IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pembrolizumab (non-small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pembrolizumab (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 November 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EQ-5D	European Quality of Life-5 Dimensions
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TPS	Tumour Proportion Score
VAS	visual analogue scale

2 Benefit assessment

2.1 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 August 2016.

Research question

The aim of this report was to assess the added benefit of pembrolizumab compared with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express programmed cell death ligand 1 (PD-L1) and who have received at least one prior chemotherapy regimen. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab.

For the benefit assessment of pembrolizumab, the research questions presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication		ACT[a]
1	Adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen; patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab	Patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated	**Docetaxel** or pemetrexed or nivolumab (pemetrexed: except in mainly squamous histology; nivolumab: only in squamous histology)
2		Patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated[b]	BSC[c]

a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: This applies especially to patients for whom cytotoxic chemotherapy is not an option due to their reduced general condition – for instance, these may be patients with an ECOG PS 4, 3 or possibly 2.
c: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The company followed the specification of the ACT. It chose docetaxel for research question 1.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results for research question 1: patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated

Study pool and study characteristics

The study KEYNOTE 010 was included in the benefit assessment for research question 1. The study was a randomized, open-label, controlled study. The study had 3 treatment arms: In 2 arms, the patients were treated with different dosages of pembrolizumab, and in a third arm, patients were treated with docetaxel. The study arm with pembrolizumab at a dosage of 2 mg/kg body weight (hereinafter referred to as "pembrolizumab arm") and the study arm with docetaxel were relevant for the present benefit assessment.

The study included adult patients with histologically or cytologically confirmed NSCLC whose tumours express PD-L1. Patients had to have confirmed radiological progression after platinum-based chemotherapy and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with EGFR mutation additionally had to have confirmed radiological progression after treatment with erlotinib, gefitinib or afatinib; patients with ALK translocation had to have confirmed radiological progression after treatment with crizotinib. The population investigated in the study corresponded to the therapeutic indication of pembrolizumab in the present research question 1.

In the study, 345 patients were randomized to the pembrolizumab arm and 343 patients to the docetaxel arm (688 patients in total). Patients in the pembrolizumab arm received 2 mg/kg body weight pembrolizumab as 30-minute infusion every 3 weeks. The administration of pembrolizumab concurred with the requirements of the Summary of Product Characteristics (SPC). Patients in the docetaxel arm received 75 mg/m^2 body surface area infused over 1 hour every 3 weeks. Docetaxel was administered without relevant deviation from the approval.

Primary outcomes of the study were overall survival and progression-free survival. Patient-relevant secondary outcomes were symptoms, health status, health-related quality of life and adverse events (AEs).

The patients were treated until disease progression, unacceptable side effects, or study discontinuation due to decision by the physician or the patient. Following discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. Switching from the comparator to the intervention group was not allowed.

Risk of bias

The risk of bias at study level was rated as low for the KEYNOTE 010 study.

The risk of bias was rated as low for the outcome "overall survival" and as high for the outcomes "symptoms", "health-related quality of life" and for all AE outcomes. There were no usable data for the outcome "health status".

Results

Mortality

- Overall survival

A statistically significant difference in favour of pembrolizumab versus docetaxel was shown for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab in comparison with docetaxel.

Morbidity

- Symptoms

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13). The time to deterioration was considered in each case. Hereinafter, at first the outcomes of symptoms for which statistically significant group differences at the level of the total population or at the level of subgroups were shown are described.

  - Fatigue

    In the total population, there was no statistically significant difference between pembrolizumab and docetaxel for the outcome "fatigue". There was proof of an effect modification by the characteristic "EGFR mutation status", however. No statistically significant differences between the treatment groups or more than marginal effects were shown for any of the subgroups, however. Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel; an added benefit for the outcome "fatigue" is therefore not proven.

  - Alopecia, sore mouth, peripheral neuropathy

    Statistically significant differences in favour of pembrolizumab versus docetaxel were shown for each of the outcomes "alopecia", "sore mouth" and "peripheral neuropathy". This resulted in a hint of an added benefit of pembrolizumab in comparison with docetaxel for each of the 3 outcomes.

  - Further outcomes on symptoms

    No statistically significant differences between the treatment groups were shown for any further outcomes on symptoms. Hence there was no hint of an added benefit of

pembrolizumab in comparison with docetaxel for any further outcomes; an added benefit is therefore not proven.

- Health status

The dossier contained no usable data for the outcome "health status". Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC-QLQ-C30. The time to deterioration was considered.

No statistically significant differences between the treatment groups were shown for any of the scales mentioned above. Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel for health-related quality of life; an added benefit is therefore not proven.

Side effects

- Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "serious adverse events (SAEs)". Hence there was no hint of greater or lesser harm from pembrolizumab in comparison with docetaxel; greater or lesser harm is therefore not proven.

- Severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

Statistically significant differences in favour of pembrolizumab versus docetaxel were shown for each of the outcomes "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3") and "discontinuation due to AEs". This resulted in a hint of lesser harm of pembrolizumab in comparison with docetaxel for both outcomes.

- Specific adverse events
  - Immune-related adverse events, serious adverse events, severe adverse events (CTCAE grade ≥ 3)

    Statistically significant differences to the disadvantage of pembrolizumab versus docetaxel were shown for each of the outcomes "immune-related AEs", "immune-related SAEs" and "immune-related severe AEs" (CTCAE grade ≥ 3). This resulted in a hint of greater harm of pembrolizumab in comparison with docetaxel for each of the 3 outcomes.

  - Further specific adverse events

    Statistically significant differences in favour of pembrolizumab versus docetaxel were shown for each of the following specific AE outcomes selected: gastrointestinal

disorders, general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, investigations (CTCAE grade ≥ 3), infections and infestations (CTCAE grade ≥ 3) and blood and lymphatic system disorders (CTCAE grade ≥ 3). This resulted in a hint of lesser harm of pembrolizumab in comparison with docetaxel for each of these outcomes.

Results for research question 2: patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated

There were no data for the assessment of the added benefit in adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen (patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab) for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated. Hence there was no hint of an added benefit of pembrolizumab in comparison with the ACT best supportive care (BSC). An added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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:

Research question 1: patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated

Overall, there are positive and negative effects. On the side of positive effects, there was an indication of considerable added benefit for the outcome "overall survival" and a hint of considerable added benefit for the outcome "symptoms". For the outcomes "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs", there was a hint of lesser harm with the extent "major". For specific AEs, there was a hint of lesser harm with the extent "major" and "considerable". On the side of negative effects, the positive effects were accompanied by hints of greater harm with the extent "considerable" for specific AEs (immune-related AEs).

Overall, the negative effects in immune-related AEs did not raise doubts about the positive effects.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

In summary, there is an indication of considerable added benefit of pembrolizumab versus the ACT docetaxel for patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen (patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab) for whom treatment with docetaxel, pemetrexed or nivolumab is indicated.

Research question 2: patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated

An added benefit of pembrolizumab is not proven for patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen (patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab) for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated.

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

Table 3: Pembrolizumab – extent and probability of added benefit

Therapeutic indication		**ACT**[a]	**Extent and probability of added benefit**
Adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen; patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab	Patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated	**Docetaxel** or pemetrexed or nivolumab (pemetrexed: except in mainly squamous histology; nivolumab: only in squamous histology)	Indication of considerable added benefit
	Patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated[b]	BSC[c]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: This applies especially to patients for whom cytotoxic chemotherapy is not an option due to their reduced general condition – for instance, these may be patients with an ECOG PS 4, 3 or possibly 2.
c: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

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

2.2 Research question

The aim of this report was to assess the added benefit of pembrolizumab compared with the ACT in adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab.

For the benefit assessment of pembrolizumab, the research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab

Research question	**Therapeutic indication**		**ACT**[a]
1	Adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen; patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab	Patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated	**Docetaxel** or pemetrexed or nivolumab (pemetrexed: except in mainly squamous histology; nivolumab: only in squamous histology)
2		Patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated[b]	BSC[c]

a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: This applies especially to patients for whom cytotoxic chemotherapy is not an option due to their reduced general condition – for instance, these may be patients with an ECOG PS 4, 3 or possibly 2.
c: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The company followed the specification of the ACT. For research question 1, it chose docetaxel from the options presented in Table 4.

For research question 1 (patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated), patients with an ECOG PS of 0, 1 and possibly 2 were considered relevant. For research question 2 (patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated), patients with an ECOG PS of 4, 3 and possibly 2 were considered relevant. This concurs with the approach of the company, which followed the G-BA's recommendations.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the inclusion criterion of the company.

2.3 Research question 1: patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated

2.3.1 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: 27 July 2016)
- bibliographical literature search on pembrolizumab (last search on 23 June 2016)
- search in trial registries for studies on pembrolizumab (last search on 20 June 2016)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 24 August 2016)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
KEYNOTE 010	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of pembrolizumab in comparison with docetaxel consisted of the KEYNOTE 010 study and concurred with that of the company.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Study design

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. docetaxel

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 010	RCT, open-label, parallel	Adult patients (≥ 18 years), with histologically or cytologically confirmed NSCLC, at least one measurable lesion as per RECIST criteria, PD-L1-expressing tumours, confirmed radiological progression after platinum-based chemotherapy[b, c] and ECOG PS ≤ 1	Pembrolizumab 2 mg/kg BW (N = 345) pembrolizumab 10 mg/kg BW (N = 346)[d] docetaxel (N = 343)	▪ Screening: ≤ 42 days prior to the start of treatment ▪ Treatment: until progression[e], unacceptable side effects, study discontinuation due to decision by the physician or the patient ▫ only in the pembrolizumab arm: until reaching complete response[f], 2 years of continuous treatment[g] ▫ only in the docetaxel arm: reaching the maximum number of allowed cycles[h] ▪ Follow-up: outcome-specific, at most until death (for the outcome "overall survival")	198 centres in 24 countries: Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, Lithuania, Netherlands, Portugal, Russia, Spain, South Africa, Taiwan, United Kingdom, United States 8/2013–9/2015	Primary: overall survival, PFS Secondary: symptoms, health status, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab vs. docetaxel (continued)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: At least 2 cycles of a platinum-based chemotherapy for tumour stage IIIB/IV or recurrent disease.
c: Patients with EGFR mutation additionally had to have confirmed radiological progression after treatment with a tyrosine kinase inhibitor (erlotinib, gefitinib or afatinib). Patients with ALK translocation additionally had to have confirmed radiological progression after treatment with crizotinib.
d: The arm is not relevant for the assessment and is not shown in the next tables.
e: After 9 weeks at the earliest time point, in case of unconfirmed progression and clinical stability, treatment could be temporarily discontinued until progression was confirmed.
f: Patients in the pembrolizumab arm were allowed to temporarily discontinue treatment after confirmed complete response (according to irRC), at least 6 months of treatment and at least 2 treatment cycles after initial complete response (or in case of partial response or stable disease after 35 treatment cycles) and restart treatment with pembrolizumab after subsequent confirmed progression ("second course phase"). Based on the study documents it can be assumed that no patient had confirmed complete response and no patient reached the "second course phase".
g: No patient had uninterrupted treatment for 2 years until the final data cut-off.
h: According to the approval of the respective local regulatory authorities. According to the SPC of docetaxel, treatment duration of docetaxel is not limited in Germany [3]. The maximum number of allowed cycles was achieved by 4.4% of the randomized patients in the docetaxel arm.

AE: adverse event; ALK: anaplastic lymphoma kinase; BW: body weight; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; irRC: immune-related response criteria; 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; RECIST: Response Evaluation Criteria in Solid Tumours; vs.: versus

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

Study	Intervention	Comparison
KEYNOTE 010	Pembrolizumab 2 mg/kg BW IV (infusion administered over 30 minutes)[a], every 3 weeks	Docetaxel 75 mg/m^2 BSA IV (as infusion administered over 1 hour), every 3 weeks Premedication: oral or injectable steroids as per approval or "standard practice". Additional premedications administered as per "standard practice"[b].
	Discontinuation of the dose and prolongation of the interval by one week due to AEs allowed (following a defined scheme)	Dose adjustments according to approval
	Pretreatment and concomitant treatment ***Non-permitted pretreatment:*** ▪ docetaxel to treat NSCLC ▪ pretreatment with drugs targeting T-cell co-stimulation including ipilimumab, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibodies ***Pretreatment:*** ▪ at least 2 cycles of a platinum-based chemotherapy for tumour stage IIIB/IV or recurrent disease ▪ patients with EGFR mutation: tyrosine kinase inhibitor (erlotinib, gefitinib or afatinib) ▪ patients with ALK translocation: crizotinib ***Non-permitted concomitant treatment:*** ▪ other concomitant antineoplastic chemotherapy, immunotherapy or radiotherapy ▪ corticosteroids, except for the treatment of AEs or in the framework of the premedication in the docetaxel arm ▪ strong CYP3A4 inhibitors ***Concomitant treatment:*** ▪ drugs necessary for the patient's wellbeing	

a: Due to the variability of the infusion pumps, a time window of −5 to +10 minutes was allowed.
b: "Standard practice" and further premedications were not further described.
AE: adverse event; ALK: anaplastic lymphoma kinase; BW: body weight; BSA: body surface area; CD: cluster of differentiation; CYP3A4: cytochrome P450 3A4; CTLA: cytotoxic T-lymphocyte-associated antigen; EGFR: epidermal growth factor receptor; IV: intravenous; NSCLC: non-small cell lung cancer; PD: programmed cell death protein; PD-L: programmed cell death ligand; RCT: randomized controlled trial; vs.: versus

The KEYNOTE 010 study was a randomized, open-label, controlled study. The study had 3 treatment arms: In 2 arms, the patients were treated with different dosages of pembrolizumab, and in a third arm, patients were treated with docetaxel. The study arm with pembrolizumab at a dosage of 2 mg/kg body weight (hereinafter referred to as "pembrolizumab arm") and the study arm with docetaxel were relevant for the present benefit assessment.

The study included adult patients with histologically or cytologically confirmed NSCLC whose tumours express PD-L1. In addition, the patients had to have confirmed radiological

progression after platinum-based chemotherapy and good general condition (corresponding to ECOG PS 0 or 1). Patients with EGFR mutation additionally had to have confirmed radiological progression after treatment with erlotinib, gefitinib or afatinib; patients with ALK translocation had to have confirmed radiological progression after treatment with crizotinib.

The population investigated in the study corresponded to the therapeutic indication of pembrolizumab in the present research question (patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated).

Randomization was stratified by PD-L1 expression (strongly positive [Tumour Proportion Score, TPS, ≥ 50%], weakly positive [TPS 1% to < 50%]), geographical region (East Asia, not East Asia) and ECOG PS (0, 1). A total of 688 patients were randomly assigned to the 2 study arms relevant for the benefit assessment, 345 patients to the pembrolizumab arm and 343 patients to the docetaxel arm.

Patients in the pembrolizumab arm received 2 mg/kg body weight pembrolizumab as 30-minute infusion every 3 weeks. The administration of pembrolizumab concurred with the requirements of the SPC [4]. Patients in the docetaxel arm received 75 mg/m^2 body surface area infused over 1 hour every 3 weeks. Oral or injectable steroids and additional premedication were administered “as per approval” or “standard practice”. Docetaxel was administered without relevant deviation from the approval [3]. Prior and concomitant treatments were also administered in accordance with the approvals in both study arms.

Primary outcomes of the study were overall survival and progression-free survival. Patient-relevant secondary outcomes were symptoms, health status, health-related quality of life and AEs.

The patients were treated until disease progression, unacceptable side effects, or study discontinuation due to decision by the physician or the patient.

Following discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. There was no limitation regarding subsequent therapy. Switching from the comparator to the intervention group was not allowed. The proportion of patients with subsequent therapy was 40.1% in the pembrolizumab arm and 44.0% in the docetaxel arm.

Planned duration of follow-up

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

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

Study **Outcome category** **Outcome**	**Planned follow-up**
KEYNOTE 010	
Mortality	
Overall survival	After discontinuation of the study medication (except due to progression): month 3 and 6 and subsequently every 9 weeks until progression After progression or initiation of a new antineoplastic treatment: every 2 months until death, at most 2 years
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)	At treatment weeks 0, 3, 6, 12, 24 and 36, at discontinuation of the study medication and 30 days after the last dose of the study medication
Health status (EQ-5D)	At treatment weeks 0, 3, 6, 12, 24 and 36, at discontinuation of the study medication and 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	At treatment weeks 0, 3, 6, 12, 24 and 36, at discontinuation of the study medication and 30 days after the last dose of the study medication
Side effects	AEs: until 30 days after the last dose of the study medication SAEs: until 90 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first) Patients with AE CTCAE grade > 1 were to be followed-up until the AE was resolved to CTCAE grade 0–1 or until initiation of a new antineoplastic treatment (whichever occurred first)

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The planned duration of follow-up of the patients for the outcome “overall survival” was conducted until death, but no longer than 2 years.

The planned duration of follow-up for the outcomes “symptoms”, “health status”, “health-related quality of life” and “AEs” was conducted until 30 days after the last dose of the study medication. For the outcome “SAEs”, the patients were followed-up until 90 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first).

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab vs. docetaxel

Study Characteristics Category	**Pembrolizumab**	**Docetaxel**
KEYNOTE 010	N[a] = 344	N = 343
Age [years], mean (SD)	62 (10)	62 (10)
Sex [F/M], %	38/62	39/61
Ethnicity, n (%)		
White	246 (71.5)	251 (73.2)
Asian	73 (21.2)	72 (21.0)
Black/African American	13 (3.8)	7 (2.0)
Other	5 (1.5)	2 (0.6)
Unknown	7 (2.0)	11 (3.2)
Region[b], n (%)		
Not East Asia	280 (81.4)	281 (81.9)
East Asia	64 (18.6)	62 (18.1)
Smoking status, n (%)		
Never-smoker	63 (18.3)	67 (19.5)
Current/former smoker	279 (81.1)	269 (78.4)
Unknown	2 (0.6)	7 (2.0)
ECOG PS, n (%)		
0	112 (32.6)	116 (33.8)
1	229 (66.6)	224 (65.3)
≥ 2	3 (0.9)	2 (0.6)
Unknown	0	1 (0.3)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab vs. docetaxel (continued)

Study Characteristics Category	**Pembrolizumab**	**Docetaxel**
KEYNOTE 010	N[a] = 344	N = 343
Disease stage, n (%)		
IA	1 (0.3)	0
IB	1 (0.3)	1 (0.3)
IIB	1 (0.3)	0
IIIA	5 (1.5)	8 (2.3)
IIIB	21 (6.1)	22 (6.4)
IV	315 (91.6)	312 (91.0)
Metastases, n (%)		
M0	29 (8.4)	31 (9.0)
M1	95 (27.6)	80 (23.3)
M1A	62 (18.0)	62 (18.1)
M1B	158 (45.9)	170 (49.6)
Brain metastases[c], n (%)		
Yes	56 (16.3)	48 (14.0)
No	288 (83.7)	295 (86.0)
Histology, n (%)		
Squamous	76 (22.1)	66 (19.2)
Non-squamous	240 (69.8)	240 (70.0)
Other	9 (2.6)	10 (2.9)
Unknown	19 (5.5)	27 (7.9)
PD-L1 expression, n (%)		
Weakly positive (TPS: 1 to < 50%)	205 (59.6)	191 (55.7)
Strongly positive (TPS: ≥ 50%)	139 (40.4)	152 (44.3)
ALK translocation status, n (%)		
Mutant	2 (0.6)	2 (0.6)
Wild type	307 (89.2)	310 (90.4)
Undetermined	22 (6.4)	20 (5.8)
Unknown	13 (3.8)	11 (3.2)
EGFR mutation status, n (%)		
Mutant	28 (8.1)	26 (7.6)
Wild type	293 (85.2)	294 (85.7)
Undetermined	15 (4.4)	13 (3.8)
Unknown	8 (2.3)	10 (2.9)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab vs. docetaxel (continued)

Study Characteristics Category	Pembrolizumab	Docetaxel
KEYNOTE 010	N[a] = 344	N = 343
Prior lines of systemic therapy, n (%)		
1	243 (70.6)	235 (68.5)
2	66 (19.2)	75 (21.9)
≥ 3	27 (7.8)	29 (8.4)
Adjuvant/neoadjuvant[d]	6 (1.7)/1 (0.3)	3 (0.9)/0 (0)
Unknown	1 (0.3)	1 (0.3)
Treatment discontinuation[e], n (%)	270 (78.5)	317 (92.4)
Study discontinuation, n (%)	ND	ND

a: The number of randomized patients in the pembrolizumab arm is N = 345; one patient was excluded after randomization due to closure of one study centre.
b: East Asia includes Japan, Korea, Taiwan; see Table 6 for non-East Asian countries.
c: Patients with active central nervous system metastases and/or carcinomatous meningitis were excluded with the following exceptions: patients with pretreated brain metastases a) without evidence of progression by magnetic resonance imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline, b) without evidence of new or enlarging brain metastases and c) without use of steroids for at least 3 days prior to study medication.
d: It remains unclear why this group is not recorded under the number of prior therapies.
e: The 2 most common reasons for treatment discontinuation were disease progression (pembrolizumab: 36.0%; docetaxel: 25.9%) and decision by the physician (pembrolizumab: 23.8%; docetaxel: 32.9%). In addition, the proportion of patients with withdrawal of consent was 1.5% in the pembrolizumab arm and 13.1% in the docetaxel arm.
ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; F: female; M: male; n: number of patients in the category; N: number of patients included; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; TPS: Tumour Proportion Score; vs.: versus

The mean age of the patients included in the KEYNOTE 010 study was 62 years. About 40% of the patients were women. About 70% of the patients were white; the proportion of Asian patients was approximately 21%. Two thirds of the patients had an ECOG PS of 1; the other patients of 0. More than 90% of the patients had disease stage IV. Most patients had no brain metastases. Approximately 70% of the patients had already received one prior therapy at study inclusion; about 8% had received ≥ 3 prior therapies. The proportion of patients with treatment discontinuation was lower in the pembrolizumab arm than in the docetaxel arm. The 2 most common reasons for treatment discontinuation were disease progression and decision by the physician.

Table 10 shows the mean and median treatment duration of the patients and the observation period for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab**	**Docetaxel**
KEYNOTE 010	N[a] = 339	N[a] = 309
Treatment duration [days]		
Median [min; max]	106 [1; 681]	62 [1; 416]
Mean (SD)	151.1 (143.9)	81.6 (72.3)
Observation duration		
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a: Safety population.

max: maximum; min: minimum; N: number of patients analysed; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration in the KEYNOTE 010 study was notably longer in the pembrolizumab arm (106 days) than in the docetaxel arm (62 days). The difference in treatment durations can be explained by differences in treatment discontinuation rates due to disease progression, decision by the physician and withdrawal of consent (see Table 9).

The dossier contained no information on observation periods of individual outcomes. It can be assumed, however, that the differences in treatment and observation duration were similar because the outcomes on morbidity, health-related quality of life and side effects (except SAEs) were each to be recorded for up to 30 days after the last administration of the study medication. The follow-up for SAEs was 90 days or until initiation of a new antineoplastic treatment, whichever occurred first. The dossier contained neither information on the proportion of those who had initiated antineoplastic treatment before the end of the 90 days nor for the actual follow-up period for SAEs.

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: pembrolizumab vs. docetaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
KEYNOTE 010	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - Overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-LC13
  - health status measured with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS)
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes concurs with that of the company, except for specific AEs (see Section 2.6.2.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: pembrolizumab vs. docetaxel

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Further specific AEs[a]
KEYNOTE 010	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: The following events (MedDRA coding, SOC) are considered: gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, investigations (CTCAE grade ≥ 3), infections and infestations (CTCAE grade ≥ 3) and blood and lymphatic system disorders (CTCAE grade ≥ 3).
b: No usable data because of important difference in the proportion of the patients not included in the analysis between the treatment groups (> 15 percentage points).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: pembrolizumab vs. docetaxel

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Further specific AEs[a]
KEYNOTE 010	L	H[b, c, d]	-[e]	H[b, c, d]	H[c, d]	H[c, d]	H[c, d]	H[c, d]	H[c, d]	H[c, d]	H[c, d]

a: The following events (MedDRA coding) are considered: gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, investigations (CTCAE grade ≥ 3), infections and infestations (CTCAE grade ≥ 3) and blood and lymphatic system disorders (CTCAE grade ≥ 3).
b: Lack of blinding in subjective recording of outcomes.
c: Important proportion of patients not included in the analysis (> 10%) or important difference between the treatment groups (> 5 percentage points) (see Section 2.6.2.4.2 of the full dossier assessment).
d: Potentially informative censoring particularly due to study discontinuation due to disease progression, decision by the physician or withdrawal of consent.
e: No usable data because of important difference in the proportion of the patients not included in the analysis between the treatment groups (> 15 percentage points) (see Section 2.6.2.4.2 of the full dossier assessment).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low. This concurs with the company's assessment.

Due to the lack of blinding in subjective recording of outcomes, important proportions of patients not included in the analysis and important differences between the treatment groups, the risk of bias for the outcomes "symptoms" and "health-related quality of life" was rated as high. In addition to the aspects mentioned, potentially informative censorings also resulted in a high risk of bias for the outcomes "symptoms" and "health-related quality of life". The company also rated the risk of bias for these outcomes as high, but partly provided slightly different reasons (see Section 2.6.2.4.2 of the full dossier assessment).

There were no usable data for the outcome "health status". This was due to the important group difference in the proportion of patients not included in the analysis. The risk of bias for this outcome was therefore not assessed. This deviates from the approach of the company,

which rated the risk of bias for this outcome as high and used the results for the assessment of the added benefit.

Due to potentially informative censoring, different treatment durations and resulting different observation periods as well as important differences in patients not included in the analysis between the treatment groups, the risk of bias was rated as high for all AE outcomes. For the outcomes "SAEs", "discontinuation due to AEs", "severe AEs" (CTCAE grade ≥ 3) and "immune-related AEs", this concurs with the assessment of the company, which only provided the first 2 reasons for a high risk of bias, however. The remaining specific AE outcomes were not included in the company's benefit assessment.

2.3.2.3 Results

Table 14 and Table 15 summarize the results on the comparison of pembrolizumab with docetaxel in adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen for whom treatment with docetaxel, pemetrexed or nivolumab is indicated.

Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. If available, Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment.

Table 14: Results (overall survival, morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab vs. docetaxel

Study Outcome category Outcome	Pembrolizumab N[a]	Pembrolizumab Median time to event in weeks [95% CI] Patients with event n (%)	Docetaxel N[a]	Docetaxel Median time to event in weeks [95% CI] Patients with event n (%)	Pembrolizumab vs. docetaxel HR [95% CI][b]; p-value
KEYNOTE 010					
Mortality[c]					
Overall survival	344	45.2 [40.9; 51.7] 172 (50.0)	343	37.0 [32.6; 42.6] 193 (56.3)	0.71 [0.58; 0.88]; 0.002
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales) – time to deterioration[d]					
Dyspnoea	331	NA [24.1; NC] 117 (35.3)	293	24.1 [18.1; 30.4] 101 (34.5)	0.90 [0.69; 1.17]; 0.418
Fatigue	331	12.1 [6.6; 15.9] 179 (54.1)	293	12.0 [7.0; 13.1] 146 (49.8)	0.96 [0.77; 1.20]; 0.741
Insomnia	331	NA [24.1; NC] 111 (33.5)	293	30.4 [25.1; NC] 80 (27.3)	1.09 [0.82; 1.45]; 0.559
Pain	331	19.4 [13.9; 27.1] 146 (44.1)	293	24.1 [18.9; 32.3] 103 (35.2)	1.13 [0.87; 1.45]; 0.355
Appetite loss	331	27.1 [20.1; NC] 131 (39.6)	293	37.7 [27.3; NC] 85 (29.0)	1.22 [0.93; 1.60]; 0.157
Diarrhoea	331	56.4 [39.4; NC] 69 (20.8)	293	41.3 [28.9; NC] 66 (22.5)	0.74 [0.52; 1.03]; 0.076
Nausea and vomiting	331	42.1 [36.6; NC] 106 (32.0)	293	NA [25.1; NC] 84 (28.7)	0.96 [0.72; 1.28]; 0.791
Constipation	331	NA [36.6; NC] 93 (28.1)	293	32.3 [24.7; NC] 80 (27.3)	0.85 [0.63; 1.15]; 0.282
EORTC QLQ-LC13 (symptom scales) – time to deterioration[d]					
Dyspnoea	331	12.4 [9.1; 22.7] 165 (49.8)	291	12.6 [9.1; 21.0] 136 (46.7)	0.96 [0.77; 1.21]; 0.733
Pain (chest)	331	NA [37.1; NC] 82 (24.8)	291	63.4 [35.0; 63.4] 64 (22.0)	0.97 [0.69; 1.34]; 0.833
Pain (arm/shoulder)	331	36.9 [24.6; NC] 108 (32.6)	291	NA [32.3; NC] 69 (23.7)	1.29 [0.95; 1.75]; 0.098
Pain (other)	331	37.1 [26.3; NC] 114 (34.4)	291	31.1 [24.1; NC] 90 (30.9)	0.96 [0.72; 1.26]; 0.751

(continued)

Table 14: Results (overall survival, morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab vs. docetaxel (continued)

Study Outcome category Outcome	Pembrolizumab N[a]	Pembrolizumab Median time to event in weeks [95% CI] Patients with event n (%)	Docetaxel N[a]	Docetaxel Median time to event in weeks [95% CI] Patients with event n (%)	Pembrolizumab vs. docetaxel HR [95% CI][b]; p-value
KEYNOTE 010					
Cough	331	42.3 [27.1; NC] 112 (33.8)	291	31.1 [22.9; NC] 89 (30.6)	1.00 [0.76; 1.33]; 0.975
Haemoptysis	331	NA [NC; NC] 41 (12.4)	291	NA [40.4; NC] 31 (10.7)	0.99 [0.62; 1.59]; 0.977
Alopecia	331	NA [46.0; NC] 35 (10.6)	291	4.1 [3.4; 6.1] 172 (59.1)	0.09 [0.06; 0.13]; < 0.001
Dysphagia	331	NA [50.0; NC] 65 (19.6)	291	NA [32.3; NC] 52 (17.9)	0.95 [0.66; 1.37]; 0.770
Sore mouth	331	50.0 [38.0; NC] 74 (22.4)	291	52.9 [27.3; 63.4] 92 (31.6)	0.53 [0.39; 0.72]; < 0.001
Peripheral neuropathy	331	NA [37.7; NC] 92 (27.8)	291	24.1 [20.1; 27.1] 102 (35.1)	0.64 [0.49; 0.86]; 0.002
Health status (EQ-5D VAS)	No usable data available[e]				
Health-related quality of life					
EORTC QLQ-C30 (functional scales) – time to deterioration[d]					
Global health status	331	20.3 [16.1; 36.1] 148 (44.7)	293	20.4 [13.1; 27.3] 116 (39.6)	1.00 [0.78; 1.28]; 0.993
Emotional functioning	331	42.9 [36.6; 69.6] 91 (27.5)	293	NA [NC; NC] 62 (21.2)	1.06 [0.76; 1.46]; 0.744
Cognitive functioning	331	36.3 [18.1; NC] 130 (39.3)	293	32.3 [24.0; 40.4] 96 (32.8)	1.08 [0.83; 1.40]; 0.580
Physical functioning	331	37.7 [19.3; 47.3] 131 (39.6)	293	24.1 [18.9; 25.3] 108 (36.9)	0.93 [0.72; 1.20]; 0.584
Role functioning	331	14.0 [9.9; 24.6] 159 (48.0)	293	13.9 [12.1; 24.0] 127 (43.3)	1.00 [0.79; 1.27]; 0.982
Social functioning	331	36.6 [18.0; 42.1] 132 (39.9)	293	27.1 [13.3; NC] 106 (36.2)	0.96 [0.74; 1.24]; 0.762

(continued)

Table 14: Results (overall survival, morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab vs. docetaxel (continued)

a: Only applies to the outcome categories “morbidity” and “health-related quality of life”: number of patients with at least one dose of the study medication and questionnaire provided at the start of the study. The number of patients with fully completed questionnaire at the start of the study was N = 318 (QLQ-C30) and 319 (QLQ-LC13) in the pembrolizumab arm, and N = 273 (QLQ-C30) and 271 (QLQ-LC13) in the docetaxel arm.
b: Cox proportional hazards model stratified by ECOG PS, region, PD-L1 expression.
c: Institute’s calculation of weeks from months.
d: The time to deterioration by at least 10 points is provided.
e: Important difference in the proportion of the patients not included in the analysis between the treatment groups (> 15 percentage points).
CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with (at least one) event; N: number of patients analysed; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Table 15: Results (side effects) – RCT, direct comparison: pembrolizumab vs. docetaxel

Study Outcome category Outcome	Pembrolizumab N[a]	Pembrolizumab Median time to event in weeks [95% CI] Patients with event n (%)	Docetaxel N[a]	Docetaxel Median time to event in weeks [95% CI] Patients with event n (%)	Pembrolizumab vs. docetaxel HR [95% CI][b]; p-value
KEYNOTE 010					
Side effects					
AEs (supplementary information)	339	2.6 [2.0; 3.0] 331 (97.6)	309	0.9 [0.7; 1.0] 297 (96.1)	
SAEs	339	68.6 [45.1; NC] 115 (33.9)	309	NA [43.1; NC] 107 (34.6)	0.83 [0.63; 1.08]; 0.164
Severe AEs (CTCAE grade ≥ 3)	339	31.1 (21.3; 45.1) 158 (46.6)	309	10.3 (8.0; 13.7) 173 (56.0)	0.54 [0.43; 0.67]; < 0.001
Discontinuation due to AEs	339	NA [NC; NC] 28 (8.3)	309	NA [NC; NC] 42 (13.6)	0.37 [0.22; 0.62]; < 0.001
Specific AEs					
Immune-related AEs	339	NA [NC; NC] 73 (21.5)	309	NA [NC; NC] 28 (9.1)	1.96 [1.26; 3.06]; 0.003
Immune-related SAEs	339	NA [NC; NC] 22 (6.5)	309	NA [NC; NC] 5 (1.6)	3.49 [1.31; 9.30]; 0.012
Immune-related severe AEs (CTCAE grade ≥ 3)	339	NA [NC; NC] 21 (6.2)	309	NA [NC; NC] 4 (1.3)	3.71 [1.26; 10.97]; 0.018
Gastrointestinal disorders	339	13.0 [9.9; 17.3] 190 (56.0)	309	6.1 [3.7; 9.0] 188 (60.8)	0.66 [0.54; 0.81]; < 0.001
General disorders and administration site conditions	339	15.7 [12.1; 19.1] 184 (54.3)	309	6.3 [4.0; 8.3] 208 (67.3)	0.56 [0.46; 0.69]; < 0.001
Nervous system disorders	339	62.1 [43.6; NC] 105 (31.0)	309	24.1 [18.0; NC] 120 (38.8)	0.53 [0.40; 0.69]; < 0.001
Skin and subcutaneous tissue disorders	339	52.6 [41.7; NC] 104 (30.7)	309	13.3 [9.1; 21.3] 148 (47.9)	0.40 [0.31; 0.52]; < 0.001
Investigations (CTCAE grade ≥ 3)	339	NA [NC; NC] 14 (4.1)	309	NA [NC; NC] 28 (9.1)	0.34 [0.18; 0.66]; 0.001

(continued)

Table 15: Results (side effects) – RCT, direct comparison: pembrolizumab vs. docetaxel (continued)

Study Outcome category Outcome	Pembrolizumab N[a]	Pembrolizumab Median time to event in weeks [95% CI] Patients with event n (%)	Docetaxel N[a]	Docetaxel Median time to event in weeks [95% CI] Patients with event n (%)	Pembrolizumab vs. docetaxel HR [95% CI][b]; p-value
KEYNOTE 010					
Infections and infestations (CTCAE grade ≥ 3)	339	NA [NC; NC] 31 (9.1)	309	NA [NC; NC] 42 (13.6)	0.49 [0.30; 0.80]; 0.004
Blood and lymphatic system disorders (CTCAE grade ≥ 3)	339	NA [NC; NC] 13 (3.8)	309	NA [NC; NC] 64 (20.7)	0.14 [0.07; 0.25]; < 0.001

a: Number of patients with at least one dose of the study medication.
b: Cox proportional hazards model stratified by ECOG PS, region, PD-L1 expression.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

From the available data, at most indications, e.g. of an added benefit, can be derived for overall survival, and at most hints for all other outcomes due to the high risk of bias.

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab versus docetaxel was shown for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab in comparison with docetaxel.

The assessment concurs with that of the company.

Morbidity

Symptoms

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-LC13. The time to deterioration by at least 10 points was considered. Hereinafter, at first the outcomes of symptoms for which statistically significant group differences at the level of the total population or at the level of subgroups were shown are described.

Fatigue

In the total population, there was no statistically significant difference between pembrolizumab and docetaxel for the outcome "fatigue". There was proof of an effect modification by the characteristic "EGFR mutation status", however. No statistically significant differences between the treatment groups or more than marginal effects were shown for any of the subgroups, however. Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel; an added benefit for the outcome "fatigue" is therefore not proven.

The assessment of added benefit concurs with the company's assessment.

Alopecia, sore mouth, peripheral neuropathy

Statistically significant differences in favour of pembrolizumab versus docetaxel were shown for each of the outcomes "alopecia", "sore mouth" and "peripheral neuropathy". This resulted in a hint of an added benefit of pembrolizumab in comparison with docetaxel for each of the 3 outcomes.

The assessments concur with those of the company.

Further outcomes on symptoms

No statistically significant differences between the treatment groups were shown for any further outcomes on symptoms. Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel for any further outcomes; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Health status

The dossier contained no usable data for the outcome "health status" (see Section 2.6.2.4.3 of the full dossier assessment). Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel for this outcome; an added benefit is therefore not proven.

This assessment deviates from that of the company, which included the results for the outcome "health status" in the benefit assessment, but also derived no proof of an added benefit from it. In addition, the company allocated this outcome to health-related quality of life.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC-QLQ-C30. The time to deterioration by at least 10 points was considered.

No statistically significant differences between the treatment groups were shown for any of the scales mentioned above. Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel for health-related quality of life; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Hence there was no hint of greater or lesser harm from pembrolizumab in comparison with docetaxel; greater or lesser harm is therefore not proven.

The assessment concurs with that of the company.

Severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

Statistically significant differences in favour of pembrolizumab versus docetaxel were shown for each of the outcomes "severe AEs (CTCAE grade ≥ 3") and "discontinuation due to AEs". This resulted in a hint of lesser harm of pembrolizumab in comparison with docetaxel for both outcomes.

These assessments concur with those of the company.

Specific adverse events

Immune-related adverse events, serious adverse events, severe adverse events (CTCAE grade ≥ 3)

Statistically significant differences to the disadvantage of pembrolizumab versus docetaxel were shown for each of the outcomes "immune-related AEs", "immune-related SAEs" and "immune-related severe AEs" (CTCAE grade ≥ 3). This resulted in a hint of greater harm of pembrolizumab in comparison with docetaxel for each of the 3 outcomes.

These assessments concur with those of the company, which only considered these results as additional information in its benefit assessment, however.

Further specific adverse events

Statistically significant differences in favour of pembrolizumab versus docetaxel were shown for each of the following specific AE outcomes selected: gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, investigations (CTCAE grade ≥ 3), infections and infestations (CTCAE grade ≥ 3) and blood and lymphatic system disorders (CTCAE grade ≥ 3). This resulted in a hint of lesser harm of pembrolizumab in comparison with docetaxel for each of these outcomes.

The company did not use these outcomes in its assessment.

The most common Preferred Terms (PTs) of the specific AE outcomes selected at System Organ Class (SOC) level were the following: for the SOC "gastrointestinal disorders": diarrhoea and nausea, for the SOC "general disorders and administration site conditions": fatigue; for the SOC "nervous system disorders": headache, peripheral neuropathy; for the SOC "skin and subcutaneous tissue disorders": alopecia; for the SOC "infections and infestations" (CTCAE grade ≥ 3): pneumonia; for the SOC "investigations" (CTCAE grade ≥ 3): neutrophil and leukocyte count decreased; for the SOC "blood and lymphatic system disorders" (CTCAE grade ≥ 3): neutropenia, febrile neutropenia. See also tables in Appendix B of the full dossier assessment.

2.3.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the present assessment:

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- region (not East Asia, East Asia)
- smoking status (never-smoker, current/former)
- EGFR mutation status (mutant, wild type)
- ALK translocation status (mutant, wild type)
- PD-L1 expression (weakly positive [TPS: 1 to < 50%], strongly positive [TPS: ≥ 50%])
- histology (squamous, non-squamous)
- number of prior therapies
- brain metastases

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. For the outcome "overall survival", results are presented if there was at least an indication of an interaction between treatment effect and subgroup characteristic. For all other outcomes, only results for which there was proof of an interaction are presented due to the different treatment durations and resulting different observation periods and the potentially informative censoring (see Section 2.6.2.2 of the full dossier assessment). In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the subgroup results on the comparison of pembrolizumab with docetaxel in the KEYNOTE 010 study.

Table 16: Subgroups (overall survival, morbidity) – RCT, direct comparison: pembrolizumab vs. docetaxel

Study Outcome category Outcome Characteristic Subgroup	Pembrolizumab N	Pembrolizumab Median survival time in weeks [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median survival time in weeks [95% CI] Patients with event n (%)	Pembrolizumab vs. docetaxel HR [95% CI]	Pembrolizumab vs. docetaxel p-value
KEYNOTE 010						
Mortality						
Overall survival[a]						
PD-L1 expression						
Weak (TPS: 1 to < 50%)	205	40.9 [37.8; 45.7] 114 (55.6)	191	37.4 [33.9; 43.0] 107 (56.0)	0.79 [0.61; 1.04]	0.088
Strong (TPS: ≥ 50%)	139	64.8 [45.2; NC] 58 (41.7)	152	35.7 [27.8; 46.5] 86 (56.6)	0.54 [0.38; 0.77]	< 0.001
					Interaction:	0.088
Region[b]						
Not East Asia	280	44.8 [39.6; 51.7] 148 (52.9)	281	34.8 [29.6; 38.3] 174 (61.9)	0.67 [0.54; 0.84]	< 0.001
East Asia	64	45.7 [41.3; NC] 24 (37.5)	62	NA [42.6; NC] 19 (30.6)	1.12 [0.60; 2.08]	0.720
					Interaction:	0.129
Morbidity						
Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration[c]						
Fatigue						
EGFR mutation status						
Wild type	281	12.1 [7.0; 18.3] 150 (53.4)	255	9.1 [6.6; 12.7] 132 (51.8)	0.89 [0.70; 1.12]	0.314
Mutant	28	6.1 [3.1; 20.1] 19 (67.9)	20	NA [5.1; NC] 6 (30.0)	2.65 [1.03; 6.78]	0.042
					Interaction:	0.027

(continued)

Table 16: Subgroups (overall survival, morbidity) – RCT, direct comparison: pembrolizumab vs. docetaxel (continued)

Study Outcome category Outcome Characteristic Subgroup	Pembrolizumab N	Pembrolizumab Median survival time in weeks [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median survival time in weeks [95% CI] Patients with event n (%)	Pembrolizumab vs. docetaxel HR [95% CI]	Pembrolizumab vs. docetaxel p-value
KEYNOTE 010						
Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[c]						
Peripheral neuropathy						
Age						
< 65 years	194	NA [24.1; NC] 63 (32.5)	176	24.1 [20.4; 27.1] 60 (34.1)	0.86 [0.60; 1.23]	0.404
≥ 65 years	137	NA [37.7; NC] 29 (21.2)	115	22.9 [12.1; NC] 42 (36.5)	0.39 [0.24; 0.64]	< 0.001
					Interaction:	0.011
EGFR mutation status						
Wild type	281	NA [37.7; NC] 75 (26.7)	253	24.1 [19.4; 25.9] 94 (37.2)	0.57 [0.42; 0.77]	< 0.001
Mutant	28	24.1 [9.1; NC] 9 (32.1)	20	27.1 [24.0; NC] 2 (10.0)	2.98 [0.63; 14.10]	0.169
					Interaction:	0.040

a: Institute's calculation of weeks from months.
b: East Asia includes Japan, Korea, Taiwan; see Table 6 for non-East Asian countries.
c: The time to deterioration by at least 10 points is provided.

CI: confidence interval; EGFR: epidermal growth factor receptor; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; TPS: Tumour Proportion Score; vs.: versus

Mortality

Overall survival

Indications of an effect modification by the characteristics "PD-L1 expression" and "region" were shown for the outcome "overall survival". For patients from non-East-Asian regions, there was a statistically significant difference between the treatment groups in favour of pembrolizumab versus docetaxel. Although patients from East Asia constituted a notably smaller proportion of the total population, it remains unclear to what extent the interaction for the characteristic "PD-L1 expression" was influenced by the characteristic "region". Hence the subgroup results for the characteristic "PD-L1 expression" cannot be meaningfully interpreted due to missing data on the investigation of possible dependencies between both

subgroup characteristics. The added benefit was therefore derived on the basis of the total population (see Section 2.3.2.3).

Morbidity

Symptoms

Fatigue

There was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome "fatigue". A statistically significant difference to the disadvantage of pembrolizumab versus docetaxel was shown for patients with EGFR mutation. The outcome "fatigue" was allocated to the category of non-serious/non-severe symptoms/late complications. Hence the extent was no more than "marginal" (reversed direction of effect to derive the extent: hazard ratio [95% confidence interval] = 0.38 [0.15; 0.97]). There was no statistically significant difference between the 2 treatment groups in the group of patients with wild type. Hence there was no hint of an added benefit of pembrolizumab in comparison with docetaxel for any of the subgroups; an added benefit for the outcome "fatigue" is therefore not proven.

Peripheral neuropathy

There was proof of an effect modification by the characteristics "age" and "EGFR mutation status" for the outcome "peripheral neuropathy". The subgroup results could not be meaningfully interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. The added benefit for the outcome "peripheral neuropathy" was therefore derived on the basis of the total population (see Section 2.3.2.3).

The approach regarding subgroups concurs with that of the company insofar as it considered no subgroup results for the outcome-related derivation of the added benefit for any of the outcomes used by the company.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for research question 1 (patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated) at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on 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.

2.3.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in the following assessments for pembrolizumab in comparison with docetaxel in patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen

(patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab) for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated:

- an indication of an added benefit for the outcome “overall survival”
- a hint of an added benefit for each of the outcomes “alopecia”, “sore mouth” and “peripheral neuropathy”
- a hint of lesser harm for each of the outcomes " “severe AEs” (CTCAE grade ≥ 3) and “discontinuation due to AEs”
- a hint of greater harm for each of the outcomes “immune-related AEs”, “immune-related SAEs” and “immune related severe AEs” (CTCAE grade ≥ 3)
- a hint of lesser harm in each case for further specific AEs (gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, investigations [CTCAE grade ≥ 3], infections and infestations [CTCAE grade ≥ 3] and blood and lymphatic system disorders [CTCAE grade ≥ 3])

Determination of the outcome category for the outcomes “symptoms” and “side effects”

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-severe/non-serious or severe/serious. The classification of these outcomes is justified below.

Since it could not be inferred from the dossier whether the outcomes on symptoms were severe or serious symptoms, these outcomes were allocated to non-serious/non-severe symptoms/late complications. The outcome “discontinuations due to AEs” was allocated to serious/severe side effects because the proportion of discontinuations due to an SAE was approximately 61%. It was inferred from information provided in the study documents that the following specific AEs were mostly non-severe events: gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders and skin and subcutaneous tissue disorders. These outcomes were therefore allocated to the category of non-serious/non-severe side effects.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. docetaxel

Outcome category **Outcome**	**Pembrolizumab vs. docetaxel** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival[c]	Median: 45.2 vs. 37.0 weeks HR: 0.71 [0.58; 0.88]; p = 0.002 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms		
EORTC QLQ-C30 (symptom scales) – time to deterioration[d]		
Dyspnoea	Median: NA vs. 24.1 weeks HR: 0.90 [0.69; 1.17]; p = 0.418	Lesser benefit/added benefit not proven
Fatigue	Median: 12.1 vs. 12.0 weeks HR: 0.96 [0.77; 1.20]; 0.741	Lesser benefit/added benefit not proven
Insomnia	Median: NA vs. 30.4 weeks HR: 1.09 [0.82; 1.45]; p = 0.559	Lesser benefit/added benefit not proven
Pain	Median: 19.4 vs. 24.1 weeks HR: 1.13 [0.87; 1.45]; p = 0.355	Lesser benefit/added benefit not proven
Appetite loss	Median: 27.1 vs. 37.7 weeks HR: 1.22 [0.93; 1.60]; p = 0.157	Lesser benefit/added benefit not proven
Diarrhoea	Median: 56.4 vs. 41.3 weeks HR: 0.74 [0.52; 1.03]; p = 0.076	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 42.1 vs. NA weeks HR: 0.96 [0.72; 1.28]; p = 0.791	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. 32.3 weeks HR: 0.85 [0.63; 1.15]; p = 0.282	Lesser benefit/added benefit not proven
EORTC QLQ-LC13 (symptom scales) – time to deterioration[d]		
Dyspnoea	Median: 12.4 vs. 12.6 weeks HR: 0.96 [0.77; 1.21]; p = 0.733	Lesser benefit/added benefit not proven
Pain (chest)	Median: NA vs. 63.4 weeks HR: 0.97 [0.69; 1.34]; p = 0.833	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	Median: 36.9 vs. NA weeks HR: 1.29 [0.95; 1.75]; p = 0.098	Lesser benefit/added benefit not proven
Pain (other)	Median: 37.1 vs. 31.1 weeks HR: 0.96 [0.72; 1.26]; p = 0.751	Lesser benefit/added benefit not proven
Cough	Median: 42.3 vs. 31.1 weeks HR: 1.00 [0.76; 1.33]; p = 0.975	Lesser benefit/added benefit not proven
Haemoptysis	Median: NA vs. NA weeks HR: 0.99 [0.62; 1.59]; p = 0.977	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. docetaxel (continued)

Outcome category **Outcome**	**Pembrolizumab vs. docetaxel** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Alopecia	Median: NA vs. 4.1 weeks HR: 0.09 [0.06; 0.13]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Dysphagia	Median: NA vs. NA weeks HR: 0.95 [0.66; 1.37]; p = 0.770	Lesser benefit/added benefit not proven
Sore mouth	Median: 50.0 vs. 52.9 weeks HR: 0.53 [0.39; 0.72]; p < 0.001; probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Peripheral neuropathy	Median: NA vs. 24.1 weeks HR: 0.64 [0.49; 0.86]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Health status (EQ-5D VAS)	No usable data available	
Health-related quality of life		
EORTC QLQ-C30 (functional scales) – time to deterioration[d]		
Global health status	Median: 20.3 vs. 20.4 weeks HR: 1.00 [0.78; 1.28]; p = 0.993	Lesser benefit/added benefit not proven
Emotional functioning	Median: 42.9 vs. NA weeks HR: 1.06 [0.76; 1.46]; p = 0.744	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 36.3 vs. 32.3 weeks HR: 1.08 [0.83; 1.40]; p = 0.580	Lesser benefit/added benefit not proven
Physical functioning	Median: 37.7 vs. 24.1 weeks HR: 0.93 [0.72; 1.20]; p = 0.584	Lesser benefit/added benefit not proven
Role functioning	Median: 14.0 vs. 13.9 weeks HR: 1.00 [0.79; 1.27]; p = 0.982	Lesser benefit/added benefit not proven
Social functioning	Median: 36.6 vs. 27.1 weeks HR: 0.96 [0.74; 1.24]; p = 0.762	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. docetaxel** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	Median: 68.6 vs. NA weeks HR: 0.83 [0.63; 1.08]; p = 0.164	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 31.1 vs. 10.3 weeks HR: 0.54 [0.43; 0.67]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs	Median: NA vs. NA weeks HR: 0.37 [0.22; 0.62]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: "major"
Specific AEs		
Immune-related AEs	Median: NA vs. NA weeks HR: 1.96 [1.26; 3.06]; p = 0.003 HR: 0.51 [0.33; 0.79][e] probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Immune-related SAEs	Median: NA vs. NA weeks HR: 3.49 [1.31; 9.30]; p = 0.012 HR: 0.29 [0.11; 0.76][e] probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Immune-related severe AEs (CTCAE grade ≥ 3)	Median: NA vs. NA weeks HR: 3.71 [1.26; 10.97]; p = 0.018 HR: 0.27 [0.09; 0.79][e]; probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Gastrointestinal disorders	Median: 13.0 vs. 6.1 weeks HR: 0.66 [0.54; 0.81]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
General disorders and administration site conditions	Median: 15.7 vs. 6.3 weeks HR: 0.56 [0.46; 0.69]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"

(continued)

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. docetaxel** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Nervous system disorders	Median: 62.1 vs. 24.1 weeks HR: 0.53 [0.40; 0.69]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Skin and subcutaneous tissue disorders	Median: 52.6 vs. 13.3 weeks HR: 0.40 [0.31; 0.52]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Investigations (CTCAE grade ≥ 3)	Median: NA vs. NA weeks HR: 0.34 [0.18; 0.66]; p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: "major"
Infections and infestations (CTCAE grade ≥ 3)	Median: NA vs. NA weeks HR: 0.49 [0.30; 0.80]; p = 0.004 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Blood and lymphatic system disorders (CTCAE grade ≥ 3)	Median: NA vs. NA weeks HR: 0.14 [0.07; 0.25]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: "major"

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation of weeks from months.
d: The time to deterioration by at least 10 points is provided.
e: 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; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of pembrolizumab in comparison with docetaxel

Positive effects	**Negative effects**
▪ Mortality ▫ overall survival: indication of an added benefit – extent: "considerable"	
▪ Non-serious/non-severe symptoms/late complications ▫ symptoms: hint of an added benefit – extent: "considerable" (including alopecia, sore mouth – extent: in each case "considerable"; peripheral neuropathy – extent: "minor")	
▪ Serious/severe side effects ▫ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "major" ▫ discontinuation due to AEs: hint of lesser harm – extent: "major" ▫ specific AEs: hint of lesser harm – extent: "major" (including: investigations, blood and lymphatic system disorders [each CTCAE grade ≥ 3] – extent: in each case "major"; infections and infestations [CTCAE grade ≥ 3] – extent: "considerable")	▪ Serious/severe side effects ▫ specific AEs: hint of greater harm – extent "considerable" (including immune-related SAEs and immune related severe AEs [CTCAE grade ≥ 3])
▪ Non-serious/non-severe side effects ▫ specific AEs: hint of lesser harm – extent: "considerable" (including: general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders – extent: in each case "considerable"; gastrointestinal disorders – extent: "minor")	▪ Non-serious/non-severe side effects ▫ specific AEs: hint of greater harm – extent "considerable" (immune-related AEs)
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

Overall, there are positive and negative effects. On the side of positive effects, there was an indication of considerable added benefit for the outcome "overall survival" and a hint of considerable added benefit for the outcome "symptoms". For the outcomes "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs", there was a hint of lesser harm with the extent "major". For specific AEs, there was a hint of lesser harm with the extent "major" and "considerable". On the side of negative effects, the positive effects were accompanied by hints of greater harm with the extent "considerable" for specific AEs (immune-related AEs).

Overall, the negative effects in immune-related AEs did not raise doubts about the positive effects.

In summary, there is an indication of considerable added benefit of pembrolizumab versus the ACT docetaxel for patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen (patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for

these mutations prior to receiving pembrolizumab) for whom treatment with docetaxel, pemetrexed or nivolumab is indicated.

2.3.4 List of included studies

Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; 387(10027): 1540-1550.

Merck Sharp & Dohme. Study of two doses of MK-3475 (pembrolizumab) versus docetaxel in previously-treated participants with non-small cell lung cancer (MK-3475-010/KEYNOTE-010): full text view [online]. In: ClinicalTrials.gov. 07.04.2016 [Accessed: 24.09.2016]. URL: https://ClinicalTrials.gov/show/NCT01905657.

Merck Sharp & Dohme. A phase II/III randomized trial of two doses of MK-3475 (SCH900475) versus docetaxel in previously treated subjects with non-small cell lung cancer [online]. In: EU Clinical Trials Register. [Accessed: 24.08.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004391-19.

Merck Sharp & Dohme. A phase II/III randomized trial of two doses of MK-3475 (SCH900475) versus docetaxel in previously treated subjects with Non-Small Cell Lung Cancer (NSCLC): study KEYNOTE-010; clinical study report [unpublished]. 2015.

2.4 Research question 2: patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated

2.4.1 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: 27 July 2016)
- bibliographical literature search on pembrolizumab (last search on 23 June 2016)
- search in trial registries for studies on pembrolizumab (last search on 20 June 2016)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 24 August 2016)

No relevant study for patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated was identified from the check.

2.4.2 Results on added benefit

There were no data for the assessment of the added benefit in adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen (patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab) for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated. Hence there was no hint of an added benefit of pembrolizumab in comparison with the ACT BSC. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of pembrolizumab in adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen (patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab) for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated, an added benefit of pembrolizumab for these patients is not proven.

2.4.4 List of included studies

Not applicable as the company presented no data for the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 19.

Table 19: Pembrolizumab – extent and probability of added benefit

Therapeutic indication		**ACT**[a]	**Extent and probability of added benefit**
Adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen; patients with EGFR- or ALK-positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab	Patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated	**Docetaxel** or pemetrexed or nivolumab (pemetrexed: except in mainly squamous histology; nivolumab: only in squamous histology)	Indication of considerable added benefit
	Patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated[b]	BSC[c]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: This applies especially to patients for whom cytotoxic chemotherapy is not an option due to their reduced general condition – for instance, these may be patients with an ECOG PS 4, 3 or possibly 2.
c: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

This assessment regarding the extent and probability of the added benefit deviates from that of the company, which derived an indication of major added benefit for adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen for whom treatment with docetaxel, pemetrexed or nivolumab is indicated.

According to the company, no conclusions on the added benefit can be drawn for adult patients with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen for whom treatment with docetaxel, pemetrexed or nivolumab or docetaxel is not indicated.

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

References for English extract

Please see full dossier assessment for full reference list.

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