[a] (≥ 3% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: tislelizumab vs. docetaxel

Study Drug class Drug	Patients with subsequent therapy, n (%) Tislelizumab N = 214	 Docetaxel N = 103
RATIONALE 303		
Total	127 (59.3)	66 (64.1)
Radiotherapy	12 (5.6)	7 (6.8)
Systemic therapy	121 (56.5)	62 (60.2)
Chemotherapy	85 (39.7)	30 (29.1)
Docetaxel	45 (21.0)	2 (1.9)
Carboplatin	19 (8.9)	2 (1.9)
Paclitaxel	13 (6.1)	1 (1.0)
Pemetrexed	12 (5.6)	5 (4.9)
Gemcitabine	11 (5.1)	6 (5.8)
Paclitaxel albumin	11 (5.1)	2 (1.9)
Cisplatin	6 (2.8)	5 (4.9)
Gimeracil; oteracil potassium; tegafur	4 (1.9)	5 (4.9)
Gemcitabine hydrochloride	1 (0.5)	6 (5.8)
Protein kinase inhibitors	61 (28.5)	37 (35.9)
Catequentinib hydrochloride	30 (14.0)	14 (13.6)
Catequentinib	9 (4.2)	15 (14.6)
Other	26 (12.1)	11 (10.7)
Bevacizumab	19 (8.9)	7 (6.8)
Immunotherapies	14 (6.5)	20 (19.4)
Tislelizumab	7 (3.3)	1 (1.0)
Pembrolizumab	3 (1.4)	5 (4.9)
Sintilimab	2 (0.9)	5 (4.9)

a. Patients may have received more than one type of subsequent therapy.

n: number of patients with subsequent therapy; N: number of randomized patients; RCT: randomized controlled trial

In the RATIONALE 303 study, there were no restrictions regarding subsequent antineoplastic therapies.

In the relevant subpopulation, 127 (59%) patients in the intervention arm and 66 (64%) patients in the comparator arm received at least one subsequent antineoplastic therapy. Assuming that patients with disease progression (tislelizumab: n = 165, docetaxel: n = 69) each received at least one subsequent therapy, 77% of patients with progression in the intervention arm and 96% of patients with progression in the comparator arm would have

received subsequent therapy. However, no separate data are available according to line of treatment of the subsequent therapy. The majority of patients with subsequent therapy received systemic chemotherapy in both study arms (39.7% versus 29.1%). Docetaxel was administered in the intervention arm in particular (21%). Furthermore, 28.5% of patients in the intervention arm and 35.9% of those in the comparator arm received protein kinase inhibitors as subsequent therapy.

The guideline recommendations [3,15,16] available at the time of the assessment do not contain any clear treatment recommendations for patients in third-line treatment of locally advanced or metastatic NSCLC who have not yet received treatment with immune checkpoint inhibitors.

The available recommendations relate to patients who have previously received immune checkpoint inhibitors (either in first- or second-line treatment). Depending on histology, general condition according to ECOG and contraindications, possible therapies include docetaxel, pemetrexed and combination therapies of docetaxel with nintedanib or ramucirumab, amongst others. It is not clear from the available recommendations whether treatment with immune checkpoint inhibitors is still recommended in the third line if treatment with this mechanism of action has not yet been carried out. Irrespective of this, immune checkpoint inhibitors in subsequent therapy in the comparator arm of the study were only used in individual patients. In contrast, different treatment options were administered to a relevant extent in both the intervention arm and the comparator arm of the study, in particular the protein kinase inhibitor catequentinib or catequentinib hydrochloride (also known as anlotinib). This is a VEGF receptor inhibitor that inhibits angiogenesis in a similar way to ramucirumab and nintedanib, but is not approved for the treatment of NSCLC in Europe (unlike in China).

Overall, there is uncertainty because the subsequent therapies administered in the study do not reflect the German health care context. In the given data situation, this has a potential influence on the results for the outcome of overall survival, as this outcome – in contrast to the other outcomes recorded in the study – was observed until the end of the study also under subsequent therapy. The described deficiencies in the subsequent therapies used are therefore taken into account in the assessment of the outcome-specific risk of bias for overall survival (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: tislelizumab vs. docetaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
RATIONALE 303	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the RATIONALE 303 study.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

From the company's perspective, the results of the RATIONALE 303 study can be transferred to the German health care context with regard to the characteristics of the included patients with PD-L1 expression < 1% and the SPC-compliant use of tislelizumab in the study. As part of its discussion on transferability, the company compared study data on the patients' age, sex ratio, and the risk factor tobacco smoking with health care data in Germany.

Regarding the patients' family origin (78.5% and 85.4% Asian, 17.8% and 12.6% Caucasian), the company described that this was a global study and that around half of all lung cancer cases worldwide occurred in Asia, so that a correspondingly large proportion of Asian study participants was to be expected. The company added that clinical studies for Asian and Caucasian patients with NSCLC had shown comparable results in terms of response rates and prolongation of overall survival when treated with immune checkpoint inhibitors. It additionally pointed out that there was no known genetic predisposition for the increased occurrence of NSCLC specific to the Asian population, but that external influences, such as tobacco smoking, were an important factor in the development of NSCLC, which is why the results of the RATIONALE 303 study could be transferred to the German population despite the large proportion of Asian study participants. In addition, the company argued that no clear modification of the treatment effect was shown based on geographical region and family origin.

Finally, the company referred to data from German tumour registries which, according to the company, showed that median overall survival in patients with advanced lung cancer was not shorter in everyday health care than in RCTs.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Chapter I 2 and Section I 3.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded using the EORTC QLQ-C30 and EORTC QLQ-LC13
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 D).

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: tislelizumab vs. docetaxel

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related AEs	Other specific AEs[b]
RATIONALE 303	Yes	No[c]	No[c]	No[c]	Yes	Yes	Yes	No[c]	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): gastrointestinal disorders (SOC, AEs); asthenia (PT, AEs); insomnia (PT, AEs); alopecia (PT, AEs); respiratory, thoracic and mediastinal disorders (SOC, SAEs); blood and lymphatic system disorders (SOC, severe AEs); neutropenia (PT, severe AEs); leukopenia (PT, severe AEs), febrile neutropenia (PT, severe AEs); investigations (SOC, severe AEs); neutrophil count decreased (PT, severe AEs); white blood cell count decreased (PT, severe AEs); infections and infestations (SOC, severe AEs); metabolism and nutrition disorders (SOC, severe AEs).
c. No suitable data; for justification, see text section below.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Analyses of patient-reported outcomes

In Module 4 D, the company presented both responder analyses and continuous analyses using a mixed-effects model with repeated measures (MMRM) for the change from baseline for the patient-reported outcomes of symptoms (recorded using the EORTC QLQ-C30 and EORTC QLQ-LC13), health status (recorded using the EQ-5D VAS), and health-related quality of life (recorded using the EORTC QLQ-C30). It used the responder analyses as the main analysis for its assessment, while it presented the continuous analyses as supporting information. However, both the responder analyses and the continuous analyses are not suitable for this benefit assessment. This is explained below.

In Module 4 D of the dossier, the company presented analyses on the time to confirmed deterioration by ≥ 15 points for the EQ-5D VAS and by ≥ 10 points for the EORTC QLQ-C30 and the EORTC QLQ-LC13 as responder analyses. Confirmed deterioration was defined as the time from randomization to the first crossing of the respective threshold value and a confirmation of this crossing at the next visit, i.e. the analyses presented by the company represent analyses of the time to the one-time confirmed deterioration. In principle, this operationalization is

patient relevant. However, the analyses of the one-time confirmed deterioration cannot be meaningfully interpreted in the given data situation.

In the RATIONALE 303 study, the observation period for the patient-reported outcomes was linked to the treatment duration and thus, on the one hand, systematically and very notably shorter compared with overall survival and, on the other, notably different between the treatment arms (see Table 8 and Table 10). Observation in the intervention arm was around twice as long as in the comparator arm (around 4 months versus 2 months). In this situation, a one-time confirmed deterioration is assumed to be potentially less likely to be detected in the comparator arm than in the intervention arm due to the shorter observation period. In the given data situation, analyses of time to first deterioration are therefore needed for the benefit assessment. The same is described by the G-BA in the "Answers to frequently asked questions on the benefit assessment procedure" [17].

Furthermore, the continuous analyses presented by the company as supporting information are also not suitable for the benefit assessment. This is due to the fact that in the RATIONALE 303 study, the questionnaire return rates in the comparator arm dropped sharply after just a few time points of observation, and there was a wide difference between the study arms. For example, after 12 weeks (in the 3rd follow-up recording since the start of the study), around 69% of the patients in the intervention arm who were still alive at this time were still under observation, while only around 51% were still under observation in the comparator arm. At Week 15, these values dropped further to around 64% versus 41%, by Week 24 to around 51% versus 23%. The MMRM analyses refer to the comparison of both study arms over the entire study period of approximately 5 years. This means that there is a high proportion of missing values in the analyses (> 50%), with additionally large differences between the study arms. Against this background, the continuous analyses presented by the company using MMRM can no longer be interpreted meaningfully.

Overall, no suitable data are therefore available for this benefit assessment for the patient-reported outcomes of symptoms (recorded using the EORTC QLQ-C30 and EORTC QLQ-LC13), health status (recorded using the EQ-5D VAS) and health-related quality of life (recorded using the EORTC QLQ-C30).

In addition to the previously described points of criticism regarding the responder analyses and continuous analyses, there is another uncertainty for the health status outcome (recorded using EQ-5D VAS). The response rates for the VAS were only 77% in the intervention arm and 67% in the comparator arm already at study start, and < 70% in both study arms at the first subsequent recording. Overall, 34% of patients were not included in the analyses for this outcome. This is probably at least partly due to the fact that recording of the EQ-5D was only introduced into the study by Protocol Amendment 1 from 14 February 2018; and thus there was no recording for some patients who had been enrolled before the questionnaire was

introduced. However, there is no information available on how many patients were included in the study before Protocol Amendment 1. It therefore remains unclear what proportion of the total missing values of 34% of patients was due to the later introduction and should therefore be regarded as missing completely at random.

Notes on outcomes of the side effects category

In Module 4 D of the dossier, the company described that progression of the underlying disease, including a fatal course, was not to be reported as an AE. Instead, symptoms, signs or clinical sequelae resulting from disease progression were to be reported as AEs, however. The company provided no further information on this. The available information on the documented AEs (at SOC and PT level, see I Appendix C of the full dossier assessment) does not provide any indication that AEs attributable to progression of the underlying disease are included to a relevant extent. Accordingly, the overall rates of AEs, SAEs and severe AEs (CTCAE grade ≥ 3) can be used for the benefit assessment.

For the outcome of SAEs, there is additional uncertainty as to which observation period was considered in the analyses presented by the company. According to the planning of the study, AEs were to be observed for up to 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment, whichever was first. However, SAEs suspected by the investigator to be related to the study medication were additionally observed until death, lost to follow-up, or withdrawal of consent, whichever was first. According to the information in the statistical analysis plan, such events are covered by the definition of "treatment emergent adverse events" if they occurred up to Day 90 after the last dose of study medication, and accordingly also by the analyses available in Module 5 of the dossier. The company did not provide any information on whether these events were also taken into account in the analyses of the SAEs presented by the company in Module 4 D. In the given data situation, however, it is not assumed that this affects events to a relevant extent (see Figure 3 in I Appendix B of the full dossier assessment). The uncertainty described is therefore of no consequence for this assessment.

Analyses on immune-related AEs

In Module 4 D of the dossier, the company presented analyses of immune-related AEs, which were recorded as AEs of special interest in the study. The company presented separate analyses on different severity grades (AEs, severe AEs [CTCAE grade ≥ 3], non-severe AEs [CTCAE grade < 3] and serious immune-related AEs).

In principle, the recording of immune-related AEs as AEs of special interest was predefined in the planning of the RATIONALE 303 study and was based on a collection of Medical Dictionary for Regulatory Activities (MedDRA) PTs, which, according to the study documents, was compiled on the basis of a search for known immune-related AEs of other PD-1/PD-L1

inhibitors and a literature search. Although the company's PT collection is considered appropriate, not all events of the listed PTs were assessed as immune-related AEs, but rather only a selection of these PTs if certain conditions were met. Initially, the study protocol required the investigator to rule out alternative causes for the potential immune-related event. If alternative causes could be excluded, only events that were treated with a specific therapy (e.g. with corticosteroids) were recorded as potentially immune-related. PTs assessed as potentially immune-related according to these steps were then subjected to a so-called medical review, in which 2 persons independently assessed whether alternative causes could be excluded (in case of disagreement, a third reviewer was consulted). Only events that were assessed as immune-related after this step were considered in the analyses presented by the company. This operationalization is unsuitable for fully representing immune-related AEs. This would require analyses based on the PT collection that not only includes a selection of PTs that fulfil certain conditions, but all PTs regardless of the investigator's or other reviewers' assessment of an association, or a need for treatment. The dossier did not contain such analyses, however. Therefore, no suitable data on immune-related AEs, severe immune-related AEs (CTCAE grade ≥ 3) or serious immune-related AEs are available for this benefit assessment.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: tislelizumab vs. docetaxel

Study	Study level	Outcomes								
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related AEs	Other specific AEs[b]
RATIONALE 303	L	H[c]	–[d]	–[d]	–[d]	H[e]	H[e]	H[f]	–[d]	H[e, g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): gastrointestinal disorders (SOC, AEs); asthenia (PT, AEs); insomnia (PT, AEs); alopecia (PT, AEs); respiratory, thoracic and mediastinal disorders (SOC, SAEs); blood and lymphatic system disorders (SOC, severe AEs); neutropenia (PT, severe AEs); leukopenia (PT, severe AEs), febrile neutropenia (PT, severe AEs); investigations (SOC, severe AEs); neutrophil count decreased (PT, severe AEs); white blood cell count decreased (PT, severe AEs); infections and infestations (SOC, severe AEs); metabolism and nutrition disorders (SOC, severe AEs).
c. Due to uncertainties in the use of adequate subsequent therapies.
d. No suitable data; for justification, see Section I 4.1 of this dossier assessment.
e. Incomplete observations for potentially informative reasons with different lengths of follow-up observation.
f. Lack of blinding in the presence of subjective decision on treatment discontinuation.
g. Lack of blinding in the presence of subjective outcome recording in non-severe and non-serious AEs.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The high risk of bias for the results of the outcome of overall survival is due to the deficiencies in the subsequent therapies used (see Section I 3.2). No suitable data are available for the outcomes of symptoms (recorded via EORTC QLQ-C30 and EORTC QLQ-LC13), health status (recorded via EQ-5D VAS), health-related quality of life (recorded via EORTC QLQ-C30), and immune-related AEs (see Section I 4.1 for explanation). Therefore, the risk of bias for the corresponding results is not assessed.

For all outcomes in the side effects category (except discontinuation due to AEs), the risk of bias of the results is rated high due to incomplete observations for potentially informative reasons. As described in Section I 3.2, the discontinuation of observation for these outcomes was linked to the end of treatment with the study medication. The observation period was thus controlled by the treatment discontinuation, which was largely determined by radiological disease progression. For these outcomes, this additionally resulted in notable differences in median observation periods between the treatment groups (4.2 months versus

2.4 months). For the results of non-serious/non-severe AEs, the risk of bias is additionally increased due to lack of blinding in the presence of subjective outcome recording.

For the results of the specific AEs of alopecia (AEs), blood and lymphatic system disorders (severe AEs) and investigations (severe AEs), a high certainty of results can be assumed despite a high risk of bias due to the size of the effects and the early occurrence of the events over time (see Figure 9, Figure 11 and Figure 15 in I Appendix B of the full dossier assessment).

The risk of bias of the results for the outcome of discontinuation due to AEs is rated as high because of lack of blinding in the presence of subjective decision on treatment discontinuation.

I 4.3 Results

Table 15 summarizes the results of the comparison of tislelizumab versus docetaxel in adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: tislelizumab vs. docetaxel (multipage table)

Study Outcome category Outcome	Tislelizumab N	Tislelizumab Median time to event in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to event in months [95% CI] Patients with event n (%)	Tislelizumab vs. docetaxel HR [95% CI]; p-value[a]
RATIONALE 303					
Mortality					
Overall survival	214	15.4 [13.2; 18.2] 166 (77.6)	103	11.7 [8.8; 14.9] 82 (79.6)	0.79 [0.61; 1.03]; 0.084
Morbidity					
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)		No suitable data[b]			
Health status (EQ-5D VAS)		No suitable data[b]			
Health-related quality of life					
EORTC QLQ-C30		No suitable data[b]			
Side effects					
AEs (supplementary information)	213	0.5 [0.4; 0.7] 209 (98.1)	98	0.2 [0.1; 0.3] 95 (96.9)	–
SAEs	213	22.4 [16.6; 48.2] 72 (33.8)	98	NA 26 (26.5)	0.87 [0.55; 1.37]; 0.549
Severe AEs[c]	213	16.4 [10.7; 21.7] 91 (42.7)	98	0.3 [0.3; 1.0] 71 (72.4)	0.25 [0.18; 0.35]; < 0.001
Discontinuation due to AEs	213	NA 23 (10.8)	98	NA 13 (13.3)	0.59 [0.29; 1.19]; 0.134
Immune-related AEs		No suitable data[b]			
Other specific AEs					
Gastrointestinal disorders (SOC, AE)	213	14.5 [7.4; 20.4] 86 (40.4)	98	2.1 [1.0; 10.6] 53 (54.1)	0.46 [0.32; 0.66]; < 0.001
Asthenia (PT, AE)	213	NA 33 (15.5)	98	NA 22 (22.4)	0.5 [0.28; 0.87]; 0.012
Insomnia (PT, AE)	213	NA 12 (5.6)	98	NA 11 (11.2)	0.36 [0.15; 0.83]; 0.013
Alopecia (PT, AE)	213	NA 2 (0.9)	98	1.6 [0.7; 5.1] 52 (53.1)	0.01 [0.003; 0.05]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	213	NA [48.2; NC] 30 (14.1)	98	NA 4 (4.1)	2.87 [1.00; 8.21]; 0.040

Table 15: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: tislelizumab vs. docetaxel (multipage table)

Study Outcome category Outcome	Tislelizumab N	Tislelizumab Median time to event in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to event in months [95% CI] Patients with event n (%)	Tislelizumab vs. docetaxel HR [95% CI]; p-value[a]
Blood and lymphatic system disorders (SOC, severe AE[c])	213	NA 14 (6.6)	98	4.6 [1.6; NC] 45 (45.9)	0.09 [0.05; 0.17]; < 0.001
Including:					
Neutropenia (PT, severe AE[c])	213	NA 2 (0.9)	98	NA [7.2; NC] 26 (26.5)	0.03 [0.01; 0.12]; < 0.001
Leukopenia (PT, severe AE[c])	213	NA 1 (0.5)	98	NA 17 (17.3)	RR: 0.03 [0.004; 0.20]; < 0.001
Febrile neutropenia (PT, severe AE[c])	213	NA 0 (0)	98	NA 16 (16.3)	RR: 0.01 [0.001; 0.23]; < 0.001
Investigations (SOC, severe AE[c])	213	NA 15 (7.0)	98	NA [5.4; NC] 36 (36.7)	0.13 [0.07; 0.24]; < 0.001
Including:					
Neutrophil count decreased (PT, severe AE[c])	213	NA 2 (0.9)	98	NA 28 (28.6)	0.01 [0.002; 0.10]; < 0.001
White blood cell count decreased (PT, severe AE[c])	213	NA 1 (0.5)	98	NA 25 (25.5)	0.02 [0.002; 0.11]; < 0.001
Infections and infestations (SOC, severe AE[c])	213	NA [48.5; NC] 19 (8.9)	98	NA 16 (16.3)	0.37 [0.19; 0.74]; 0.004
Metabolism and nutrition disorders (SOC, severe AE[c])	213	NA 14 (6.6)	98	NA 13 (13.3)	0.45 [0.21; 0.96]; 0.034

a. Cox proportional hazards model and log-rank test; each stratified by histology (squamous cell carcinoma vs. non-squamous cell carcinoma), and line of treatment (second vs. third line of treatment).
b. For an explanation, see Section I 4.1.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, no more than indications, e.g. of an added benefit, can be determined for the outcomes of alopecia (AEs), blood and lymphatic system disorders

(severe AEs) and investigations (severe AEs), and no more than hints for the outcome of overall survival and the other outcomes in the side effects category due to the high risk of bias.

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13) and health status (EQ-5D VAS)

No suitable data are available for the outcomes of symptoms (recorded using EORTC QLQ-C30 and EORTC QLQ-LC13) and health status (recorded using EQ-5D VAS) (for justification, see Section I 4.1). In each case, there is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30)

No suitable data are available for the outcome of health-related quality of life (recorded using EORTC QLQ-C30) (for justification, see Section I 4.1). There is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. There is no hint of greater or lesser harm from tislelizumab in comparison with docetaxel for either of them; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of tislelizumab in comparison with docetaxel was found for the outcome of severe AEs (CTCAE grade ≥ 3). There is a hint of lesser harm from tislelizumab in comparison with docetaxel.

Immune-related AEs

No suitable data are available for the outcome of immune-related AEs (for justification, see Section I 4.1). There is no hint of greater or lesser harm from tislelizumab in comparison with docetaxel; greater or lesser harm is therefore not proven.

Other specific AEs

Gastrointestinal disorders (AEs), asthenia (AEs) and insomnia (AEs)

A statistically significant difference in favour of tislelizumab in comparison with docetaxel was found for each of the outcomes of gastrointestinal disorders (AEs), asthenia (AEs) and insomnia (AEs). For each of these outcomes, there is a hint of lesser harm from tislelizumab in comparison with docetaxel.

Alopecia (AEs)

A statistically significant difference in favour of tislelizumab compared with docetaxel was shown for the outcome of alopecia (AE). There is an indication of lesser harm from tislelizumab in comparison with docetaxel.

Respiratory, thoracic and mediastinal disorders (SAEs)

A statistically significant difference to the disadvantage of tislelizumab in comparison with docetaxel was shown for the outcome of respiratory, thoracic and mediastinal disorders (SAEs). There is a hint of greater harm from tislelizumab in comparison with docetaxel.

Blood and lymphatic system disorders (severe AEs) (including: neutropenia [severe AEs], leukopenia [severe AEs], febrile neutropenia [severe AEs]) and investigations (severe AEs) (including: neutrophil count decreased [severe AEs], white blood cell count decreased [severe AEs])

A statistically significant difference in favour of tislelizumab compared with docetaxel was shown for the outcomes of blood and lymphatic system disorders (severe AEs) and investigations (severe AEs), as well as the PTs (severe AEs) neutropenia, leukopenia, febrile neutropenia, neutrophil count decreased, and white blood cell count decreased, which are included in these SOCs. There is an indication of lesser harm from tislelizumab compared with docetaxel for each of the outcomes of blood and lymphatic system disorders (severe AEs) and investigations (severe AEs).

Infections and infestations (severe AEs) and metabolism and nutrition disorders (severe AEs)

A statistically significant difference in favour of tislelizumab in comparison with docetaxel was shown for each of the outcomes of infections and infestations (severe AEs) and metabolism and nutrition disorders (severe AEs). For each of these outcomes, there is a hint of lesser harm from tislelizumab in comparison with docetaxel.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for this benefit assessment:

- age (< 65/≥ 65)

- sex (female versus male)
- brain metastases at baseline (yes versus no)

Subgroup analyses for these characteristics were prespecified for overall survival according to the planning of the study.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results do not reveal any effect modifications.

Regarding the prior therapies, the G-BA additionally pointed out in the context of the specification of the ACT that subgroup analyses according to the number of prior therapies should be presented in order to investigate a potential effect in patients with a different number of prior therapies. For the RATIONALE 303 study, subgroup analyses were available for patients who were in the second or third line of treatment during the study. When applying the methods described above, no effect modifications were revealed for this characteristic either.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is assessed based on the results presented in Chapter I 4 (see Table 16).

Table 16: Extent of added benefit at outcome level: tislelizumab vs. docetaxel (multipage table)

Outcome category **Outcome**	**Tislelizumab vs. docetaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	15.4 vs. 11.7 months HR: 0.79 [0.61; 1.03]; p = 0.084	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC-QLQ C30, EORTC-QLQ LC13)	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[c]	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: tislelizumab vs. docetaxel (multipage table)

Outcome category **Outcome**	**Tislelizumab vs. docetaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	22.4 vs. NA months HR: 0.87 [0.55; 1.37]; p = 0.549	Greater/lesser harm not proven
Severe AEs	16.4 vs. 0.3 months HR: 0.25 [0.18; 0.35]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 0.59 [0.29; 1.19]; p = 0.134	Greater/lesser harm not proven
Immune-related AEs	No suitable data[c]	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	14.5 vs. 2.1 months HR: 0.46 [0.32; 0.66]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: "considerable"
Asthenia (AEs)	NA vs. NA HR: 0.50 [0.28; 0.87]; p = 0.012 Probability: "hint"	Outcome category: non-serious/non-severe side effects 0.80 ≤ CI_u < 0.90 Lesser harm, extent: "minor"
Insomnia (AEs)	NA vs. NA HR: 0.36 [0.15; 0.83]; p = 0.013 Probability: "hint"	Outcome category: non-serious/non-severe side effects 0.80 ≤ CI_u < 0.90 Lesser harm, extent: "minor"
Alopecia (AEs)	NA vs. 1.6 months HR: 0.01 [0.003; 0.05]; p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SAEs)	NA vs. NA HR: 2.87 [1.00; 8.21]; HR: 0.34 [0.12; 1.00][d]; p = 0.040 Probability: "hint"	Outcome category: serious/severe side effects Greater harm[e], extent: "minor"[f]
Blood and lymphatic system disorders (severe AEs)	NA vs. 4.6 months HR: 0.09 [0.05; 0.17]; p = < 0.001 Probability: "indication"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: "major"

Table 16: Extent of added benefit at outcome level: tislelizumab vs. docetaxel (multipage table)

Outcome category **Outcome**	**Tislelizumab vs. docetaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Including:		
Neutropenia (severe AEs)	NA vs. NA HR: 0.03 [0.01; 0.12]; p < 0.001	
Leukopenia (severe AEs)	NA vs. NA RR: 0.03 [0.004; 0.20]; p < 0.001	
Febrile neutropenia (severe AEs)	NA vs. NA RR: 0.01 [0.001; 0.23]; p < 0.001	
Investigations (severe AEs)	NA vs. NA HR: 0.13 [0.07; 0.24]; p < 0.001 Probability: “indication”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: “major”
Including:		
Neutrophil count decreased (severe AEs)	NA vs. NA HR: 0.01 [0.002; 0.10]; p < 0.001	
White blood cell count decreased (severe AEs)	NA vs. NA HR: 0.02 [0.002; 0.11]; p < 0.001	
Infections and infestations (severe AEs)	NA vs. NA HR: 0.37 [0.19; 0.74]; p = 0.004 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: “major”
Metabolism and nutrition disorders (severe AEs)	NA vs. NA HR: 0.45 [0.21; 0.96]; p = 0.034 Probability: “hint”	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Lesser harm, extent: “minor”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. See Section I 4.1 for reasons.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The result of the statistical test is decisive for the derivation of the added benefit.
f. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

Table 16: Extent of added benefit at outcome level: tislelizumab vs. docetaxel (multipage table)

Outcome category **Outcome**	**Tislelizumab vs. docetaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of tislelizumab in comparison with docetaxel

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
Serious/severe side effects ▪ Severe AEs: hint of lesser harm – extent: “major” ▫ Blood and lymphatic system disorders (severe AEs, including: neutropenia [severe AEs], leukopenia [severe AEs], febrile neutropenia [severe AEs]): indication of lesser harm – extent: “major” ▫ Investigations (severe AEs, including: neutrophil count decreased [severe AEs], white blood cell count decreased [severe AEs]): indication of lesser harm – extent: “major” ▫ Infections and infestations (severe AEs): hint of lesser harm – extent: “major” ▫ Metabolism and nutrition disorders (severe AEs): hint of lesser harm – extent: “minor”	Serious/severe side effects ▪ Respiratory, thoracic and mediastinal disorders (SAEs): hint of greater harm – extent: “minor”
Non-serious/non-severe side effects ▪ Gastrointestinal disorders (AEs): hint of lesser harm – extent: “considerable” ▪ Asthenia (AEs): hint of lesser harm – extent: “minor” ▪ Insomnia (AEs): hint of lesser harm – extent: “minor” ▪ Alopecia (AEs): indication of lesser harm – extent: “considerable”	–
For outcomes of the morbidity and health-related quality of life categories as well as immune-related AEs, no suitable data are available.	
AE: adverse event; SAE: serious adverse event	

Overall, there are several positive and one negative effect of tislelizumab compared with docetaxel for outcomes in the side effects category. There are advantages particularly in terms of severe AEs, in some cases to a major extent. However, there are no suitable data for outcomes in the categories of morbidity and health-related quality of life. Furthermore, there is a lack of suitable data on immune-related AEs. However, no disadvantages are expected to an extent that would completely challenge the positive effects in severe AEs, though the extent of the added benefit cannot be quantified due to the lack of data on other outcomes.

In summary, there is a hint of a non-quantifiable added benefit of tislelizumab compared with the ACT for adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy, with PD-L1-negative tumours (PD-L1 expression < 1%).

No data are available to assess the added benefit of tislelizumab in comparison with the ACT specified by the G-BA for adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy with PD-L1-positive tumours (PD-L1 expression ≥ 1%). An added benefit of tislelizumab in comparison with the ACT is not proven for patients with PD-L1-positive tumours (PD-L1 expression ≥ 1%).

Table 18 summarizes the result of the assessment of the added benefit of tislelizumab in comparison with the ACT.

Table 18: Tislelizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with locally advanced or metastatic NSCLC after prior treatment with platinum-based chemotherapy; in addition, patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving tislelizumab[b]	▪ docetaxel (only for patients with PD-L1-negative tumours) or ▪ pemetrexed (only for patients with PD-L1-negative tumours and except in mainly squamous histology) or ▪ nivolumab or ▪ pembrolizumab (only for patients with PD-L1 expressing tumours, [TPS ≥ 1%]) or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib (only for patients with PD-L1-negative tumours and adenocarcinoma histology)	▪ Patients with PD-L1-negative tumours[c]: hint of non-quantifiable added benefit[d] ▪ Patients with PD-L1-positive tumours[e]: added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In accordance with the G-BA, it is assumed that for the given therapeutic indication patients have no medical indication for definitive local therapy. In addition, it is assumed that no (other) molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon 20, HER2, KRAS G12C, METex14, RET or ROS1) is an option for the patients at the time of treatment with tislelizumab.
c. PD-L1 expression < 1%.
d. The RATIONALE 303 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. In addition, the study only included patients in the second or third line of treatment and patients who had not received targeted therapies against EGFR-mutant or ALK-positive NSCLC. Therefore, it also remains unclear whether the observed effects are transferable to patients in the fourth or later lines of treatment and patients who have already received targeted therapies against EGFR-mutant or ALK-positive NSCLC.
e. PD-L1 expression ≥ 1%.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene homologue; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: proto-oncogene tyrosine-protein kinase 1; TPS: Tumour Proportion Score

The assessment described above deviates from that by the company, which claimed a hint of considerable added benefit for patients with PD-L1 expression < 1%. For patients with PD-L1 expression ≥ 1%, the assessment described above concurs with that by the company.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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