Pembrolizumab (NSCLC, adjuvant)

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
AEOSI	adverse events of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
APaT	All Participants as Treated
BSC	best supportive care
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EFS	event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EORTC QLQ-LC13	EORTC Quality of Life Questionnaire – Lung Cancer 13
EQ-5D VAS	EQ-5D visual analogue scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IASLC	International Association for the Study of Lung Cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MD	mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PD-L1/L2	programmed cell death ligand 1/2
PT	Preferred Term
RCT	randomized controlled trial

Abbreviation	Meaning
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
TPS	Tumour Proportion Score
UICC	Union for International Cancer Control

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) 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 pembrolizumab. 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 25 April 2024.

Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in comparison with watchful waiting as appropriate comparator therapy (ACT) for the adjuvant treatment of patients with non-small cell lung cancer (NSCLC) who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

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

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a]
Adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment	Watchful waiting
a. Presented is the ACT specified by the G-BA. The ACT was determined for stages IB to IIIA on the basis of the currently valid TNM tumour classification in the 8th edition of the UICC. The G-BA assumes that tumours in stage IA or IB (T < 4 cm) and ≥ IIIB (according to classification 8) are not eligible for treatment with pembrolizumab. ACT: appropriate comparator therapy; G-BA: Joint Federal Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control	

The company followed the G-BA's specification of the ACT.

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 added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

A subpopulation of the KEYNOTE 091 study is used for the benefit assessment of pembrolizumab.

The KEYNOTE 091 study is an ongoing, triple-blind, randomized study comparing pembrolizumab with placebo. The study included adult patients with pathologically confirmed NSCLC who are at high risk of recurrence, defined as stages IB (T2a ≥ 4 cm) to IIIA (classification

according to the 7th edition of the International Association for the Study of Lung Cancer [IASLC]/Union for International Cancer Control [UICC]/American Joint Committee on Cancer [AJCC]), following complete tumour resection (R0 resection) and regardless of the histological classification. There had to be no evidence of the disease within 12 weeks prior to randomization. Patients also had to be in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1. Patients were included regardless of their PD-L1 status.

Prior to randomization to the treatment arms, patients could receive a maximum of 4 cycles of adjuvant chemotherapy in accordance with the study protocol. A total of 1177 patients were randomly allocated at a 1:1 ratio to treatment with pembrolizumab (N = 590) or placebo (N = 587).

Treatment with pembrolizumab in the intervention arm was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). According to the study protocol, treatment with pembrolizumab was limited to 18 cycles of 3 weeks each and could be interrupted for up to 12 weeks if necessary. This corresponds approximately to the maximum treatment duration of up to 1 year specified in the SPC. The study materials do not contain any information on restrictions regarding subsequent therapies.

Relevant subpopulation

The approval of pembrolizumab in the present therapeutic indication is limited to patients who are at high risk of recurrence following complete resection and platinum-based chemotherapy. In Module 4 A of the dossier, the company presented results for the subpopulation of patients with previous adjuvant chemotherapy. This subpopulation comprised 506 patients in the pembrolizumab arm and 504 patients in the comparator arm and is considered relevant.

The present benefit assessment uses the results from the 3rd data cut-off of 24 January 2023.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. The KEYNOTE 091 study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting. Despite deviations in the recommended time intervals when performing the imaging procedures specified in the guidelines, the study regimen in the KEYNOTE 091 study as a whole is considered to be a sufficient approximation to the ACT “watchful waiting” for the present benefit assessment.

Limitations of the KEYNOTE 091 study

Tumour staging was conducted based the 7th edition of the IASLC/UICC/AJCC classification

The KEYNOTE 091 study was launched in November 2015 when the 7th edition of the IASLC/UICC/AJCC staging criteria was the most recent. This classification was revised during the study period and the currently applicable 8th edition of the staging criteria came into effect on 1 January 2017. The company stated that the classification of tumour stage at study inclusion will continue to be based on the 7th edition for the entire duration of the study for reasons of consistency. However, there are differences between the 7th and 8th editions of the staging criteria, which may lead to a change in the tumour classification of some patients. The company did not convert the staging to the currently applicable 8th edition. There is uncertainty regarding the proportion of patients in the presented subpopulation who have stage IIIB tumours according to the current 8th classification and are therefore not covered by the research question of the present benefit assessment. For this reason, the certainty of conclusions of the study results is limited. Thus, based on the results of the KEYNOTE 091 study, only hints, e.g. of added benefit, can be derived in the present situation.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes is rated as low for the KEYNOTE 091 study. No suitable data are available for the outcome of overall survival (for explanation see below); therefore, the risk of bias of the results is not assessed. The risk of bias for the results of the outcomes of recurrence and the outcomes on symptoms, health status and health-related quality of life, assessed using the EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D VAS, is classified as low in each case.

All results on outcomes in the adverse events category, except “discontinuation due to AEs”, have a high risk of bias due to an unclear proportion of incomplete observations for potentially informative reasons, despite equal median observation durations. Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is reduced. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs which would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Taking into account the uncertainty with regard to the included patient population, at most hints, for example of an added benefit, can be determined for all outcomes on the basis of the KEYNOTE 091 study.

Results

Mortality

Overall survival

The data for the outcome of overall survival cannot be interpreted, as the subsequent systemic therapies administered in the comparator arm of the KEYNOTE-091 study are not an adequate reflection of the current standard of therapy after recurrence. The data on the overall population show that only a maximum of 35% of patients with locoregional recurrence and/or distant metastases in the comparator arm received an immune checkpoint inhibitor during the course of treatment. Furthermore, it is uncertain whether testing for the molecular markers recommended in the guidelines was carried out as part of the study. It is therefore unclear whether patients in advanced stages were offered suitable molecularly stratified therapies as a subsequent therapy.

There is no hint of an added benefit of pembrolizumab for overall survival compared to "watchful waiting"; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and disease-free survival [DFS]), a statistically significant difference between the treatment arm in favour of pembrolizumab in comparison with watchful waiting is shown. This results in a hint of added benefit of pembrolizumab in comparison with watchful waiting for this outcome.

Symptoms

EORTC QLQ-C30

Appetite loss

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of appetite loss. The standardized mean difference (SMD) was analysed to examine the relevance of the result. The 95% confidence interval (CI) of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. There is no hint of an added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation, and diarrhoea

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation, and diarrhoea. This results in no hint of

added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

EORTC QLQ-LC13

Dyspnoea, cough, haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain (chest), pain (arm/shoulder), pain (other)

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for all outcomes assessed with the EORTC QLQ-LC13. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

On the basis of the mean difference, no statistically significant difference between treatment arms was found for the outcome of health status measured with the EQ-5D VAS. There is no hint of an added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Social functioning

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of social functioning. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant difference between treatment arms to the disadvantage of pembrolizumab in comparison with watchful waiting was found for each of the outcomes of

SAEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and discontinuation due to AEs. In each case, there was a hint of greater harm from pembrolizumab in comparison with watchful waiting.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab compared with placebo between the treatment arms was shown for each of the outcomes "immune-mediated SAEs" and "immune-mediated severe AEs (CTCAE grade ≥ 3)". In each case, there was a hint of greater harm from pembrolizumab in comparison with watchful waiting.

Endocrine disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs), hepatobiliary disorders (Severe AEs), infections and infestations (Severe AEs)

A statistically significant difference to the disadvantage of pembrolizumab compared with placebo was shown between the treatment arms for each of the following outcomes: endocrine disorders (SAEs) respiratory, thoracic and mediastinal disorders (SAEs), hepatobiliary disorders (severe AEs), and infections and infestations (severe AEs). In each case, there was a hint of greater harm from pembrolizumab in comparison with watchful waiting.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug pembrolizumab compared with the ACT is assessed as follows:

Overall, there are both positive and negative effects for pembrolizumab in comparison with watchful waiting.

On the side of positive effects, there is a hint of a minor added benefit only for the outcome of recurrence. On the other hand, there are hints of greater harm with different, in some cases major extent for numerous outcomes in the side effects category. Even taking into account the fact that the treatment is limited to 1 year, these negative effects of major extent significantly outweigh the minor positive effect.

[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].

In summary, for patients with NSCLC at high risk of recurrence following complete resection and platinum-based chemotherapy for adjuvant treatment, there is a hint of lesser benefit of pembrolizumab in comparison with the ACT watchful waiting.

Table 3 presents a summary of the probability and extent of added benefit of pembrolizumab.

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment	Watchful waiting	Hint of lesser benefit

a. Presented is the ACT specified by the G-BA. The ACT was determined for stages IB to IIIA on the basis of the currently applicable TNM tumour classification in the 8th edition of the UICC. The G-BA assumes that tumours in stage IA or IB (T < 4 cm) and ≥ IIIB (according to classification 8) are not eligible for treatment with pembrolizumab.

ACT: appropriate comparator therapy; G-BA: Joint Federal Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

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 the present report is the assessment of the added benefit of pembrolizumab in comparison with watchful waiting as appropriate comparator therapy (ACT) for the adjuvant treatment of patients with non-small cell lung cancer (NSCLC) who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

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

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT[a]**
Adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment	Watchful waiting
a. Presented is the ACT specified by the G-BA. The ACT was determined for stages IB to IIIA on the basis of the currently applicable TNM tumour classification in the 8th edition of the UICC. The G-BA assumes that tumours in stage IA or IB (T < 4 cm) and ≥ IIIB (according to classification 8) are not eligible for treatment with pembrolizumab. ACT: appropriate comparator therapy; G-BA: Joint Federal Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control	

The company followed the G-BA's specification of the ACT.

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 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 of the company in the dossier:

- study list on pembrolizumab (status: 7 February 2024)
- bibliographical literature search on pembrolizumab (last search on 5 February 2024)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 5 February 2024)
- search on the G-BA website for pembrolizumab (last search on 13 February 2024)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 8 May 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

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: pembrolizumab vs. watchful waiting

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 [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
KEYNOTE 091[c] (PEARLS)	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

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 following tables, the study is referred to with this designation.

CSR: clinical study report; RCT: randomized controlled trial

For the benefit assessment of pembrolizumab, the procedure in the placebo-controlled KEYNOTE 091 study is rated as sufficient implementation of the ACT (see Section I 3.2.1) and the KEYNOTE 091 study is included.

The study pool concurred with the one of the company.

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: pembrolizumab vs. watchful waiting (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 091	RCT, triple-blind, placebo-controlled	Adult patients ▪ with pathologically confirmed stage IB (T2a ≥ 4 cm) to IIIA NSCLC[b] ▪ following complete tumour resection (R0 resection) ▪ ECOG PS 0 or 1	Pembrolizumab (N = 590) placebo (N = 587) Relevant subpopulation thereof[c]: pembrolizumab (n = 506) placebo (n = 504)	Screening: within 12 weeks before randomization Treatment: pembrolizumab for a maximum of 18 cycles or until disease progression, unacceptable toxicity, or treatment discontinuation due to the decision of the investigator or the patient Observation[d]: outcome-specific, at most until death, loss to follow-up, withdrawal of consent or end of study	206 study centres in 29 countries: Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Latvia, Netherlands, Peru, Poland, Portugal, Russia, Slovenia, South Korea, Spain, Switzerland, Turkey, United Kingdom 11/2015–ongoing Data cut-offs[e]: ▪ 10 September 2020[f] ▪ 20 September 2021[g] ▪ 24 January 2023[h]	Primary: DFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab vs. watchful waiting (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 information only on relevant available outcomes for this benefit assessment. b. Staging based on UICC/AJCC classification, edition 7 (see also Section I 3.4). c. Patients received adjuvant chemotherapy following tumour resection. d. Outcome-specific information is provided in Table 8. e. The final analysis of overall survival, which has not yet been performed, is planned after the death of 130 patients with high PD-L1 expression (TPS ≥ 50%) and 497 patients in the overall population, but no later than 10 years after randomization of the first patient. f. The 1st interim analysis was planned after 90 DFS events in the subpopulation of patients with high PD-L1 expression (TPS ≥ 50%). g. The 2nd interim analysis was planned after 118 DFS events in the subpopulation of patients with high PD-L1 expression (TPS ≥ 50%). h. The final DFS analysis was planned after 141 DFS events in the subpopulation of patients with high PD-L1 expression (TPS ≥ 50%) and 551 DFS events in the total population. At this point and after the database was locked, the study was unblinded according to the study protocol. AE: adverse event; AJCC: American Joint Committee on Cancer; DFS: disease-free survival; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; n: relevant subpopulation; N: number of randomized patients; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; TPS: tumour proportion score; UICC: Union for International Cancer Control					

Table 7: Characteristics of the intervention – pembrolizumab vs. watchful waiting

Study	Intervention	Comparison
KEYNOTE 091	Pembrolizumab 200 mg IV every 3 weeks (for a maximum of 18 cycles)	Pembrolizumab 200 mg IV every 3 weeks (for a maximum of 18 cycles)
	Dose adjustment: ▪ no dose adjustment allowed; interruption allowed for up to 12 weeks for immune-mediated AEs, medical/surgical events or logistical reasons not related to study therapy	
	Pretreatment ▪ complete surgical resection of NSCLC (lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy)[a] Disallowed ▪ previous neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy ▪ > 4 cycles of adjuvant chemotherapy[b] ▪ pretreatment with anti-PD-1, anti-PD-L1/2, anti-CD137, CTLA-4 modulators or other immunomodulatory drugs ▪ live vaccines ≤ 30 days before first study treatment[c] **Concomitant treatment** Allowed ▪ all concomitant treatments deemed necessary by the investigator for the wellbeing of the patient Disallowed ▪ any concurrent oncological treatment (surgery, radiotherapy, systemic therapy) ▪ immunosuppressants, except for the treatment of immune-mediated AEs ▪ immunomodulators ▪ systemic glucocorticoids with an equivalent of more than 7.5 mg prednisone[d]	

a. No evidence of disease based on the findings of a clinical examination and a radiological baseline examination (CT of chest and abdomen, as well as CT/MRI of the brain) ≤ 12 weeks before randomization.
b. Adjuvant chemotherapy was not mandatory but was considered for patients with stage IB (T2a ≥ 4 cm) and strongly recommended for stages II and IIIA and administered according to national and local guidelines.
c. Vaccination with live vaccines was disallowed throughout the course of the study.
d. Patients who developed endocrinopathies requiring hormone replacement therapy during the study were excluded.

AE: adverse event; CT: computed tomography; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; MRI: magnetic resonance imaging; NSCLC: non-small cell lung cancer; PD-1: programmed cell death-1; PD-L1/L2: programmed cell death ligand 1/2; RCT: randomized controlled trial

I 3.2.1 Design of the KEYNOTE 091 study

The KEYNOTE 091 study is an ongoing, triple-blind, randomized study comparing pembrolizumab with placebo. The study included adult patients with pathologically confirmed NSCLC who are at high risk of recurrence, defined as stages IB (T2a ≥ 4 cm) to IIIA (classification according to the 7th edition of the IASLC/UICC/AJC classification, following complete tumour resection (R0 resection) and regardless of the histological classification. There had to be no evidence of the disease within 12 weeks prior to randomization. The corresponding assessment was based on the findings of a clinical examination and a radiological baseline

examination (computed tomography [CT] of the chest and upper abdomen, as well as CT or magnetic resonance imaging [MRI] of the brain). Patients also had to be in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1. Samples taken during tumour resection were examined in a central laboratory for programmed cell death ligand 1 (PD-L1) expression using immunohistochemistry. The test used for PD-L1 testing was the Agilent PD-L1 IHC 22C3 pharmDx kit [7]. Patients were included regardless of their PD-L1 status.

Prior to randomization to the treatment arms, patients could receive a maximum of 4 cycles of adjuvant chemotherapy in accordance with the study protocol. Patients receiving adjuvant chemotherapy should start it within 12 weeks of surgery, and the first study treatment should be administered at least 3 weeks but no more than 12 weeks after the last dose of chemotherapy.

A total of 1177 patients were randomly allocated at a 1:1 ratio to treatment with pembrolizumab (N = 590) or placebo (N = 587). Randomization was stratified by tumour stage (IB vs. II vs. IIIA), adjuvant chemotherapy (no adjuvant chemotherapy vs. adjuvant chemotherapy), PD-L1 status categorized by Tumour Proportion Score (TPS) (negative [TPS = 0%] vs. weakly positive [TPS = 1 to 49%] vs. strongly positive [TPS ≥ 50%]) and region (Western Europe vs. Eastern Europe vs. rest of the world vs. Asia). Only a subpopulation of the global cohort is relevant for the present benefit assessment; this is explained in the section on the relevant subpopulation (see Section I 3.2.4).

Treatment with pembrolizumab in the intervention arm was largely in compliance with the specifications of the SPC [8]. According to the study protocol, treatment with pembrolizumab was limited to 18 cycles of 3 weeks each and could be interrupted for up to 12 weeks if necessary. This corresponds approximately to the maximum treatment duration of up to 1 year specified in the SPC. A regular switch of the patients from the comparator arm to a treatment with pembrolizumab was not provided for in the KEYNOTE 091 study. The study materials do not contain any information on restrictions regarding subsequent therapies.

The primary outcome of the KEYNOTE 091 study was disease-free survival (DFS). Further secondary outcomes were outcomes of the categories “mortality”, “morbidity” and “side effects”.

I 3.2.2 Implementation of the ACT

The G-BA specified watchful waiting as the ACT.

The KEYNOTE 091 study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but it is nonetheless suitable for such a comparison. This is explained below.

The following examinations were performed for the assessment of the disease status or the detection of recurrences in the KEYNOTE 091 study:

- contrast-enhanced CT scan of the chest/upper abdomen every 12 weeks (± 2 weeks) during the treatment phase; during the follow-up every 6 months (± 4 weeks) in years 2 and 3, as well as annually (± 4 weeks) from year 4
- CT and / or MRI of the brain, if clinically indicated, e.g. for headaches or neurological symptoms
- physical examination (ECOG PS, blood pressure, weight, heart rate, temperature), if clinically indicated according to the investigator

According to the current S3 Guideline on the Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer [9] no optimal follow-up care concept is yet in place for patients with NSCLC following complete tumour resection. The guideline recommends a quarterly examination in the first 2 years, followed by a semi-annual examination and inclusion in a lung cancer screening program after 5 years. The examination should comprise a dedicated anamnesis, a physical examination and suitable imaging techniques. According to the European guideline for the treatment of early and locally advanced NSCLC, semi-annual and then annual examinations using imaging techniques are recommended in the first 2 years [10,11].

Despite the deviations in the recommended time intervals when performing the imaging procedures specified in the above mentioned guidelines, the study regimen in the KEYNOTE 091 study as a whole is considered to be a sufficient approximation to the ACT "watchful waiting" for the present benefit assessment.

I 3.2.3 Data cut-offs

Two data cut-offs are currently available for the KEYNOTE 091 study:

- 1st data cut-off from 10 September 2020: prespecified DFS interim analysis after 90 DFS events in the subpopulation of patients with high PD-L1 expression (TPS ≥ 50%)
- 2nd data cut-off from 20 September 2021: prespecified DFS interim analysis after 118 DFS events in the subpopulation of patients with high PD-L1 expression (TPS ≥ 50%)
- 3rd data cut-off from 24 October 2021: final DFS analysis was planned after 141 DFS events in the subpopulation of patients with high PD-L1 expression (TPS ≥ 50%) and 551 DFS events in the total population

The current 3rd data cut-off is relevant for the present benefit assessment. The company also uses this data cut-off to derive the added benefit. The final data cut-off for the analysis of overall survival is still pending and should take place no later than 10 years after randomization of the first patient (see Table 6).

I 3.2.4 Subpopulation presented by the company

The approval of pembrolizumab in the present therapeutic indication is limited to patients who are at high risk of recurrence following complete resection and platinum-based chemotherapy. In Module 4 A of the dossier, the company presented results for the subpopulation of patients with previous adjuvant chemotherapy. This subpopulation comprised 506 patients in the pembrolizumab arm and 504 patients in the comparator arm and is considered relevant.

I 3.2.5 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 – pembrolizumab vs. watchful waiting

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE 091	
Mortality	
Overall survival	Until death, revocation of consent, or end of study[a] (whichever occurred first)
Morbidity	
Recurrence[b]	Until recurrence, death, revocation of consent, or end of study (whichever occurred first), maximum of 10 years
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), health status (EQ-5D VAS)	Up to 5 years
Health-related quality of life	
EORTC QLQ-C30	Up to 5 years
Side effects	
AEs/severe AEs	Up to 30 days after the last dose of the study medication
SAEs	Up to 90 days after the last dose of the study medication or 30 days in case of initiation of a subsequent antineoplastic therapy

a. According to the study protocol, the study is completed once all of the following conditions are met: 1) when the last patient has completed the last study-related contact, withdraws from the study or is lost to follow-up, 2) the study is ready for analysis of the primary outcome, and 3) when the database for this analysis is fully purged and locked.
b. Represented by the recurrence rate and DFS, includes the events death, distant metastases and/or locoregional recurrence, new malignancy and not disease-free at baseline.

AE: adverse event; DFS: disease-free survival; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-LC13: EORTC Quality of Life Questionnaire – Lung Cancer 13; EQ-5D VAS: EQ-5D visual analogue scale; RCT: randomized controlled trial; SAE: serious adverse event

The KEYNOTE 091 study surveyed only overall survival to the end of the study.

Follow-up observation for the outcome of recurrence or disease-free survival is to be carried out for up to 10 years. Since the final analysis of overall survival should also take place at the latest 10 years after the randomization of the 1st patient, the outcome here is considered to be observed approximately over the entire study duration. In addition, at the time of the 3rd data cut-off on 24 January 2023, all patients were observed for significantly less than 10 years (see Section I 3.2.7).

A follow-up observation of up to 5 years is planned for the outcomes on symptoms, health status and health-related quality of life. The observation times for these outcomes are thus systematically shortened, but they still cover a period of 5 years. It should be noted as a positive aspect that the survey of patient-reported outcomes was continued after the end of treatment regardless of the occurrence of disease progression.

The observation periods for the side effects outcomes were recorded only for the duration of treatment with the study medication (plus 30 or 90 days). 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.

I 3.2.6 Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: pembrolizumab versus watchful waiting (multipage table)

Study **Characteristic** **Category**	**Pembrolizumab** **N[a] = 506**	**Placebo** **N[a] = 504**
KEYNOTE 091		
Age [years], mean (SD)	63 (8)	64 (8)
Sex [F/M], %	33/67	31/69
Region, n (%)		
Western Europe	261 (52)	266 (53)
Eastern Europe	105 (21)	96 (19)
Rest of the world	53 (10)	55 (11)
Asia	87 (17)	87 (17)
ECOG PS, n (%)		
0	326 (64)	292 (58)
1	180 (36)	212 (42)
Tumour stage[b], n (%)		
IB	60 (12)	57 (11)
II	283 (56)	295 (59)
IIIA	163 (32)	150 (30)
IV	0 (0)	2 (< 1)
PD-L1 status, n (%)		
< 1%	198 (39)	198 (39)
1 – 49%	165 (33)	165 (33)
≥ 50%	143 (28)	141 (28)
Histology, n (%)		
Squamous	157 (31)	184 (37)
Non-squamous	349 (69)	320 (63)
EGFR mutation status, n (%)		
Negative	190 (38)	192 (38)
Positive	36 (7)	30 (6)
Unknown	280 (55)	282 (56)
Smoking status, n (%)		
Never smoker	80 (16)	57 (11)
Ex-smoker	362 (72)	375 (74)
Current smoker	64 (13)	72 (14)

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: pembrolizumab versus watchful waiting (multipage table)

Study **Characteristic** **Category**	**Pembrolizumab** **N[a] = 506**	**Placebo** **N[a] = 504**
Time between surgery and 1st dose of adjuvant chemotherapy, n (%)		
≤ 60 days	417 (82)	411 (82)
> 60 and ≤ 84 days	79 (16)	84 (17)
> 84 days	9 (2)	9 (2)
Missing	1 (< 1)	0 (0)
Treatment discontinuation, n (%)[c]	235 (47)	175 (35)
Study discontinuation, n (%)[d]	134 (26)	152 (30)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Staging based on IASLC/UICC/AJCC classification, edition 7.
c. Common reasons for treatment discontinuation in the intervention vs. control arm were: toxicity due to the study medication (19% vs. 4%), recurrence/relapse/death due to disease progression (12% vs. 22%), patient's decision not related to toxicity (8% vs. 4%). The percentages refer to the APaT cohort (intervention arm vs. control arm: N = 496 vs. N = 499).
d. Common reasons for study discontinuation in the intervention arm vs. control arm were death (22% vs. 27%) and withdrawal of consent (4% vs. 2%).

AJCC: American Joint Committee on Cancer; APaT: All Participants as Treated; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; EGFR: epidermal growth factor receptor; f: female; IASLC: International Association for the Study of Lung Cancer; m: male; n: number of patients in the category; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; UICC: Union for International Cancer Control

The characteristics of the patients are largely balanced between the 2 treatment arms of the KEYNOTE 091 study. The patients' mean age was 63 and 64 years, they were predominantly male (67% versus 69%) and were enrolled in the study mainly in Western Europe (52% and 53%). 64% of the patients in the intervention arm had an ECOG PS of 0, compared to only 58% in the comparator arm.

Tumour staging in the study was based on the 7th edition of the IASLC/UICC/AJCC classification and most patients were included in the study as having stage II (56% and 59% respectively) and IIIA (32% and 30% respectively). For 82% of patients, the time between surgery and the first dose of adjuvant chemotherapy was ≤ 60 days.

Treatment was discontinued more frequently in the intervention arm than in the comparator arm (47% vs. 35%). The main reason for treatment discontinuation in the intervention arm was toxicity due to the study medication, whereas in the comparator arm it was disease progression.

I 3.2.7 Course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab** **N = 506**	**Placebo** **N = 504**
KEYNOTE 091		
Treatment duration [months]		
Median [Q1; Q3]	11.7 [ND]	11.8 [ND]
Observation period[a] [months]		
Overall survival		
Median [Q1; Q3]	45.8 [ND]	45.0 [ND]
Morbidity		
Recurrence		
Median [Q1; Q3]	35.1 [ND]	34.7 [ND]
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), health-related quality of life (EORTC QLQ-C30)		
Median [Q1; Q3]	35.2 [ND]	35.0 [ND]
Health status (EQ-5D VAS)		
Median [Q1; Q3]	35.1 [ND]	35.0 [ND]
Side effects		
AEs		
Median [Q1; Q3]	12.7 [ND]	12.7 [ND]
SAEs		
Median [Q1; Q3]	14.7 [ND]	14.7 [ND]

a. The company did not provide any information on the calculation method of the observation period.

DFS: disease-free survival; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13; EQ-5D VAS: EQ-5D visual analogue scale; N: number of patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

In the KEYNOTE 091 study, the median treatment duration at the first data cut-off is approximately 12 months in both treatment arms.

The median observation period for the outcome of overall survival is approximately 45 months at the 3rd data cut-off. a. However, the company did not provide any information on the calculation method of the observation period.

The median observation period for the outcome of recurrence and for the patient-reported symptoms outcomes (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire – Core 30 [QLQ-C30], EORTC Quality of Life Questionnaire – Lung Cancer 13 [QLQ-LC13], EQ-5D visual analogue scale [VAS]) and for health-related quality of life (EORTC QLQ-C30) is approximately 35 months each. The difference to the observation period for the outcome of overall survival can be explained in part by the fact that, according to the study protocol, recurrence and patient-reported outcomes were only surveyed annually after 3 years, while the survival status was surveyed every 12 weeks in the first 4 years. There is a discrepancy here with the information in Module 4, where the company describes that the patient-reported outcomes should only be surveyed annually after 2 years.

The median observation period for the outcomes in the adverse events category is around 13 months (AEs) and 15 months (SAEs) in both arms and is systematically shorter compared to overall survival.

I 3.2.8 Subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies and surgeries[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (KEYNOTE 091 study) (multipage table)

Study	**Patients with subsequent therapy, n (%)[c]**	
Drug class[b]	**Pembrolizumab**	**Placebo**
Drug	**N = 506**	**N = 504**
KEYNOTE 091 study		
Total	125 (24.7)	180 (35.7)
1st subsequent therapy: systemic therapy	65 (12.8)	102 (20.2)
1st subsequent therapy: radiotherapy	52 (10.3)	73 (14.5)
1st subsequent therapy: systemic therapy and radiotherapy	8 (1.6)	5 (1.0)
1st subsequent systemic therapy[d]	73 (14.4)	107 (21.2)
Anaplastic lymphoma kinase (ALK) inhibitors	3 (4.1)	4 (3.7)
Alectinib hydrochloride	1 (1.4)	2 (1.9)
Anti-androgens	2 (2.7)	0 (0)
Bicalutamide	2 (2.7)	0 (0)
Combinations of antineoplastic drugs	40 (54.8)	42 (39.3)
Carboplatin, pemetrexed	15 (20.5)	12 (11.2)
Carboplatin, paclitaxel	8 (11.0)	7 (6.5)
Cisplatin, pemetrexed	4 (5.5)	3 (2.8)
Carboplatin, vinorelbine	0 (0)	5 (4.7)
Carboplatin, etoposide	2 (2.7)	2 (1.9)
Cisplatin, etoposide	2 (2.7)	2 (1.9)
Carboplatin, gemcitabine	2 (2.7)	1 (0.9)
Cisplatin; vinorelbine	0 (0)	3 (2.8)
Carboplatin; pembrolizumab; pemetrexed	0 (0)	2 (1.9)
Fluorouracil; folinic acid; oxaliplatin	2 (2.7)	0 (0)
Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors	7 (9.6)	15 (14.0)
Osimertinib mesylate	2 (2.7)	6 (5.6)
Gefitinib	2 (2.7)	3 (2.8)
Osimertinib	2 (2.7)	2 (1.9)
Afatinib dimaleate	0 (0)	2 (1.9)
Folic acid analogues	3 (4.1)	7 (6.5)
Pemetrexed	2 (2.7)	7 (6.5)
Several[e]	8 (11.0)	6 (5.6)
Paclitaxel	6 (8.2)	2 (1.9)
Bevacizumab	3 (4.1)	2 (1.9)

Table 11: Information on subsequent antineoplastic therapies and surgeries[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (KEYNOTE 091 study) (multipage table)

Study Drug class[b] Drug	Patients with subsequent therapy, n (%)[c] Pembrolizumab N = 506	 Placebo N = 504
PD-1/PD-L1(programmed cell death protein 1/programmed cell death ligand 1) inhibitors	8 (11.0)	34 (31.8)
Pembrolizumab	3 (4.1)	24 (22.4)
Atezolizumab	1 (1.4)	6 (5.6)
Nivolumab	2 (2.7)	3 (2.8)
Durvalumab	2 (2.7)	1 (0.9)
Platinum compounds	7 (9.6)	9 (8.4)
Carboplatin	5 (6.8)	7 (6.5)
Cisplatin	1 (1.4)	2 (1.9)
Pyrimidine analogues	1 (1.4)	4 (3.7)
Gimeracil/oteracil potassium/tegafur	0 (0)	2 (1.9)
Taxanes	6 (8.2)	4 (3.7)
Docetaxel	5 (6.8)	3 (2.8)
1st subsequent oncological surgery	36 (7.1)	50 (9.9)

a. Subsequent therapies which were administered in ≥ 2 patients in one study arm.
b. Assignment of the drugs to their drug classes according to Module 4.
c. The percentages at the level of the drug classes/drugs were calculated in-house and refer to all patients with 1st subsequent systemic therapy (intervention arm vs. control arm: n = 73 vs. n = 107).
d. Alone or in combination with radiotherapy.
e. Unclear classification of the drugs by the company.

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

The company presented data on the 1st subsequent antineoplastic therapy for the relevant subpopulation. Compared with the number of recurrences (see Section I 4.3), it is evident that a relevant proportion of patients with recurrence did not receive subsequent therapy and the proportion of checkpoint inhibitors as subsequent therapy was low. This affects the interpretability of the results for the outcome “overall survival”. See Section I 4.1 for more details.

I 3.2.9 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: pembrolizumab vs. watchful waiting

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			
KEYNOTE 091	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the KEYNOTE 091 study.

I 3.3 Transferability of the study results to the German health care context

The company stated that the results of KEYNOTE 091 study can be transferred to the German health care context due to the characteristics of the investigated patient population, the study design and the approval-compliant use of pembrolizumab. According to the company, the subgroups by region also showed no indication of deviating efficacy or safety of pembrolizumab.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 3.4 Limitations of the KEYNOTE 091 study

Tumour staging was conducted based the 7th edition of the IASLC/UICC/AJCC classification

The KEYNOTE 091 study was launched in November 2015 when the 7th edition of the IASLC/UICC/AJCC staging criteria [12] was the most recent. This classification was revised during the study period and the currently applicable 8th edition of the staging criteria came into effect on 1 January 2017 [13,14]. The company stated that the classification of tumour stage at study inclusion will continue to be based on the 7th edition for the entire duration of the study for reasons of consistency. However, there are differences between the 7th and 8th editions of the staging criteria, which may lead to a change in the tumour classification of some patients. This and the associated uncertainties are explained below.

The KEYNOTE 091 study included adult patients with pathologically confirmed stage IB (T2a ≥ 4 cm) to IIIA NSCLC, each staged according to the 7th edition. In the present therapeutic indication, however, the G-BA assumes that tumours in stage IA or IB (T < 4 cm) and ≥ IIIB (according the 8th edition) are not eligible for treatment with pembrolizumab (see Table 4).

The staging changes are no problem for patients with a tumour size > 4 cm who were assigned to stage IB according to the 7th edition. These are now classified as stage II according to the current 8th edition. They are therefore still covered by the research question of the present benefit assessment. However, it is a problem that patients with a tumour size of T3-4 and a lymph node status of N2 are assigned to stage IIIA based on the 7th edition, but to stage IIIB according to the 8th edition. They are therefore no longer covered by the research question of the present benefit assessment.

The company did not convert the staging to the currently applicable 8th edition. Overall, around 30% of patients were included as having tumour stage IIIA (see Table 9). How many of these have stage IIIB tumours according to the current 8th classification and are therefore no longer covered by the research question of this benefit assessment cannot be estimated on the basis of the available data. In this respect, however, the suitability of the KEYNOTE 091 study for the benefit assessment would only be called into question if > 67% of patients (> 20% of the relevant subpopulation) in tumour stage IIIA were assigned to stage IIIB according to the 8th edition. However, based on a publication comparing the 7th and 8th editions of the IASLC/UICC/AJCC classification and information in a benefit assessment of the drug atezolizumab (NSCLC) [15,16], it is assumed that this affects a significantly lower proportion of the patients included. The two sources cited show that around 19 to 25% of patients in tumour stage IIIA would be assigned to stage IIIB according to the 8th edition.

However, uncertainty remains regarding the proportion of patients in the presented subpopulation that are not covered by the research question of the present benefit assessment. For this reason, the certainty of conclusions of the study results is limited. Thus, based on the results of the KEYNOTE 091 study, only hints, e.g. of added benefit, can be derived in the present situation.

Further points of criticism

In the subpopulation of the KEYNOTE 091 study presented by the company, the time interval between tumour resection and the start of adjuvant platinum-based chemotherapy was > 60 days for approx. 18% of the patients. However, there is no evidence from randomized prospective comparative studies for the effectiveness of adjuvant chemotherapy, used at a time interval of > 60 days after tumour resection. The guidelines therefore recommend starting adjuvant chemotherapy within 60 days of tumour resection [9,13]. However, based on the available data, it remains unclear whether a delayed start of adjuvant chemotherapy (> 60 days) has an influence on the observed effects.

To exclude cerebral metastasis, both a MRI scan and a CT scan were accepted in the KEYNOTE 091 study. According to the guideline recommendation, however, a CT scan to exclude brain metastases should only be performed if there is a contraindication to an MRI

scan [9]. The sole examination by means of CT is not suitable to exclude patients with cerebral metastases with certainty. It is therefore possible that patients with brain metastases were included in the study who were not covered by the therapeutic indication. The company did not present information on the use of CT and MRI scans of the cranium.

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
  - Recurrence
  - Symptoms, recorded with the EORTC QLQ-C30 and the EORTC QLQ-LC13
  - Health status recorded with the EQ-5D VAS
- Health-related quality of life
  - Recorded with the EORTC QLQ-C30
- Side effects
  - Serious AEs (SAEs)
  - Severe AEs (Common-Terminology-Criteria-for-Adverse-Events[CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-mediated SAEs
  - Immune-mediated severe AEs
  - Further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	Outcomes										
	Overall survival	Recurrences[a]	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Immune-mediated SAEs[d]	Immune-mediated severe AEs[c, d]	Further specific AEs[e]
KEYNOTE 091	No[f]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Represented by the recurrence rate and disease-free survival, includes the events death, distant metastases and/or locoregional recurrence, new malignancy and not disease-free at baseline.
b. Progression events of the underlying disease are not included (PTs “neoplasm progression”, “malignant neoplasm progression” and “disease progression”).
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. The MedDRA PT collection "adverse events of special interest" ("AEOSI, Version 23.1"), defined by the company, is used.
e. The following events are considered (coded according to MedDRA): endocrine disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), hepatobiliary disorders (SOC, severe AEs), infections and infestations (SOC, severe AEs).
f. Data not interpretable; see body of text for reasons.

AE: adverse event; AEOSI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer – Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13; EQ-5D VAS: EQ-5D visual analogue scale; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Results on overall survival not interpretable due to inadequate subsequent therapies

The overall survival of patients in the present therapeutic indication is composed of a phase of DFS until recurrence and the subsequent stage of advanced and/or metastatic NSCLC.

An observed effect in the outcome “overall survival” is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [17-19]. In order for an observed effect in the outcome of overall survival to be interpreted meaningfully, adequate guideline-compliant subsequent treatment of patients after progression or recurrence of the disease is therefore necessary, especially in the adjuvant therapy situation.

The guideline recommendations for the advanced therapy stage of NSCLC are decisive for the assessment of the administered subsequent therapies in the KEYNOTE 091 study. According to the S3 Guideline on the Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer and the guideline of the German Society for Haematology and Medical Oncology, patients

with advanced or metastatic NSCLC who have no treatable mutations and no contraindication to immune checkpoint inhibitors (in the present therapeutic indication primarily PD-1/PD-L1 inhibitors) should receive systemic therapy with an immune checkpoint inhibitor or a combination of immune checkpoint inhibitor and chemotherapy in the first line [9,13]. These recommendations are based on advantages in overall survival through the use of immune checkpoint inhibitors (also in combination with chemotherapy) compared to chemotherapy [9,13]. According to these findings and the recommendations of the guidelines, it can therefore be assumed that subsequent therapy using an immune checkpoint inhibitor would have been indicated for almost all patients with recurrence, especially in the presence of distant metastases, in the comparator arm of the KEYNOTE 091 study subpopulation presented by the company.

In the KEYNOTE 091 study, subsequent therapies were allowed without restrictions after disease recurrence. Based on the available data, however, it is assumed that the subsequent systemic therapies administered are not an adequate reflection of the current standard of therapy after recurrence. This is explained below.

At the 3rd data cut-off, in the comparator arm in the subpopulation presented by the company, a total of 262 patients had an event in the outcome of recurrence, with 18 of them dying without a previous recurrence. This means that 244 patients had a potential need for subsequent therapy, although it should be noted that it is unclear from the available data which subsequent therapies would be indicated for new malignancies or if the disease was present at baseline. A total of 208 patients had locoregional recurrence and/or distant metastases. Within this patient group, 136 people had distant metastases (see also Table 15). Only 107 patients in the comparator arm underwent subsequent systemic therapy, 34 of whom received an immune checkpoint inhibitor as 1st subsequent systemic therapy (see Table 11). The company did not provide information on how many patients in the relevant subpopulation received an immune checkpoint inhibitor in the further course of their therapy. The CSR contains information on all subsequent therapies administered for the entire population of the KEYNOTE 091 study. It is clear that the immune checkpoint inhibitor proportion remains very low even in the further course of therapy. Only a maximum of 35% of patients with locoregional recurrence and/or distant metastases in the comparator arm of the overall population received an immune checkpoint inhibitor.

This is of particular importance in the present research question, the adjuvant treatment of NSCLC: Treatment with an immune checkpoint inhibitor-based therapy in advanced or metastatic disease is associated with a survival advantage. The research question to be answered is therefore whether overall survival is improved if patients who are considered disease-free receive adjuvant therapy with an immune checkpoint inhibitor, instead of immune checkpoint inhibitor-based therapy only being used after recurrence, as has been the

case up to now [20]. Thus, treatment with an immune checkpoint inhibitor is advanced in the adjuvant treatment situation also in the KEYNOTE 091 study presented by the company. However, due to the insufficient treatment with an immune checkpoint inhibitor-based therapy after recurrence in the comparator arm of the KEYNOTE 091 study, this research question cannot be answered.

It should also be noted that, according to current guidelines, testing for anaplastic lymphoma kinase (ALK) translocations and EGFR exon 18-21 mutations as molecular markers is recommended for all NSCLC patients in operable stages. For patients in advanced stages, the guideline recommendation even includes further diagnostic tests for therapy-relevant mutations (including BRAF V600 mutations, ROS1 fusions, RET fusions and NTRK1-3 fusions) [9,13].

In the KEYNOTE 091 study, the tumours were not regularly tested for EGFR and ALK mutations, which is why information on the mutation status was missing for most patients. It is also not clear from the study documents that testing for the molecular markers recommended in the guidelines should be carried out in the event of recurrence. It is therefore unclear whether patients in advanced stages were offered a suitable molecular-stratified therapy as a subsequent therapy [9,13].

Overall, the results for overall survival of the KEYNOTE 091 study cannot be interpreted. This also applies to the other planned data cut-offs for the outcome of overall survival. Irrespective of this, the 3rd data cut-off shows no statistically significant effects for the outcome "overall survival" (see I Appendix D of the full dossier assessment).

Recurrence

The recurrence outcome is a combined outcome and comprises the components death (without previous recurrence), locoregional recurrence and/or distant metastases, new malignancy and non-disease-free status at baseline. According to the study protocol, patients who were not disease-free at baseline should not have been included. Since the proportion of these patients is < 1%, there are no consequences for the benefit assessment.

The results of the operationalizations “proportion of patients with recurrence” (hereinafter referred to as “recurrence rate”) and disease-free survival are presented for the outcome of recurrence. The patients considered in the present stage of the disease are a group of patients who were treated with a curative treatment approach. The occurrence of a recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful. At the time point of the data cut-off of 24 January 2023 used for the benefit assessment, the median observation period for the outcome “recurrence” was about 35 months (see Table 10). Since the probability of recurrence is highest in the first two years after

resection [21], the observation period is considered sufficient for the evaluation of the outcome “recurrence” or “disease-free survival”.

It should also be noted that in the KEYNOTE 091 study, despite blinding, it may be recognisable to the investigator which treatment group a patient is assigned to due to the toxicity profiles of the study treatments and this could influence the assessment of the outcome “recurrence”. The European Medicines Agency (EMA) also addresses a potential bias in such situations in its guidelines [22]. However, as there is no information indicating a relevant bias, there are no consequences for the assessment.

Analyses presented on the outcomes of morbidity and health-related quality of life

According to the statistical analysis plan, analyses of the patient-reported outcomes of morbidity and health-related quality of life were planned using the constrained longitudinal data analysis (cLDA) model. Such an assessment was not presented by the company, however. In Module 4 A, the company instead presented analyses using a mixed-effects model with repeated measures (MMRM). Both methods of analysis are considered to be sufficiently similar so that no relevant differences between the results of the two analyses are assumed. The MMRM analyses are taken into account for the benefit assessment.

Responder analyses for first or permanent deterioration or improvement were not prespecified and were not presented.

Note on the immune-mediated AEs

In Module 4 A of the dossier, the company presented analyses on predefined AEs of special interest (AEOSI). Analyses are available for severe events (operationalized as CTCAE grade ≥ 3) and serious events. This operationalization with the underlying predefined collection of Preferred Terms (PTs) is considered a sufficient approximation for the immune-mediated AEs. Both severe AEs (CTCAE grade ≥ 3) and SAEs were considered. There is no analysis at the level of PTs or superordinate categories.

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: pembrolizumab vs. watchful waiting

Study	Study level	Outcomes										
		Overall survival	Recurrences[a]	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-mediated SAEs[c]	Immune-mediated severe AEs[b, c]	Further specific AEs[d]
KEYNOTE 091	L	–[e]	L	L	L	L	H[f]	H[f]	L[g]	H[f]	H[f]	H[f]

a. Represented by the recurrence rate and disease-free survival, includes the events death, distant metastases and/or locoregional recurrence, new malignancy and not disease-free at baseline.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The MedDRA PT collection "adverse events of special interest" ("AEOSI, Version 23.1"), defined by the company, is used.
d. The following events are considered (coded according to MedDRA): endocrine disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), hepatobiliary disorders (SOC, severe AEs), infections and infestations (SOC, severe AEs).
e. Data not interpretable; see Section I 4.1 for reasons.
f. Unclear proportion of incomplete observations for potentially informative reasons.
g. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be limited (see body of text).

AE: adverse event; AEOSI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer – Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13; EQ-5D VAS: EQ-5D visual analogue scale; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

No suitable data are available for the outcome of overall survival (for reasons, see Section I 4.1); therefore, the risk of bias of the results is not assessed. The outcome-specific risk of bias for the results of the outcomes of recurrence and the patient-reported outcomes on symptoms, health status and health-related quality of life, assessed using the EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D VAS, is classified as low in each case.

All results on outcomes in the adverse events category, except "discontinuation due to AEs", have a high risk of bias due to an unclear proportion of incomplete observations for potentially informative reasons, despite equal median observation durations. Since the Kaplan-Meier curves of the study arms for disease-free survival already diverge from the 6th month onwards (see Figure 1) and the company does not provide any information on the time of occurrence of AEs, it cannot be ruled out that a relevant proportion of patients were observed for AEs for

different lengths of time between the individual study arms for potentially informative reasons.

Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is reduced. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs which would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

Taking into account the uncertainty with regard to the included patient population, at most hints, for example of an added benefit, can be determined for all outcomes on the basis of the KEYNOTE 091 study (see Section I 3.4 for explanation).

I 4.3 Results

Table 15, Table 16, and Table 17 summarize the results comparing pembrolizumab with watchful waiting for adjuvant treatment of patients with NSCLC at high risk of recurrence after complete resection and platinum-based chemotherapy. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. For assessing clinical relevance, an SMD is used, provided the mean difference (MD) is statistically significant.

The Kaplan-Meier curves are presented in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment. A list of the occurred immune-mediated AEs, immune-mediated SAEs and severe immune-mediated AEs (CTCAE grade ≥ 3) by SOC, PT or grouped by category is not available.

Table 15: Results (mortality, morbidity, time analysis) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. placebo HR [95% CI]; p-value[a]
KEYNOTE 091					
Mortality					
Overall survival	No suitable data[b]				
Morbidity					
Recurrence					
Recurrence rate	506	– 225 (44.5)	504	– 262 (52.0)	RR[c] 0.86 [0.75; 0.97]; 0.018
Death	506	– 30 (5.9)	504	– 18 (3.6)	–
Distant metastases	506	– 74 (14.6)	504	– 96 (19.0)	–
Locoregional recurrent	506	– 51 (10.1)	504	– 72 (14.3)	–
Locoregional recurrence and distant metastases	506	– 31 (6.1)	504	– 40 (7.9)	–
New malignancy	506	– 34 (6.7)	504	– 32 (6.3)	–
Not disease-free at baseline	506	– 5 (1.0)	504	– 4 (0.8)	–
Disease-free survival[d]	506	53.8 [46.2; 70.4] 225 (44.5)	504	40.5 [32.9; 47.4] 262 (52.0)	0.76 [0.64; 0.91]; 0.003

a. Cox proportional hazards model, stratified by tumour stage (IB vs. II vs. IIIA), PD-L1 status (< 1% vs. 1–49% vs. ≥ 50%), region (Western Europe vs. Eastern Europe vs. rest of the world vs. Asia), histology (squamous vs. non-squamous) and smoking status (non-smoker vs. former/current smoker).
b. See Section I 4.1 for reasons.
c. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [23]).
d. Operationalized as time from the day of randomization to the first occurrence of an event, for individual components see recurrence rate.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Outcome category	Pembrolizumab			Placebo			Pembrolizumab vs. placebo
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Change in the course of the study mean[b] (SE)**	**N[a]**	**Values at baseline mean (SD)**	**Change in the course of the study mean[b] (SE)**	**MD [95% CI][b,]**
KEYNOTE 091							
Morbidity							
Symptoms (EORTC QLQ-C30[c])							
Fatigue	472	30.0 (22.6)	-3.7 (1.1)	492	30.5 (22.1)	-5.0 (1.1)	1.21 [-0.69; 3.12]
Nausea and vomiting	472	6.0 (14.1)	-2.0 (0.5)	492	6.7 (14.8)	-2.7 (0.5)	0.68 [-0.25; 1.60]
Pain	473	15.6 (20.2)	0.5 (1.1)	493	16.2 (20.5)	0.4 (1.2)	0.09 [-1.93; 2.10]
Dyspnoea	466	29.3 (26.6)	-5.0 (1.2)	490	32.0 (28.2)	-6.1 (1.2)	1.05 [-1.11; 3.21]
Insomnia	471	19.5 (26.2)	-0.0 (1.2)	492	20.1 (27.1)	0.3 (1.3)	-0.29 [-2.48; 1.90]
Appetite loss	469	10.7 (19.5)	-2.3 (1.0)	489	14.1 (23.1)	-4.5 (1.0)	2.23 [0.45; 4.00] SMD: 0.11 [0.02; 0.20]
Constipation	473	13.7 (24.3)	-2.6 (1.0)	492	12.0 (22.0)	-3.6 (1.0)	0.98 [-0.76; 2.72]
Diarrhoea	468	6.4 (15.8)	2.3 (0.8)	490	5.9 (15.2)	1.1 (0.9)	1.25 [-0.25; 2.75]
Symptoms (EORTC QLQ-LC13[c])							
Dyspnoea	465	24.0 (19.0)	-1.5 (0.9)	484	24.9 (20.1)	-2.2 (0.9)	0.75 [-0.89; 2.39]
Cough	471	26.3 (23.9)	-3.6 (1.1)	488	26.9 (23.5)	-3.7 (1.1)	0.16 [-1.79; 2.11]
Haemoptysis	470	0.3 (3.8)	0.2 (0.2)	488	0.6 (5.8)	0.1 (0.2)	0.09 [-0.29; 0.47]
Sore mouth	470	4.2 (13.9)	0.3 (0.6)	488	5.1 (15.1)	-0.5 (0.7)	0.76 [-0.38; 1.90]
Dysphagia	470	4.4 (13.6)	0.3 (0.6)	487	3.7 (12.3)	0.1 (0.6)	0.21 [-0.80; 1.22]
Peripheral neuropathy	469	14.7 (23.6)	3.9 (1.3)	484	16.9 (27.2)	3.1 (1.4)	0.84 [-1.56; 3.25]
Alopecia	466	26.4 (33.0)	-19.9 (0.8)	484	26.5 (33.0)	-20.6 (0.8)	0.65 [-0.74; 2.05]
Pain (chest)	467	13.6 (20.9)	-2.9 (0.9)	485	13.8 (22.3)	-2.6 (0.9)	-0.21 [-1.85; 1.42]
Pain (arm/shoulder)	466	10.3 (19.9)	4.0 (1.1)	486	12.3 (21.2)	2.9 (1.1)	1.04 [-0.88; 2.95]
Pain (other)	450	14.0 (22.6)	2.0 (1.2)	466	16.8 (26.3)	1.3 (1.3)	0.69 [-1.54; 2.92]
Health status (EQ-5D VAS)[d]	457	74.6 (17.0)	0.5 (0.9)	472	72.8 (16.4)	1.3 (0.9)	-0.82 [-2.41; 0.76]

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Outcome category	Pembrolizumab			Placebo			Pembrolizumab vs. placebo
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Change in the course of the study mean[b] (SE)**	**N[a]**	**Values at baseline mean (SD)**	**Change in the course of the study mean[b] (SE)**	**MD [95% CI][b,]**
Health-related quality of life							
EORTC-QLQ-C30[d]							
Global health status	467	68.9 (18.9)	1.8 (0.9)	492	66.0 (19.8)	3.3 (1.0)	-1.57 [-3.25; 0.11]
Physical functioning	472	80.6 (16.3)	1.0 (0.8)	494	79.7 (16.7)	0.8 (0.9)	0.22 [-1.27; 1.71]
Role functioning	471	78.2 (25.1)	1.7 (1.2)	493	77.3 (25.0)	3.4 (1.2)	-1.66 [-3.80; 0.47]
Emotional functioning	471	82.8 (19.7)	2.4 (0.9)	491	81.7 (20.6)	2.5 (0.9)	-0.03 [-1.69; 1.63]
Cognitive functioning	471	88.9 (17.2)	-1.3 (0.8)	492	87.1 (18.3)	-1.1 (0.9)	-0.14 [-1.65; 1.38]
Social functioning	471	82.1 (23.7)	4.3 (1.1)	492	81.5 (22.9)	6.4 (1.2)	-2.07 [-4.14; -0.01] SMD: −0.10 [−0.20; 0.00]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. MMRM of change at baseline adjusted for baseline value, tumour stage (IB vs. II vs. IIIA), PD-L1 status (< 1% vs. 1–49% vs. ≥ 50%), region (Western Europe vs. Eastern Europe vs. rest of the world vs. Asia), histology (squamous vs. non-squamous) and smoking status (non-smoker vs. former/current smoker). The survey dates are continuously included in the model. The company did not provide the p-values required for the MDs according to the dossier template .
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparator) indicate an advantage for the intervention (scale range of 0 to 100).
d. Higher (increasing) values indicate better health status or better health-related quality of life; positive effects (intervention minus comparator) indicate an advantage for the intervention (scale range 0 to 100).

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13; EQ-5D VAS: EQ-5D visual analogue scale; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patient; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

Table 17: Results (side effects) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome category Outcome	Pembrolizumab		Placebo		Pembrolizumab vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
KEYNOTE 091					
Side effects					
AEs[b] (supplementary information)	496	475 (95.8)	499	454 (91.0)	–
SAEs[b]	496	127 (25.6)	499	76 (15.2)	1.68 [1.30; 2.17]; < 0.001
Severe AEs[b, c]	496	170 (34.3)	499	128 (25.7)	1.34 [1.10; 1.62]; 0.003
Discontinuation due to AEs[b]	496	103 (20.8)	499	29 (5.8)	3.57 [2.41; 5.29]; < 0.001
Immune-mediated AEs[d] (presented as supplementary information)	496	ND	499	ND	–
Immune-mediated SAEs[d]	496	44 (8.9)	499	8 (1.6)	5.53 [2.63; 11.63]; < 0.001
Immune-mediated severe AEs[c, d]	496	42 (8.5)	499	10 (2.0)	4.23 [2.14; 8.33]; < 0.001
Endocrine disorders (SOC, SAEs)	496	10 (2.0)	499	0 (0)	21.13 [1.24; 359.55]; 0.002
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	496	27 (5.4)	499	11 (2.2)	2.47 [1.24; 4.92]; 0.008
Hepatobiliary disorders (SOC, severe AEs[c])	496	14 (2.8)	499	1 (0.2)	14.08 [1.86; 106.70]; < 0.001
Infections and infestations (SOC, severe AEs[c])	496	34 (6.9)	499	19 (3.8)	1.80 [1.04; 3.11]; 0.033

a. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [23]).
b. Progression events of the underlying disease are not included (PTs “neoplasm progression”, “malignant neoplasm progression” and “disease progression”).
c. Operationalized as CTCAE grade ≥ 3.
d. The MedDRA PT collection "adverse events of special interest" ("AEOSI, Version 23.1"), defined by the company, is used.

AE: adverse event; AEOSI: adverse event of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

As described in Section I 3.4, there are uncertainties regarding the patient population that affect the certainty of results. On the basis of the available information, no more than hints, e.g. of an added benefit, can therefore be determined for all outcomes.

Mortality

No suitable data are available for the outcome of overall survival (see Section I 4.1 for reasons). There is no hint of an added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and disease-free survival [DFS]), a statistically significant difference between the treatment arm in favour of pembrolizumab in comparison with watchful waiting is shown. This results in a hint of added benefit of pembrolizumab in comparison with watchful waiting for this outcome.

Symptoms

Data on the symptoms outcomes were recorded using the instruments EORTC QLQ-C30 and EORTC QLQ-LC13.

EORTC QLQ-C30

Appetite loss

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of appetite loss. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. There is no hint of an added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation, and diarrhoea

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation, and diarrhoea. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

EORTC QLQ-LC13

Dyspnoea, cough, haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain (chest), pain (arm/shoulder), pain (other)

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for all outcomes assessed with the EORTC QLQ-LC13. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

On the basis of the mean difference, no statistically significant difference between treatment arms was found for the outcome of health status measured with the EQ-5D VAS. There is no hint of an added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Social functioning

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of social functioning. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with watchful waiting is shown between the treatment arms for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. In each case, there was a hint of greater harm from pembrolizumab in comparison with watchful waiting.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab compared with placebo between the treatment arms was shown for each of the outcomes "immune-mediated SAEs” and "immune-mediated severe AEs (CTCAE grade ≥ 3)”. In each case, there was a hint of greater harm from pembrolizumab in comparison with watchful waiting.

Endocrine disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs), hepatobiliary disorders (severe AEs), infections and infestations (severe AEs)

A statistically significant difference to the disadvantage of pembrolizumab compared with placebo was shown between the treatment arms for each of the following outcomes: endocrine disorders (SAEs) respiratory, thoracic and mediastinal disorders (SAEs), hepatobiliary disorders (severe AEs), and infections and infestations (severe AEs). In each case, there was a hint of greater harm from pembrolizumab in comparison with watchful waiting.

I 4.4 Subgroups and other effect modifiers

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

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)

The subgroup characteristics selected in the present benefit assessment had been defined a priori, but only for the outcomes of disease-free survival and overall survival.

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.

For the outcomes “immune-mediated SAEs” and “immune-mediated severe AEs”, the company did not present subgroup analyses in the dossier.

Applying the methods described above, there were no effect modifications for the characteristics of age and sex.

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 estimated from the results presented in Section I 4.3 (see Table 18).

Determination of the outcome category for outcomes on symptoms and side effects

Discontinuation due to AEs

The outcome of discontinuation due to AEs was allocated to the outcome category of non-serious/non-severe side effects because no information was available on the severity of the AEs which led to discontinuation of therapy.

Table 18: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	No suitable data[c]	Lesser/added benefit not proven
Morbidity		
Recurrence[d]		Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: “minor”
Recurrence rate	44.5% vs. 52.0% RR: 0.86 [0.75; 0.97]; p = 0.018 Probability: “hint”	
Disease-free survival	53.8 vs. 40.5 months HR: 0.76 [0.64; 0.91]; p = 0.003 Probability: “hint”	
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	-3.7 vs. -5.0 MD: 1.21 [-0.69; 3.12]; p = ND	Lesser/added benefit not proven
Nausea and vomiting	-2.0 vs. -2.7 MD: 0.68 [-0.25; 1.60]; p = ND	Lesser/added benefit not proven
Pain	0.5 vs. 0.4 MD: 0.09 [-1.93; 2.10]; p = ND	Lesser/added benefit not proven
Dyspnoea	-5.0 vs. -6.1 MD: 1.05 [-1.11; 3.21]; p = ND	Lesser/added benefit not proven
Insomnia	-0.0 vs. 0.3 MD: -0.29 [-2.48; 1.90]; p = ND	Lesser/added benefit not proven
Appetite loss	-2.3 vs. -4.5 MD: 2.23 [0.45; 4.00]; p = ND SMD: 0.11 [0.02; 0.20][e]	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Constipation	-2.6 vs. -3.6 MD: 0.98 [-0.76; 2.72]; p = ND	Lesser/added benefit not proven
Diarrhoea	2.3 vs. 1.1 MD: 1.25 [-0.25; 2.75]; p = ND	Lesser/added benefit not proven
Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-LC13])		
Dyspnoea	-1.5 vs. -2.2 MD: 0.75 [-0.89; 2.39]; p = ND	Lesser/added benefit not proven
Cough	-3.6 vs. -3.7 MD: 0.16 [-1.79; 2.11]; p = ND	Lesser/added benefit not proven
Haemoptysis	0.2 vs. 0.1 MD: 0.09 [-0.29; 0.47]; p = ND	Lesser/added benefit not proven
Sore mouth	0.3 vs. -0.5 MD: 0.76 [-0.38; 1.90]; p = ND	Lesser/added benefit not proven
Dysphagia	0.3 vs. 0.1 MD: 0.21 [-0.80; 1.22]; p = ND	Lesser/added benefit not proven
Peripheral neuropathy	3.9 vs. 3.1 MD: 0.84 [-1.56; 3.25]; p = ND	Lesser/added benefit not proven
Alopecia	-19.9 vs. -20.6 MD: 0.65 [-0.74; 2.05]; p = ND	Lesser/added benefit not proven
Pain (chest)	-2.9 vs. -2.6 MD: -0.21 [-1.85; 1.42]; p = ND	Lesser/added benefit not proven
Pain (arm/shoulder)	4.0 vs. 2.9 MD: 1.04 [-0.88; 2.95]; p = ND	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Pain (other)	2.0 vs. 1.3 MD: 0.69 [-1.54; 2.92]; p = ND	Lesser/added benefit not proven
Health status		
EQ-5D VAS	0.5 vs. 1.3 MD: -0.82 [-2.41; 0.76]; p = ND	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30		
Global health status	1.8 vs. 3.3 MD: -1.57 [-3.25; 0.11]; p = ND	Lesser/added benefit not proven
Physical functioning	1.0 vs. 0.8 MD: 0.22 [-1.27; 1.71]; p = ND	Lesser/added benefit not proven
Role functioning	1.7 vs. 3.4 MD: -1.66 [-3.80; 0.47]; p = ND	Lesser/added benefit not proven
Emotional functioning	2.4 vs. 2.5 MD: -0.03 [-1.69; 1.63]; p = ND	Lesser/added benefit not proven
Cognitive functioning	-1.3 vs. -1.1 MD: -0.14 [-1.65; 1.38]; p = ND	Lesser/added benefit not proven
Social functioning	4.3 vs. 6.4 MD: -2.07 [-4.14; -0.01]; p = ND SMD: -0.10 [-0.20; -0.00][e]	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	25.6% vs. 15.2% RR: 1.68 [1.30; 2.17]; RR: 0.60 [0.46; 0.77][f]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: "considerable"
Severe AEs	34.3% vs. 25.7% RR: 1.34 [1.10; 1.62]; RR: 0.75 [0.62; 0.91][f]; p = 0.003 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Discontinuation due to AEs	20.8% vs. 5.8% RR: 3.57 [2.41; 5.29]; RR: 0.28 [0.19; 0.41][f]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: "considerable"
Immune-mediated SAEs	8.9% vs. 1.6% RR: 5.53 [2.63; 11.63]; RR: 0.18 [0.09; 0.38][f]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Immune-mediated severe AEs	8.5% vs. 2.0% RR: 4.23 [2.14; 8.33]; RR: 0.24 [0.12; 0.47][f]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_o < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Endocrine disorders (SAEs)	2.0% vs. 0% RR: 21.13 [1.24; 359.55]; RR: 0.05 [0.003; 0.81][f]; p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SAEs)	5.4% vs. 2.2% RR: 2.47 [1.24; 4.92]; RR: 0.40 [0.20; 0.81][f]; p = 0.008 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: "considerable"

Table 18: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Hepatobiliary disorders (severe AEs)	2.8% vs. 0.2% RR: 14.08 [1.86; 106.70]; RR: 0.07 [0.01; 0.54][f]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk < 5% Greater harm; extent: "considerable"
Infections and infestations (severe AEs)	6.9% vs. 3.8% RR: 1.80 [1.04; 3.11]; RR: 0.56 [0.32; 0.96][f]; p = 0.033 Probability: "hint"	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Greater harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
c. See Section I 4.1 for reasons.
d. The outcome "recurrence" was followed up until the occurrence of recurrence, death, withdrawal of informed consent or end of study (whichever occurred first) and for a maximum of 10 years. Since the final analysis of overall survival should also take place at the latest 10 years after the randomization of the 1st patient, the outcome here is considered to be observed approximately over the entire study duration.
e. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13; EQ-5D VAS: EQ-5D visual analogue scale; CI_u: upper limit of the confidence interval; CI_l: lower limit of confidence interval; HR: hazard ratio; MD: mean difference; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of pembrolizumab in comparison with watchful waiting

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Morbidity Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: “minor”	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "considerable" ▫ Including: - Immune-mediated SAEs: hint of greater harm – extent: major - Endocrine disorders: hint of greater harm – extent: “considerable” - Respiratory, thoracic, and mediastinal disorders: hint of greater harm – extent: “considerable” ▪ Severe AEs: hint of greater harm – extent: “minor” ▫ Including: - Severe immune-mediated AEs: hint of greater harm – extent major - Hepatobiliary disorders: hint of greater harm – extent: “considerable” - infections and infestations: hint of greater harm – extent: “minor” Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm - extent: “considerable”
There are no suitable data on the outcome of overall survival.	
AE: adverse event; SAE: serious adverse event	

Overall, there are both positive and negative effects for pembrolizumab in comparison with watchful waiting.

On the side of positive effects, there is a hint of a minor added benefit only for the outcome of recurrence.

On the other hand, there are hints of greater harm with different, in some cases major extent for numerous outcomes in the side effects category. Even taking into account the fact that the

treatment is limited to 1 year, these negative effects of major extent significantly outweigh the minor positive effect.

In summary, for patients with NSCLC at high risk of recurrence following complete resection and platinum-based chemotherapy for adjuvant treatment, there is a hint of lesser benefit of pembrolizumab in comparison with the ACT watchful waiting.

Table 20 summarizes the results of the assessment of the added benefit of pembrolizumab in comparison with the ACT.

Table 20: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment	Watchful waiting	Hint of lesser benefit

a. Presented is the ACT specified by the G-BA. The ACT was determined for stages IB to IIIA on the basis of the currently applicable TNM tumour classification in the 8th edition of the UICC. The G-BA assumes that tumours in stage IA or IB (T < 4 cm) and ≥ IIIB (according to classification 8) are not eligible for treatment with pembrolizumab.

ACT: appropriate comparator therapy; G-BA: Joint Federal Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The assessment described above deviates from that of the company, which derived an indication of minor added benefit.

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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