IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Nivolumab (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Nivolumab (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 November 2015). 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
BSA	body surface area
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
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)
LCSS	Lung Cancer Symptom Scale
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TI	therapeutic indication
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 nivolumab. 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 17 August 2015.

Research question

The aim of this report was to assess the added benefit of nivolumab compared with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy.

The G-BA defined docetaxel as ACT for patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy. For patients for whom treatment with docetaxel is not indicated, the G-BA specified best supportive care (BSC) as ACT.

This resulted in the following 2 research questions for the benefit assessment:

Table 2: Research questions and ACTs for nivolumab

Research question	Subindication[a]	Appropriate comparator therapy
1	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is indicated	Docetaxel
2	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is not indicated[b]	BSC[c]

a: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB/IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. Treatment is palliative. After completion of the first-line treatment, subsequent therapy depends on the course of disease, general condition, success and tolerability of the first-line treatment, accompanying diseases and the patient's treatment request. It is also assumed that the patients received platinum-based chemotherapy in their first-line treatment.
b: This applies especially to patients for whom cytotoxic chemotherapy is not indicated due to their reduced general condition (in particular, these may be patients with an ECOG PS 4, 3 and 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; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The present assessment was conducted in comparison with the ACT specified by the G-BA. Patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1

and possibly 2 were considered relevant for research question 1, and patients with an ECOG PS 4, 3 and possibly 2 were considered relevant for research question 2.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

Research question 1: patients for whom treatment with docetaxel is indicated

The study CA209-017 was included in the benefit assessment.

Study characteristics

The CA209-017 study was a randomized, open-label, active-controlled approval study on the comparison of nivolumab and docetaxel, in which adult patients with locally advanced or metastatic squamous NSCLC after pretreatment with platinum-based chemotherapy were included.

The patients had to present with stage IIIB or IV disease according to the International Association for the Study of Lung Cancer (IASLC) or with recurrent or progressive disease following multimodal therapy and had to have a good general condition (corresponding to ECOG PS 0 or 1). A total of 272 patients were randomized in a ratio of 1:1 (135 patients to the nivolumab arm and 137 patients to the docetaxel arm).

The administration of nivolumab in the study was in compliance with the requirements of the Summary of Product Characteristics (SPC). In contrast, the administration of docetaxel deviated from the SPC because of the possibility of a 2-step dose reduction from 75 mg/m^2 body surface area (BSA) to 55 mg/m^2 BSA and possibly to 37.5 mg/m^2 BSA. The SPC only recommends a single reduction to 60 mg/m^2. However, since only 9.3% of all doses were reduced, it is not assumed that this had a relevant influence on the results.

Overall survival was the primary outcome of the study; symptoms, health status, health-related quality of life and adverse events (AEs) were secondary outcomes.

In the CA209-017 study, the final analysis on overall survival was planned after at least 231 deaths, and an interim analysis after at least 196 deaths. The study was ended prematurely because the formal interim analysis conducted by the Data Monitoring Committee (DMC) (data cut-off on 15 December 2014) showed a statistically significant difference in favour of nivolumab for overall survival.

Risk of bias

The risk of bias at study level was rated as low for the CA209-017 study.

Evaluable results were available only for the outcomes “overall survival”, “treatment discontinuation due to AEs”, “severe AEs (Common Terminology Criteria for Adverse

Events [CTCAE] grade 3-4)" and "specific AEs". The risk of bias for the outcome "overall survival" was rated as low.

A high risk of bias was assumed for the outcome "treatment discontinuation due to AEs" because of possible subjective influencing from the open-label study design and possible informative censoring in different observation durations between the study arms (mean observation duration 6.75 months under nivolumab and 3.39 months under docetaxel). The risk of bias for the outcome "severe AEs (CTCAE grade 3-4)" was also rated as high because of potential informative censoring with great differences in observation periods. The risk of bias for specific AEs was not assessed because survival time analyses were lacking for these AEs so that the results were only considered in qualitative terms.

No evaluable data were available on the benefit outcomes "symptoms", "health status" and "health-related quality of life" because of the low proportion of analysed patients (already under 70% at the start of the study). The results on serious adverse events (SAEs) were not evaluable because of the high proportion of recorded results representing progression of the underlying disease.

Results

Mortality

There was a statistically significant advantage of nivolumab compared with docetaxel for the outcome "overall survival".

There was proof of an effect modification by the characteristic "age" for this outcome. The results for patients < 75 years and ≥ 75 years were therefore interpreted separately. There was an indication of an added benefit of nivolumab in comparison with docetaxel for patients under 75 years of age. There was no hint of an added benefit for patients older than 75 years; an added benefit is therefore not proven for this patient group.

Morbidity

The dossier contained no evaluable data for the outcomes "symptoms" recorded with the questions 1 to 6 of the Lung Cancer Symptom Scale (LCSS) questionnaire, and "health status" recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel for these outcomes; an added benefit is therefore not proven.

Health-related quality of life

No suitable data were available for the outcome "health-related quality of life" measured with the questions 7 to 9 of the LCSS questionnaire. Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel for this outcome; an added benefit is therefore not proven.

Adverse events

- Treatment discontinuation due to adverse events

There was a statistically significant result in favour of nivolumab for the outcome "treatment discontinuation due to AEs". Comparatively few progression events were documented under this outcome, and these were almost equally distributed between both arms, so that the results of the time to first event were interpretable with sufficient certainty. There was a hint of lesser harm from nivolumab in comparison with docetaxel.

- Severe adverse events (CTCAE grade 3-4)

There was a statistically significant result in favour of nivolumab for the outcome "severe AEs (CTCAE grade 3-4)". Under this outcome, 3.1 to 10.7% of the results (nivolumab arm) and 2.3 to 7.0% of the results (docetaxel arm) were recorded as progression events. However, the effect in favour of nivolumab was so pronounced that the consideration of the events of disease progression did not raise doubts about this effect and that the results of the time to first event were interpretable with sufficient certainty for the benefit assessment. There was a hint of lesser harm from nivolumab in comparison with docetaxel for severe AEs (CTCAE grade 3-4).

- Serious adverse events

The survival time analyses on SAEs presented by the company were not evaluable because of the high proportion of events caused by progression of the underlying disease. Based on the qualitative consideration of the naive proportions of the patients with events, there was at least no sign of a disadvantage of nivolumab despite the longer observation period in the nivolumab arm. Hence there was no hint of greater or lesser harm from nivolumab compared with docetaxel for this outcome; greater or lesser harm is therefore not proven for this outcome.

- Specific adverse events

Due to the different observation durations in the 2 treatment arms and the lack of survival time analyses for specific AEs (myalgia, peripheral neuropathy, alopecia and blood and lymphatic system disorders), the naive proportions were interpreted in qualitative terms. Despite the considerably shorter observation duration, notably more events occurred in the docetaxel arm for these AEs; and, in addition, the absolute number of events in the nivolumab arm was very low. Due to the open-label study design, there was a hint of lesser harm of nivolumab compared with docetaxel for the non-severe specific AEs "myalgia", "peripheral neuropathy", and "alopecia". There was an indication of lesser harm of nivolumab compared with docetaxel for the severe specific AE "blood and lymphatic system disorders".

Research question 2: patients for whom treatment with docetaxel is not indicated

No data were available for the assessment of the added benefit of nivolumab in comparison with BSC in patients for whom treatment with docetaxel is not indicated. Hence there is no

hint of an added benefit of nivolumab in comparison with the ACT 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 nivolumab versus the ACT is assessed as follows.

Research question 1: patients for whom treatment with docetaxel is indicated

Patients < 75 years

For patients under 75 years of age, there was an indication of major added benefit of nivolumab for the outcome "overall survival", and hints of major added benefit of nivolumab for the outcomes "treatment discontinuation due to AEs" and "severe AEs (CTCAE grade 3-4)" on the side of positive effects. SAEs were not finally assessed because of the data availability. The qualitative assessment of the naive proportions of the patients with at least one SAE did not raise doubts about the effects in favour of nivolumab, however. There was a hint of lesser harm of nivolumab with the extent "considerable" for the specific AEs "myalgia", "peripheral neuropathy" and "alopecia". There was an indication of lesser harm with the extent "major" for the outcome "blood and lymphatic system disorders (severe AE with CTCAE grade 3-4)". No evaluable data were available for the outcomes on morbidity and health-related quality of life.

Overall, there is an indication of major added benefit of nivolumab in comparison with the ACT docetaxel for patients for whom docetaxel treatment is indicated and who are younger than 75 years.

Patients ≥ 75 years

There was no hint of an added benefit for the outcome "overall survival" for patient ≥ 75 years; an added benefit is therefore not proven for this outcome in this patient group. Due to the position of the effect estimate and the width of the confidence interval, an important negative effect of nivolumab in this patient group cannot be excluded with certainty. At the same time, there are hints of major added benefit of nivolumab for the outcomes "treatment discontinuation due to AEs" and "severe AEs (CTCAE grade 3-4)" for patients over 75 years of age on the side of positive effects. The outcome "SAEs" was not finally assessed because of the data availability. The qualitative assessment of the naive

[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].

proportions of the patients with at least one SAE did not raise doubts about the effects in favour of nivolumab, however. There was a hint of lesser harm of nivolumab with the extent "considerable" for the specific AEs "myalgia", "peripheral neuropathy" and "alopecia". There was an indication of lesser harm with the extent "major" for the outcome "blood and lymphatic system disorders (severe AE with CTCAE grade 3-4)". No evaluable data were available for the outcomes on morbidity and health-related quality of life.

Overall, a hint of a non-quantifiable added benefit of nivolumab versus the ACT docetaxel remains for patients who are 75 years of age or older.

Research question 2: patients for whom treatment with docetaxel is not indicated

Since the company presented no evaluable data for patients for whom treatment with docetaxel is not indicated, an added benefit of nivolumab in comparison with BSC is not proven for this subpopulation.

Extent and probability of added benefit – summary

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

Table 3: Nivolumab – extent and probability of added benefit

Research question	**Subindication**	**ACT**	**Subgroup**	**Extent and probability of added benefit**
1	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is indicated	Docetaxel	< 75 years	Indication of major added benefit
			≥ 75 years	hint of a non-quantifiable added benefit
2	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is not indicated	BSC	Added benefit not proven	
ACT: appropriate comparator therapy; BSC: best supportive care; NSCLC: non-small cell lung cancer				

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 nivolumab compared with the ACT in adult patients with locally advanced or metastatic squamous NSCLC after prior chemotherapy.

The G-BA defined docetaxel as ACT for patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy. For patients for whom treatment with docetaxel is not indicated, the G-BA specified BSC as ACT. 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.

This resulted in the following 2 research questions for the benefit assessment:

Table 4: Research questions and ACTs for nivolumab

Research question	Subindication[a]	ACT
1	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is indicated	Docetaxel
2	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is not indicated[b]	BSC[c]

a: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB/IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. Treatment is palliative. After completion of the first-line treatment, subsequent therapy depends on the course of disease, general condition, success and tolerability of the first-line treatment, accompanying diseases and the patient's treatment request. It is also assumed that the patients received platinum-based chemotherapy in their first-line treatment.
b: This applies especially to patients for whom cytotoxic chemotherapy is not indicated due to their reduced general condition (in particular, these may be patients with an ECOG PS 4, 3 and 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; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The present assessment was conducted in comparison with the ACT specified by the G-BA. Patients with an ECOG PS 0, 1 and possibly 2 were considered relevant for research question 1, and patients with an ECOG PS 4, 3 and possibly 2 were considered relevant for research question 2. This concurs with the company's approach.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 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 nivolumab (status: 23 July 2015)
- bibliographical literature search on nivolumab (last search on 3 June 2015)
- search in trial registries for studies on nivolumab (last search on 16 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 3 September 2015)

No additional relevant study was identified from the check.

2.3.1 Research question 1: patients for whom treatment with docetaxel is indicated

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: nivolumab 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)
CA209-017	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of nivolumab in comparison with docetaxel consisted of the CA209-017 study and concurred with that of the company.

Section 2.6 contains a reference list for the study included.

2.3.1.2 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: nivolumab vs. docetaxel

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-017	RCT, open-label, parallel with optional extension phase[b]	Adult patients with histologically or cytologically confirmed NSCLC stage IIIB/IV[c, d] according to IASLC, following prior platinum-based chemotherapy, ECOG PS 0 or 1	Nivolumab (N = 135) docetaxel (N = 137)	Screening: within 28 days before randomization Treatment phase: until occurrence of disease progression (or, in the nivolumab arm, after progression for as long as the investigator considers the treatment to be beneficial to the patient), an unacceptable AE or withdrawal of consent Observation phase: outcome-specific, at most up to death, lost to follow-up or discontinuation of study participation	95 centres in 21 countries (Argentina, Australia, Austria, Canada, Chile, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Netherlands, Norway, Peru, Poland, Romania, Russia, Spain, United Kingdom, USA) 10/2012–11/2014	Primary: overall survival Secondary: symptoms, health status, health-related quality of life, AEs

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: According to the information provided in Amendment 11 to the study protocol (26 January 2015), which was included after the final analysis of the outcome "overall survival", patients in the docetaxel arm could be treated with nivolumab in the optional extension phase.
c: Stratified by pretreatment (paclitaxel: yes vs. no) and region (USA/Canada vs. Europe vs. rest of the world).
d: Patients with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive radiochemotherapy for locally advanced disease) were also eligible for study inclusion.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IASLC: International Association for the Study of Lung Cancer; N: number of randomized patients; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: nivolumab vs. docetaxel

Study	Intervention	Comparison	Prior and concomitant medication
CA209-017	No premedication envisaged	Premedication with dexamethasone 8 mg BID, orally, on the day before, on the same day, and on the day after administration of docetaxel	**Pretreatment** ▪ no pretreatment with docetaxel and T-cell costimulating drugs including ipilimumab **Concomitant treatment** ▪ drugs for the treatment of symptoms associated with the disease if this treatment was started before the first dose of the study medication ▪ palliative radiotherapy (only non-target bone lesions or CNS lesions) **Non-permitted concomitant treatment** ▪ concomitant administration of antineoplastic treatment: e.g. chemotherapy, hormonal therapy, immunotherapy ▪ immunosuppressants ▪ immunosuppressant doses of systemic corticosteroids (> 10 mg/day prednisolone equivalent) ▪ strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin
	nivolumab 3 mg/kg body weight every 2 weeks IV no dose escalation or reduction allowed	docetaxel 75 mg/m² BSA every 3 weeks IV dose reduction in 2 steps[a] on occurrence of prespecified AEs[b]	
	Postponement of the planned dose up to < 6 weeks allowed		

a: Reduction step 1: to 55 mg/m^2 BSA; reduction step 2: to 37.5 mg/m^2 BSA.
b: The docetaxel dose could be reduced if the following treatment-induced AEs occurred: febrile neutropenia, neutrophil count < 500/mm^3 for longer than 7 days, severe and cumulative skin reactions or non-haematological toxicity CTCAE grade 3-4.
AE: adverse event; BID: twice daily; BSA: body surface area; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; IV: intravenous; RCT: randomized controlled trial; vs.: versus

Study design

The CA209-017 study was a randomized, open-label, active-controlled approval study on the comparison of nivolumab and docetaxel. The CA209-017 study was a multicentre study conducted in 95 centres in 21 countries.

Patients with locally advanced or metastatic squamous NSCLC after pretreatment with platinum-based chemotherapy were included in the study. The patients had to present with stage IIIB or IV disease according to the IASLC or with recurrent or progressive disease following multimodal therapy. They also had to have a good general condition (corresponding to ECOG PS 0 or 1). The population investigated in the study corresponds to the therapeutic indication of nivolumab in the present research question (for more details, see Section 2.7.2.4.1 of the full dossier assessment). Since no patients with ECOG PS 2 were included in the CA209-017 study, no conclusions can be derived from the available data for these patients.

The patients were stratified by pretreatment with paclitaxel (yes versus no) and region (USA/Canada versus Europe versus rest of the world) and randomly assigned to nivolumab or docetaxel in a ratio of 1:1. A total of 272 patients were randomized (135 patients to the nivolumab arm and 137 patients to the docetaxel arm).

The patients in the nivolumab arm received 3 mg nivolumab per kg body weight intravenously every 2 weeks; dose modification was not allowed. This concurs with the requirement of the SPC [3].

The patients in the docetaxel arm received 75 mg docetaxel per m^2 BSA intravenously every 3 weeks. Premedication consisting of dexamethasone (8 mg twice daily) was given for 3 days, starting with the day before administration of docetaxel. On occurrence of prespecified treatment-induced AEs, the docetaxel dose was reduced in 2 steps to 55 mg/m^2 and subsequently to 37.5 mg/m^2 BSA. According to the specifications of the SPC of docetaxel, however, only a single dose reduction to 60 mg/m^2 BSA is recommended [4]. However, since only 9.3% of all doses were reduced, it is not assumed that this had a relevant influence on the results.

Patients in both study arms could additionally receive drugs for the treatment of symptoms associated with the disease if this treatment had already started before the first study dose. Palliative radiotherapy was only allowed for the treatment of non-target bone lesions or CNS lesions. Restrictions beyond that referred to therapy with antineoplastic treatments, among other things. No relevant differences that could not be explained by the administration of docetaxel itself (e.g. premedication with dexamethasone) were shown between the study arms.

Treatment in both study arms was to be conducted until withdrawal of consent, occurrence of unacceptable AEs or occurrence of disease progression (measured with the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1). The patients in the nivolumab arm could also continue their treatment after progression if the investigator considered the treatment to be still beneficial to the patient. This was the case in 21% of the patients in the nivolumab arm. The different specifications on treatment discontinuation in the 2 study arms do not contradict the corresponding SPCs [3,4], but they contributed to the longer treatment and observation period in the nivolumab arm (see Section on the duration of treatment and follow-up below).

There were no restrictions regarding the administration of subsequent therapy after completion of the randomized treatment phase. Almost half of the patients (48.9%) in the nivolumab arm received subsequent therapy; and 38.7% in the docetaxel arm. The most common subsequent therapies were radiotherapy (20.0% in the nivolumab arm and 17.5% in the docetaxel arm) and chemotherapy (35.6% in the nivolumab arm and 24.1% in the docetaxel arm). Subsequent therapy with docetaxel was notably more common in the nivolumab arm than in the docetaxel arm (24.4% and 3.6% of the patients).

Analysis and data cut-offs

Overall survival was the primary outcome of the study; symptoms, health status, health-related quality of life and AEs were secondary outcomes.

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: nivolumab vs. docetaxel

Study Outcome category	Planned follow-up
CA209-017	
Overall survival	Until death, discontinuation of participation in the study or lost to follow-up
Symptoms and health-related quality of life (LCSS)	Up to 100 days after treatment discontinuation
Health status (EQ-5D VAS)	In parallel with overall survival[a]
Adverse events	Up to 100 days after treatment discontinuation
a: According to the study documents, "as allowed by local legislation". The effects on the recording/analysis remain unclear. EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

Two follow-up visits, after 30 and after 100 days, were planned in the CA209-017 study after the end of the randomized treatment phase. The outcomes on symptoms and health-related quality of life, both recorded with the LCSS, as well as AEs were recorded up to the second follow-up visit. Overall survival and health status according to the EQ-5D VAS were recorded until the end of participation in the study.

The planned duration of the CA209-017 study depended on reaching a predefined number of deaths. The final analysis on overall survival was planned after at least 231 deaths, and an interim analysis after at least 196 deaths. The study was ended prematurely because the formal interim analysis conducted by the DMC (data cut-off on 15 December 2014) showed a statistically significant difference in favour of nivolumab for overall survival. Subsequently, patients in the docetaxel arm were provided with the possibility to participate in an optional extension phase with nivolumab. The present benefit assessment refers to the results of the data cut-off from 15 December 2014. The data of this data cut-off were not yet affected by the treatment switching. The CA209-017 study is continued as extension study.

Characteristics of the study populations

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

Table 9: Characteristics of the study populations – RCT, direct comparison: nivolumab vs. docetaxel

Study **Characteristics** **Category**	**Nivolumab** **N = 135[a]**	**Docetaxel** **N = 137[a]**
CA209-017		
Age [years], mean (SD)	62 (8)	64 (8)
Sex [F/M], %	18/82	29/71
Ethnicity, n (%)		
White	122 (90.4)	130 (94.9)
Black/African American	6 (4.4)	2 (1.5)
Others[b]	7 (5.2)[c]	5 (3.6)[c]
Region, n (%)		
USA/Canada	43 (31.9)	43 (31.4)
Europe	77 (57.0)	78 (56.9)
Rest of the world	15 (11.1)	16 (11.7)
Disease stage, n (%)		
IIIB	29 (21.5)	24 (17.5)
IV	105 (77.8)	112 (81.8)
Not reported	1 (0.7)	1 (0.7)
ECOG performance status, n (%)		
0	27 (20.0)	37 (27.0)
1	106 (78.5)	100 (73.0)
Not reported	2 (1.5)	0
PD-L1 status, n (%)		
Positive (≥ 5% tumour cell membrane staining)	42 (31.1)	39 (28.5)
Negative (< 5% tumour cell membrane staining)	75 (55.6[c])	69 (50.4[c])
Non-quantifiable	18 (13.3)	29 (21.2)
CNS metastases, n (%)		
Yes	9 (6.7)	8 (5.8)
No	126 (93.3)	129 (94.2)
Smoking status, n (%)		
Current/former smoker	121 (89.6)	129 (94.2)
Never smoker	10 (7.4)	7 (5.1)
Unknown	4 (3.0)	1 (0.7)
Disease duration: time between diagnosis and randomization [years], median [min; max]	0.74 (0.1; 10.0)	0.73 (0.1; 4.6)
Pretreatment with platinum-based therapy, n (%)		
Cisplatin	54 (40.0)	36 (26.3)
Carboplatin	81 (60.0)	101 (73.7)
Other	0 (0)	0 (0)

(continued)

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

Study **Characteristics** **Category**	**Nivolumab** **N = 135[a]**	**Docetaxel** **N = 137[a]**
Pretreatment with paclitaxel, n (%)		
Yes	46 (34.1)	46 (33.6)
No	89 (65.9)	91 (66.4)
Study discontinuations, n (%)	ND[d]	ND[d]
Treatment discontinuations, n (%)	110 (84.0)[e]	127 (98.4)[e]

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: Including Asians, American Indians or Native Alaskans, Hawaiians or Pacific islanders, "others" and "not reported".
c: Institute's calculation.
d: No explicit information available, number cannot be derived.
e: Information for the treated patients (nivolumab: N = 131, docetaxel: N = 129). The most common reason for treatment discontinuation was disease progression (nivolumab arm: 67.2%; docetaxel arm: 62.0%).
CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; F: female; M: male; max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and disease-specific patient characteristics were sufficiently comparable between the 2 study arms.

The mean age of the patients in the CA209-017 study was 62 and 64 years (nivolumab and docetaxel arm). The majority of the patients were white men originating from Europe, the USA or Canada. The proportion of current or former smokers was 89.6% in the nivolumab arm and 94.2% in the docetaxel arm.

The median disease duration at the start of the study was about 9 months. Most patients had stage IV disease and an ECOG PS of 1. Only a small proportion of the patients had CNS metastases (< 7%).

The proportion of treatment discontinuations was 84.0% in the nivolumab arm and 98.4% in the docetaxel arm. There was no information on patients who discontinued the study.

Duration of treatment and follow-up

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

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

Study **Duration of the study phase** **Outcome category**	**Nivolumab** **N = 135**	**Docetaxel** **N = 137**
CA209-017		
Treatment duration[a] [months]		
Median [min; max]	3.25 [< 0.1; 21.7]	1.41 [< 0.1; 20.0]
Mean (SD)	5.94 (6.08)	2.47 (2.93)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	9.23 [4.63; 14.19]	5.95 [3.02; 11.07]
Mean (SD)	9.79 (6.13)	7.39 (5.49)
Adverse events		
Median [Q1; Q3]	ND	ND
Mean (SD) 30 days follow-up/ mean (SD) 100 days follow-up	6.75[b] (ND)/8.08[b] (ND)	3.39[b] (ND)/4.96[b] (ND)
Symptoms, health status, health-related quality of life		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND

a: Information for the treated patients: nivolumab N = 131, docetaxel N = 129.
b: Institute's calculation.
max: maximum; min: minimum; N: number of randomized patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment durations differed considerably between the 2 study arms (3.25 months under nivolumab and only 1.41 months under docetaxel). The observation periods for the outcomes "overall survival" and on AEs were also considerably longer in the nivolumab arm. The treatment duration and the associated observation period for the outcomes on AEs were mainly caused by discontinuation of the study treatment due to disease progression and by the different requirements on treatment discontinuation in the 2 study arms. The resulting consequences are explained in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment. No information on the observation duration was available for the outcomes on morbidity (symptoms and health status) and health-related quality of life.

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: nivolumab 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			
CA209-017	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment. Restrictions resulting from the open-label study design and the different observation periods in the treatment arms are described in Section 2.4.1.2 and in Section 2.7.2.4.2 of the full dossier assessment under the outcome-specific risk of bias.

2.3.2 Research question 2: patients for whom treatment with docetaxel is not indicated

The company presented no study for the assessment of the added benefit of nivolumab in comparison with BSC in patients for whom treatment with docetaxel is not indicated. Instead it argued that the advantage of nivolumab observed in research question 1 is transferable to the patients for whom docetaxel is not indicated. The company's rationale was not followed (see Section 2.7.2.3.2 of the full dossier assessment). Overall, no relevant data were therefore available for the assessment of the added benefit of nivolumab in patients for whom treatment with docetaxel is not indicated.

2.4 Results on added benefit

2.4.1 Research question 1: patients for whom treatment with docetaxel is indicated

2.4.1.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom questions of the LCSS questionnaire
  - health status measured with the VAS of the EQ-5D questionnaire
- Health-related quality of life
  - measured with the summation items of the LCSS questionnaire
- Adverse events
  - SAEs
  - treatment discontinuation due to AEs
  - severe AEs (CTCAE grade 3-4)
  - if applicable, specific AEs (common AEs with potentially important differences between the treatment arms)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.7.2.4.3 of the full dossier assessment).

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

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

Study	Outcomes							
	Overall survival	Symptoms (LCSS)[a]	Health status (EQ-5D VAS)	Health-related quality of life (LCSS)[b]	SAEs	Treatment discontinuation due to AEs	Severe AEs (CTCAE grade 3-4)	Specific AEs
CA209-017	Yes	No[c]	No[c]	No[c]	No[c]	Yes	Yes	(Yes)[d]

a: Measured with the symptom questions (1 to 6) of the LCSS.
b: Measured with the summation items (7 to 9) of the LCSS.
c: No evaluable data available; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.
d: Results only interpretable in qualitative terms; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.1.2 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: nivolumab vs. docetaxel

Study	Study level	Outcomes							
		Overall survival	Symptoms (LCSS)[a]	Health status (EQ-5D VAS)	Health-related quality of life (LCSS)[b]	SAEs	Treatment discontinuation due to AEs	Severe AEs (CTCAE grade 3-4)	Specific AEs
CA209-017	L	L	-[c]	-[c]	-[c]	-[c]	H[d]	H[e]	-[f]

a: Measured with the symptom questions (1 to 6) of the LCSS.
b: Measured with the summation items (7 to 9) of the LCSS.
c: No evaluable data available (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment).
d: Possibly subjective influencing due to the open-label study design, great differences in observation periods with potential informative censoring (see Section 2.7.2.4.2 of the full dossier assessment).
e: Great differences in observation periods with potential informative censoring (see Section 2.7.2.4.2 of the full dossier assessment).
f: Only qualitative interpretation of the results possible (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; LCSS: Lung Cancer Symptom Scale; 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.

No evaluable data were available on the outcomes on symptoms, health status and health-related quality of life because of the low proportion of analysed patients (already under 70% at the start of the study). The risk of bias for these outcomes was therefore not assessed. This assessment deviates from that of the company. The company rated the risk of bias for these outcomes as high and used the results for the assessment of the added benefit.

Results based on the 30-day follow-up visit were considered for the assessment of the data on the outcomes on AEs (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

A high risk of bias was assumed for the outcome “treatment discontinuation due to AEs” because of possible subjective influencing from the open-label study design and different observation periods with potential informative censoring. This assessment concurs with that of the company.

The risk of bias for the outcome "severe AEs (CTCAE grade 3-4)" was also rated as high because of the great differences in observation periods with potential informative censoring. This deviates from the company's evaluation, which assumed a low risk of bias.

The results on SAEs were not evaluable because of the high proportion of recorded results representing progression of the underlying disease (see Table 24 in Appendix B of the full dossier assessment). This deviates from the company's assessment, which rated the risk of bias as low and used the results on SAEs for the assessment of the added benefit.

The results on the specific AEs with potentially notable differences were only considered in qualitative terms: There were no survival time analyses for these AEs, which represent an adequate analysis in different lengths of observation periods in the 2 study arms. The risk of bias for these harm outcomes was therefore not assessed. The choice of specific AEs in the present benefit assessment deviates from that of the company. Moreover, the company did not use the specific AEs it had defined to assess the added benefit.

In summary, evaluable results were only available for the outcomes "overall survival", "treatment discontinuation due to AEs", "severe AEs" and "specific AEs". For the reasons stated above, for the harm outcomes "treatment discontinuation due to AEs" and "severe AEs", at most a hint, and for the outcome "overall survival" at most an indication of an added benefit or harm of nivolumab was derived.

2.4.1.3 Results

Table 14 summarizes the results on the comparison of nivolumab with docetaxel in patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is indicated. The Kaplan-Meier curve on overall survival is presented in Appendix A of the full dossier assessment. Common AEs with potentially important differences between the treatment arms are presented in Table 15.

Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 14: Results – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome	Nivolumab		Docetaxel		Nivolumab vs. docetaxel	
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
CA209-017						
Mortality						
Overall survival	135	9.23 [7.33; 13.27][c] 86 (63.7)	137	6.01 [5.13; 7.33][c] 113 (82.5)	0.59 [0.44; 0.79]	< 0.001
Morbidity						
Symptoms (LCSS)	No evaluable data[d]					
Health status (EQ-5D VAS)	No evaluable data[d]					
Health-related quality of life						
LCSS	No evaluable data[d]					
Adverse events	**N**	**Median time to first AE in months [95% CI] Patients with event n (%)**	**N**	**Median time to first AE in months [95% CI] Patients with event n (%)**	**HR [95% CI][a]**	**p-value[b]**
AEs[e] (supplementary information)	131	0.30 [0.26; 0.49] 127 (96.9)	129	0.16 [0.13; 0.23] 125 (96.9)	-	-
SAEs	No evaluable data[f]					
Treatment discontinuation due to AEs[e]	131	NC [NC; NC] 14 (10.7)	129	NC [6.83; NC] 26 (20.2)	0.31 [0.16; 0.62]	< 0.001
Severe AEs (CTCAE grade 3-4)[e]	131	9.56 [4.70; NC] 57 (43.5)	129	0.33 [0.26; 0.92] 93 (72.1)	0.25 [0.17; 0.36]	< 0.001

a: Cox model, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
b: Log-rank test, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
c: The 2-sided 95% CI was calculated with a log-log transformation (according to Brookmeyer and Crowley).
d: Proportion of the patients included in the analysis too small.
e: Including events reported between the first dose and 30 days after the last dose of the study medication.
f: The analyses presented by the company in Module 4 B include a large number of events caused by progression of the underlying disease.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IVRS: interactive voice response system; LCSS: Lung Cancer Symptom Scale; N: number of analysed patients; NC: not calculated or not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Table 15: Results (common AEs with potentially important differences between the treatment arms), 30 days follow-up – RCT, direct comparison: nivolumab vs. docetaxel

Study	Nivolumab		Docetaxel	
Outcome category Outcome	N	Patients with event n (%)	N	Patients with event n (%)
CA209-017				
Specific adverse events				
Myalgia[a]	131	3 (2.3)	129	15 (11.6)
Peripheral neuropathy[a]	131	4 (3.1)	129	15 (11.6)
Alopecia[a]	131	1 (0.8)	129	29 (22.5)
Blood and lymphatic system disorders (severe AEs with CTCAE grade 3-4)[b]	131	5 (3.8)	129	50 (38.8)

a: MedDRA PT.
b: MedDRA SOC.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least one) event; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Mortality

Overall survival

A statistically significant advantage of nivolumab was shown for the outcome "overall survival".

However, there was proof of an effect modification by the characteristic "age (< 75 years, ≥ 75 years)" for this outcome. The results for patients < 75 years and ≥ 75 years were therefore interpreted separately (see Section 2.4.1.4). For the outcome "overall survival", there was an indication of an added benefit of nivolumab in comparison with docetaxel for patients under 75 years of age. There was no hint of an added benefit for patients older than 75 years; an added benefit is therefore not proven for this patient group.

This deviates from the company's assessment, which did not rely on the result of the interaction test because of the small patient numbers in the subgroup ≥ 75 years and therefore used only the results of the total population for the derivation of the added benefit. Based on the total population, the company derived proof of an added benefit for this outcome.

Morbidity

Symptoms and health status

The dossier contained no evaluable data for the outcomes "symptoms" recorded with the questions 1 to 6 of the LCSS questionnaire, and "health status" recorded with the EQ-5D VAS (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment). Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel for these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment, which used the analyses, but derived no added benefit because of missing statistically significant or clinically relevant differences.

Health-related quality of life

No suitable data were available for the outcome "health-related quality of life" measured with the questions 7 to 9 of the LCSS questionnaire (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment). Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel for this outcome; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived a hint of an added benefit for this outcome.

Adverse events

Treatment discontinuation due to AEs

There was a statistically significant result in favour of nivolumab for the outcome "treatment discontinuation due to AEs". For this outcome, there was an uncertainty of how progression of the underlying disease was to be treated in the recording of events (see Section 2.7.2.4.3 of the full dossier assessment). However, inspection of the study results showed that comparatively few progression events were documented under this outcome, and that these were almost equally distributed between both arms, so that the results of the time to first event were interpretable with sufficient certainty. Moreover, the effect in favour of nivolumab in each case was so pronounced that the additional consideration of the events of disease progression did not raise doubts about this effect. Hence there was a hint of lesser harm from nivolumab in comparison with docetaxel.

This assessment deviates from that of the company, which derived an indication of an added benefit of nivolumab for the outcome "treatment discontinuation due to AEs".

Severe adverse events (CTCAE grade 3-4)

There was a statistically significant result in favour of nivolumab for the outcome "severe AEs (CTCAE grade 3-4)". For this outcome, there was an uncertainty of how progression of the underlying disease was to be treated in the recording of events (see Section 2.7.2.4.3 of the full dossier assessment). Inspection of the study results showed that 3.1 to 10.7% events (nivolumab arm) and 2.3 to 7.0% events (docetaxel arm) were recorded as progression events under this outcome. However, the effect in favour of nivolumab was so pronounced that the consideration of the events of disease progression did not raise doubts about this effect and that the results of the time to first event were interpretable with sufficient certainty for the benefit assessment. There was a hint of lesser harm from nivolumab in comparison with docetaxel for severe AEs (CTCAE grade 3-4).

This assessment deviates from that of the company, which derived proof of an added benefit of nivolumab for the outcome "severe AEs (CTCAE grade 3-4)".

Serious adverse events

The survival time analyses on SAEs presented by the company were not evaluable because of the high proportion of events caused by progression of the underlying disease (see Section 2.7.2.4.3 and Table 24, Appendix B, of the full dossier assessment). Based on the qualitative consideration of the naive proportions of the patients with events, there was at least no sign of a disadvantage of nivolumab despite the longer observation period in the nivolumab arm. Hence there was no hint of greater or lesser harm from nivolumab for this outcome; greater or lesser harm is therefore not proven for this outcome.

This deviates from the company's assessment, which derived proof of an added benefit of nivolumab for the outcome "SAEs".

Specific adverse events

The common AEs with potentially important differences between the treatment arms listed in Table 15 were identified in the tables presented in Appendix B of the full dossier assessment. Due to the different observation periods in the 2 treatment arms and the missing survival time analyses for these outcomes, the naive proportions were only interpreted in qualitative terms. There was potential informative censoring also for these outcomes. Despite the considerably shorter observation duration, notably more events occurred in the docetaxel arm for these AEs; and, in addition, the absolute number of events in the nivolumab arm was very low. The potential informative censoring was therefore in a magnitude that had no important influence on the results. There was an indication of lesser harm of nivolumab compared with docetaxel for the severe specific AE "blood and lymphatic system disorders". Because of the possible subjective influencing due to the open-label study design, there was a hint of lesser harm of nivolumab compared with docetaxel for the non-severe specific AEs "myalgia", "peripheral neuropathy", and "alopecia".

2.4.1.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- region I (USA/Canada, Europe, rest of the world)
- age group III (< 65 years, ≥ 65 to < 75 years, ≥ 75 years), the results of the subgroup II (< 75 years, ≥ 75 years) were used for the interpretation, however (see below for reasons)
- sex (male, female)
- ECOG PS (0, 1)
- disease stage (IIIB, IV)
- pretreatment with paclitaxel (yes, no)
- programmed cell death ligand 1 (PD-L1) status (positive, negative/non-quantifiable)

All subgroup characteristics and cut-off values mentioned were predefined in the CA209-017 study. However, only analyses for the outcome "overall survival" were presented in the dossier for the characteristic "pretreatment with paclitaxel (stratification characteristic)". Corresponding analyses were therefore not considered further.

Hereinafter, for the outcome "overall survival", only the results for subgroups are presented for which at least an indication of an effect modification was shown (p-value ≤ 0.2). There was a high risk of bias of possibly different degree in the subgroups for the remaining outcomes because of the different observation periods and informative censorings. Due to this uncertainty, only proof of interaction ($p < 0.05$) was considered for these outcomes (see Section 2.7.2.2 of the full dossier assessment).

The consideration of the subgroups by the characteristic "age" with the cut-off values < 65 years, ≥ 65 to < 75 years and ≥ 75 years (age group III) for the outcome "overall survival" resulted in an indication ($p = 0.060$), and for the outcome "severe AEs" (CTCAE grade 3-4) in proof ($p = 0.043$) of an effect modification. The pairwise consideration of neighbouring subgroups for both outcomes showed that there was no important heterogeneity between the subgroups < 65 years and ≥ 65 to < 75 years (interaction test overall survival: $p = 0.816$; interaction test severe AEs [CTCAE grade 3-4]: $p = 0.940$). As a result, the cut-off value of < 75 years, ≥ 75 years (corresponding to the age group II) was more adequate in the consideration of the subgroups by the characteristic "age" (see Table 16).

Table 16: Subgroups (dichotomous outcomes) – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median survival time in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median survival time in months [95% CI] Patients with event n (%)	Nivolumab vs. docetaxel HR [95% CI][a]	Nivolumab vs. docetaxel p-value[b]
CA209-017						
Overall survival						
Age						
< 75 years	124	9.54 [7.59; 15.54] 76 (61.3)	119	6.01 [5.06; 7.33] 100 (84.0)	0.53 [0.39; 0.72]	< 0.001
≥ 75 years	11	6.34 [2.60; 7.66] 10 (90.9)	18	6.37 [3.65; 15.54] 13 (72.2)	1.85 [0.76; 4.51]	0.167
					Interaction:	0.010[c]
	N	**Median time to first AE in months [95% CI] Patients with event n (%)**	**N**	**Median time to first AE in months [95% CI] Patients with event n (%)**		
Severe AEs (CTCAE grade 3-4)						
Age						
< 75 years	120	9.56 [4.70; NC] 55 (45.8)	112	0.54 [0.26; 1.38] 77 (68.8)	0.34 [0.23; 0.48]	< 0.001
≥ 75 years	11	NC [3.98; NC] 2 (18.2)	17	0.26 [0.16; 0.26] 16 (94.1)	0.04 [0.01; 0.29]	< 0.001
					Interaction:	0.020[c]

a: Unstratified Cox model.
b: Unstratified log-rank test.
c: Unstratified Cox model with treatment, subgroup characteristic and the interaction term treatment*subgroup characteristic for the assessment of the significance of the interaction between treatment and subgroup characteristic.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; NC: not calculable or not achieved; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

There was proof of an effect modification by the characteristic "age (< 75 years, ≥ 75 years)" for the outcome "overall survival".

A statistically significant effect in favour of nivolumab in comparison with docetaxel was shown for patients < 75 years. This resulted in an indication of an added benefit of nivolumab in comparison with docetaxel in patients < 75 years for this outcome.

There was no statistically significant difference between the treatment arms for patients ≥ 75 years. Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel for this outcome in patients ≥ 75 years; an added benefit for these patients is therefore not proven.

This deviates from the company's assessment, which, on the basis of the total population, derived proof of an added benefit and did not consider the proof of an effect modification.

Adverse events

Severe adverse events (CTCAE grade 3-4)

There was proof of an effect modification by the characteristic "age (< 75 years, ≥ 75 years)" for the outcome "severe AEs (CTCAE grade 3-4)".

A statistically significant effect in favour of nivolumab in comparison with docetaxel was shown for both subgroups. Since the results of the subgroup analyses did not differ from the total population regarding statistical significance and extent of the effect, they are not presented separately below.

The derivation of the added benefit of nivolumab for this outcome based on the total population corresponds to the company's approach. However, the company derived no hint for this outcome, but proof.

2.4.2 Research question 2: patients for whom treatment with docetaxel is not indicated

No data were available for the assessment of the added benefit of nivolumab in comparison with BSC in patients for whom treatment with docetaxel is not indicated (in particular, these may be patients with ECOG PS 4, 3 and possibly 2). Hence there is no hint of an added benefit of nivolumab in comparison with the ACT BSC. An added benefit is therefore not proven.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subpopulation is presented below at outcome level, taking into account the different 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.

2.5.1 Research question 1: patients for whom treatment with docetaxel is indicated

2.5.1.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 resulted in an indication of an added benefit of nivolumab in comparison with docetaxel for the total population for the outcome “overall survival”, and in hints of lesser harm for the outcomes “treatment discontinuation due to AEs” and “severe AEs (CTCAE grade 3-4)”. Only qualitative interpretation was possible of the results on specific AEs. The interpretation resulted in a hint of lesser harm of nivolumab in comparison with docetaxel for the specific AEs “myalgia”, “peripheral neuropathy” and “alopecia”, and in an indication of lesser harm for the outcome “blood and lymphatic system disorders”. In addition, there was proof of an effect modification by the subgroup characteristic “age” for the outcome “overall survival”.

The extent of the respective added benefit under consideration of the outcome category at outcome level was estimated from these results (see Table 17). The outcome “treatment discontinuation due to AEs” was allocated to the outcome category “serious/severe AEs” because of the high proportion of underlying severe events (about 64% and 77% of the patients in the nivolumab and in the docetaxel arm).

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. docetaxel** **Median of time to event** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Age		
< 75 years	9.54 vs. 6.01 months HR 0.53 [0.39; 0.72] p < 0.001 probability: "indication"	Outcome category: mortality CI_u < 0.85 added benefit, extent: "major"
≥ 75 years	6.34 vs. 6.37 months HR 1.85 [0.76; 4.51] p = 0.167	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (LCSS)	No evaluable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No evaluable data	Lesser benefit/added benefit not proven
Health-related quality of life		
LCSS	No evaluable data	Lesser benefit/added benefit not proven
Adverse events		
Serious adverse events	No evaluable data	Greater/lesser harm not proven
Treatment discontinuation due to AEs	NC vs. NC HR 0.31 [0.16; 0.62] p < 0.001 probability: "hint"	Outcome category: serious/severe AEs CI_u < 0.75 lesser harm, extent: "major"
Severe AEs (CTCAE grade 3-4)	9.56 vs. 0.33 months HR 0.25 [0.17; 0.36] p < 0.001 probability: "hint"	Outcome category: serious/severe AEs CI_u < 0.75 lesser harm, extent: "major"
Specific AEs (blood and lymphatic system disorders)	Qualitative consideration Probability: "indication"	Outcome category: serious/severe AEs lesser harm, extent: "major"[c]
Specific AEs (myalgia, peripheral neuropathy, alopecia)	Qualitative consideration probability: "hint"	Outcome category: non-serious/non-severe AEs lesser harm, extent: "considerable"[d]

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: Due to the observed event numbers and the known direction of the bias rated as "major".
d: Due to the observed event numbers and the known direction of the bias rated as "considerable".

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; NC: not calculable or not achieved; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.1.2 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 nivolumab in comparison with docetaxel

Positive effects	Negative effects
Mortality ▪ Overall survival ▫ Age < 75 years; indication, extent: "major" ≥ 75 years: lesser benefit/added benefit not proven Serious/severe AEs ▪ Treatment discontinuation due to AEs: hint, extent: "major" ▪ Severe AEs (CTCAE grade 3-4); hint, extent: "major" ▪ Specific AEs (blood and lymphatic system disorders); indication, extent: "major" Non-serious/non-severe AEs ▪ Specific AEs (myalgia, peripheral neuropathy, alopecia); hint, extent: "considerable"	-
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events;	

Since there was proof of an effect modification by the subgroup characteristic "age" for the outcome "overall survival", the added benefit is presented separately for patients aged < 75 years and ≥ 75 years.

Patients < 75 years

For patients under 75 years of age, there was an indication of major added benefit of nivolumab for the outcome "overall survival", and hints of major added benefit of nivolumab for the outcomes "treatment discontinuation due to AEs" and "severe AEs (CTCAE grade 3-4)" on the side of positive effects. SAEs could not be finally assessed because of the data availability. The qualitative assessment of the naive proportions of the patients with at least one SAE did not raise doubts about the effects in favour of nivolumab, however. There was a hint of lesser harm of nivolumab with the extent "considerable" for the specific AEs "myalgia", "peripheral neuropathy" and "alopecia". There was an indication of lesser harm with the extent "major" for the outcome "blood and lymphatic system disorders (severe AE with CTCAE grade 3-4)". No evaluable data were available for the outcomes on morbidity and health-related quality of life.

Overall, there is an indication of major added benefit of nivolumab in comparison with the ACT docetaxel for patients for whom docetaxel treatment is indicated and who are younger than 75 years.

Patients ≥ 75 years

There was no hint of an added benefit for the outcome "overall survival" for patient ≥ 75 years; an added benefit is therefore not proven for this outcome in this patient group. Due to the position of the effect estimate and the width of the confidence interval, an important negative effect of nivolumab in this patient group cannot be excluded with certainty.

At the same time, there are hints of major added benefit of nivolumab for the outcomes "treatment discontinuation due to AEs" and "severe AEs (CTCAE grade 3-4)" for patients over 75 years of age on the side of positive effects. The outcome "SAEs" could not be finally assessed because of the data availability. Based on the qualitative assessment of the naive proportions of the patients with at least one SAE, there was at least no sign of a disadvantage of nivolumab despite the longer observation period in the nivolumab arm. There was a hint of lesser harm of nivolumab with the extent "considerable" for the specific AEs "myalgia", "peripheral neuropathy" and "alopecia". There was an indication of lesser harm with the extent "major" for the outcome "blood and lymphatic system disorders (severe AE with CTCAE grade 3-4)". No evaluable data were available for the outcomes on morbidity and health-related quality of life.

In the overall consideration of the results, the extent of added benefit was assessed as "non-quantifiable". Hence a hint of a non-quantifiable added benefit of nivolumab versus the ACT docetaxel remains for patients who are 75 years of age or older.

Summary

In summary, there is an indication of major added benefit for the age group < 75 years and a hint of a non-quantifiable added benefit for the age group ≥ 75 years of nivolumab compared with the ACT docetaxel for patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy.

2.5.2 Research question 2: patients for whom treatment with docetaxel is not indicated

Since the company presented no evaluable data for patients for whom treatment with docetaxel is not indicated, an added benefit of nivolumab in comparison with BSC is not proven for this subpopulation.

2.5.3 Extent and probability of added benefit – summary

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

Table 19: Nivolumab – extent and probability of added benefit

Research question	Subindication	ACT	Subgroup	Extent and probability of added benefit
1	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is indicated	Docetaxel	< 75 years	Indication of major added benefit
			≥ 75 years	hint of a non-quantifiable added benefit
2	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is not indicated	BSC	Added benefit not proven	
ACT: appropriate comparator therapy; BSC: best supportive care; NSCLC: non-small cell lung cancer				

This deviates from the company's approach, which claimed proof of major added benefit for all patients without consideration of age in research question 1, and a hint of a non-quantifiable added benefit in research question 2.

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

2.6 List of included studies

CA209-017

Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015; 373(2): 123-135.

Bristol-Myers Squibb. Core safety statistical analysis plan for multiple indications: nivolumab program; protocols ca209; version # 4 [unpublished]. Bristol-Myers Squibb Company.

Bristol-Myers Squibb. An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC): study CA209017; final clinical study report [unpublished]. 2015.

Bristol-Myers Squibb. Study of BMS-936558 (nivolumab) compared to docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC) (checkmate 017): full text view [online]. In: ClinicalTrials.gov 3 September 2015 [accessed: 7 September 2015]. URL: https://ClinicalTrials.gov/show/NCT01642004.

Bristol-Myers Squibb International. An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC): revised protocol number 04, incorporates amendment 11; pharmacogenetics blood sample protocol amendment 01 version 1.0 dated 12-Jun-12 [online]. In: EU Clinical Trials Register. [Accessed: 27 October 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-004792-36.

Bristol-Myers Squibb International. An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell nonsmall cell lung cancer (NSCLC); revised protocol number 04, incorporates amendment 11; pharmacogenetics blood sample protocol amendment 01 version 1.0 dated 12-Jun-12 [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 26 October 2015]. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

References for English extract

Please see full dossier assessment for full reference list.

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3. Bristol-Myers Squibb. Nivolumab BMS 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. July 2015 [accessed: 27 October 2015]. URL: http://www.fachinfo.de.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-32-nivolumab-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6893.html.