IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-25

Nivolumab (non-squamous NSCLC) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (nicht plattenepitheliales NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 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
BSA	body surface area
BSC	best supportive care
CNS	central nervous system
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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
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 2 May 2016.

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 non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy. The research questions shown in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication[a]	ACT[b]
1	Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	▪ **docetaxel** or pemetrexed or ▪ gefitinib or erlotinib (only for patients with confirmed activating EGFR mutation who have not been pretreated with gefitinib or erlotinib) or ▪ crizotinib (only for patients with confirmed ALK translocation)
2	Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed, gefitinib, erlotinib, and crizotinib is not indicated[c]	BSC[d]

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: Presentation of the respective 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.
c: 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).
d: 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; 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) of 0, 1 and possibly 2 were considered relevant for research question 1 (patients who are suitable for chemotherapy or treatment with a tyrosine kinase inhibitor [TKI]), and patients with an ECOG PS of 4, 3, and possibly 2 were considered relevant for research question 2 (patients who are unsuitable for chemotherapy or treatment with a TKI).

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

Results for research question 1: patients who are suitable for chemotherapy or treatment with a TKI

One study of direct comparison (study CA209-057) was available for the benefit assessment.

Study characteristics

The CA209-057 study was a randomized, open-label, active-controlled approval study on the comparison of nivolumab and docetaxel. Patients with progressive or recurrent stage IIIB or IV non-squamous NSCLC were included in the study. The patients could initiate second-line treatment after prior platinum-based chemotherapy or third-line treatment after therapy with an epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-TKI (in case of confirmed activating EGFR mutation or ALK translocation of their tumour) and a platinum-based chemotherapy. A total of 582 patients were randomized in a ratio of 1:1, 292 patients to the nivolumab arm and 290 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). 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 then possibly to 37.5 mg/m^2 BSA. The SPC only recommends a single reduction to 60 mg/m^2. In the course of the study, the docetaxel dose was first reduced to 55 mg/m^2 in 25.4% of the patients in the docetaxel arm, and, in a further step, to 37.5 mg/m^2 in 3.4% of the patients. This had no consequence for the assessment, however.

Overall survival was the primary outcome of the CA209-057 study; symptoms, health status, health-related quality of life and adverse events (AEs) were secondary outcomes.

For the study, the final analysis was planned after 442 deaths, and an interim analysis after 380 deaths. The data cut-off for the interim analysis was 18 March 2015. Since a statistically significant difference in favour of nivolumab was shown for overall survival already at this time point, all patients in the docetaxel arm were offered the opportunity to receive treatment with nivolumab in the framework of an extension phase.

Risk of bias

The risk of bias at study level was rated as low for the CA209-057 study.

Usable results were only available for the outcomes “overall survival” and “side effects”. The risk of bias for the outcome “overall survival” and for “severe AEs” (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) was rated as low. Due to the potential informative censoring, the risk of bias was rated as high for the outcomes “serious adverse events (SAEs)”, “discontinuation due to AEs”, and “specific AEs”. The subjective components in an open-label study design were another reason to assess the risk of bias as high for the outcomes “discontinuation due to AEs” and “alopecia”.

Results

Mortality

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

In addition, there was proof of an effect modification by the characteristic “programmed cell death ligand 1 (PD-L1) status” for this outcome. There was no hint of an added benefit of nivolumab for PD-L1-negative patients; an added benefit is therefore not proven. For PD-L1-positive patients, there was an indication of an added benefit of nivolumab for the outcome “overall survival”.

Morbidity

No usable data were available for the outcomes “symptoms” recorded with the Lung Cancer Symptom Scale (LCSS) and “health status” recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). 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

The dossier contained no adequate data for the outcome “health-related quality of life”. 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.

Side effects

- Serious adverse events

A statistically significant advantage of nivolumab was shown for the outcome “SAEs”. The risk of bias for this outcome was rated as high. In addition, there was an indication of an effect modification by the characteristic “PD-L1 status” for this outcome. There was no hint of an added benefit of nivolumab for PD-L1-negative patients; an added benefit for these patients is therefore not proven. For PD-L1-positive patients, there was a hint of lesser harm from nivolumab in comparison with docetaxel for the outcome “SAEs”.

- Severe adverse events (CTCAE grade 3–4)

A statistically significant advantage of nivolumab was shown for the outcome "severe AEs" (CTCAE grade 3–4). Hence there was an indication of lesser harm from nivolumab than from docetaxel.

- Discontinuation due to adverse events

A statistically significant advantage of nivolumab was shown for the outcome "discontinuation due to AEs". The risk of bias for this outcome was rated as high. Hence there was a hint of lesser harm from nivolumab than from docetaxel.

- Alopecia

A statistically significant advantage of nivolumab was shown for the outcome "alopecia". The risk of bias for this outcome was rated as high. Hence there was a hint of lesser harm from nivolumab than from docetaxel.

- Blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant advantage of nivolumab was shown for the outcome "blood and lymphatic system disorders". The risk of bias for this outcome was rated as high. For this outcome, this assessment was solely due to the different observation periods. Due to the known direction of bias to the disadvantage of nivolumab, the high risk of bias with a statistically significant advantage of nivolumab did not lead to a downgrading of the certainty of results. Hence there was an indication of lesser harm from nivolumab than from docetaxel.

Results for research question 2: patients who are unsuitable for chemotherapy or treatment with a TKI

There were no data for the assessment of the added benefit of nivolumab in patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy for whom chemotherapy or treatment with a TKI is unsuitable. Hence there was 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:

[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].

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

Therapeutic indication[a]	**ACT**[b]	**Extent and probability of added benefit**
Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	▪ **docetaxel** or pemetrexed or ▪ gefitinib or erlotinib (only for patients with confirmed activating EGFR mutation who have not been pretreated with gefitinib or erlotinib) or ▪ crizotinib (only for patients with confirmed ALK translocation)	Indication of major added benefit
Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed, gefitinib, erlotinib, and crizotinib is not indicated[c]	BSC[d]	Added benefit not proven

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: Presentation of the respective 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.

c: 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).

d: 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; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

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 non-squamous NSCLC after prior chemotherapy.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication[a]	ACT[b]
1	Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	▪ **docetaxel** or pemetrexed or ▪ gefitinib or erlotinib (only for patients with confirmed activating EGFR mutation who have not been pretreated with gefitinib or erlotinib) or ▪ crizotinib (only for patients with confirmed ALK translocation)
2	Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed, gefitinib, erlotinib, and crizotinib is not indicated[c]	BSC[d]

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: Presentation of the respective 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.
c: 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).
d: 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; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

Following the specification of the ACT, the company chose docetaxel from the options mentioned in Table 4 for research question 1. The present assessment was conducted in comparison with the ACT specified by the G-BA. Patients with an ECOG PS of 0, 1 and possibly 2 were considered relevant for research question 1 (patients who are suitable for chemotherapy or treatment with a TKI), and patients with an ECOG PS of 4, 3, and possibly 2 were considered relevant for research question 2 (patients who are unsuitable for chemotherapy or treatment with a TKI). 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 Research question 1: patients who are suitable for chemotherapy or treatment with a TKI

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 nivolumab (status: 9 March 2016)
- bibliographical literature search on nivolumab (last search on 3 March 2016)
- search in trial registries for studies on nivolumab (last search on 9 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 18 May 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: 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)
CA209-057	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 nivolumab in comparison with docetaxel consisted of the CA209-057 study and concurred with that of the company.

Section 2.3.4 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 studies 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]
CA209-057	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed non-squamous NSCLC stage IIIB/IV[b] according to IASLC, following prior platinum-based chemotherapy[c], ECOG PS 0 or 1	Nivolumab (N = 292) docetaxel (N = 290)	Screening: within 28 days before randomization Treatment: until progression (in the nivolumab arm beyond progression), unacceptable toxicity, until study discontinuation or end of study Follow-up: until death or discontinuation of study participation Extension[d]: optional	106 centres in 22 countries (Argentina, Australia, Austria, Brazil, Canada, Chile, Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Mexico, Norway, Peru, Poland, Romania, Russia, Singapore, Spain, Switzerland, USA) 11/2012-2/2015 Data cut-offs: 3/2015[e] 7/2015	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 inclusion criteria, patients with recurrent or progressive disease following multimodal therapy (radiotherapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease) and/or with EGFR mutations or ALK (CD246) translocations were also allowed to participate in the study.
c: Stratified by prior maintenance treatment (yes vs. no) and line of treatment (second vs. third line).
d: In the extension phase, patients in the docetaxel arm were allowed to be treated with nivolumab (Amendment 8 to the study protocol). Patients in the nivolumab arm continued treatment.
e: Planned after at least 380 deaths for the outcome "overall survival".

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; 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
CA209-057	No premedication recommended	Premedication with dexamethasone 8 mg twice daily, orally, on the day before, on the same day, and on the day after administration of docetaxel	**Non-permitted pretreatment:** ▪ docetaxel ▪ antitumour vaccines or other immunostimulant antitumour drugs ▪ drugs targeting T-cell co-stimulation, including ipilimumab
	Nivolumab 3 mg/kg body weight every 2 weeks IV infusion	Docetaxel 75 mg/m² BSA every 3 weeks IV infusion	**Concomitant treatment** ▪ palliative and supportive treatment of disease-related symptoms (including bisphosphonates and RANKL inhibitors) if these treatments were started before the first dose of the study medication ▪ palliative radiotherapy[c] (only non-target bone lesions or CNS lesions) ▪ corticosteroids with minimal systemic absorption (e.g. topical, ocular, intraarticular, inhaled) ▪ < 3 weeks of treatment with corticosteroids for prophylaxis (allergy to contrast agent) or for treatment of non-autoimmunological diseases (e.g. contact allergy) ▪ adrenal hormone replacement therapy (no active autoimmune disorder) steroid dosages > 10 mg prednisolone
	No dose adjustment allowed	Dose reduction in 2 steps[a] on occurrence of prespecified AEs[b]	
	Postponement of the planned dose up to < 6 weeks due to AEs allowed		**Non-permitted concomitant treatment** ▪ concomitant antineoplastic treatments (e.g. chemotherapy, hormonal therapy, immunotherapy) ▪ immunosuppressant doses of systemic corticosteroids (corresponding to 10 mg/day prednisolone equivalent) ▪ for patients in the docetaxel arm: strong CYP3A4 inhibitors

a: Reduction step 1: to 55 mg/m² BSA; reduction step 2: to 37.5 mg/m² BSA.
b: The docetaxel dose could be reduced in the following treatment-induced AEs: febrile neutropenia, neutrophils < 500/mm³ for more than 7 days, severe and cumulative skin reactions or other non-haematological toxicity with CTCAE grade 3–4.
c: Not recommended for nivolumab. If palliative radiotherapy was necessary, nivolumab treatment was discontinued for at least one week before, during, and one week after the radiation.
AE: adverse event; BSA: body surface area; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; IV: intravenous; RANKL: receptor activator of nuclear factor-κB ligand; RCT: randomized controlled trial; vs.: versus

Study design

The CA209-057 study was a randomized, open-label, active-controlled approval study on the comparison of nivolumab and docetaxel. The CA209-057 study was a multicentre study conducted in 106 centres in 22 countries.

Patients with progressive or recurrent stage IIIB or IV non-squamous NSCLC were included. The patients could initiate second-line treatment after prior platinum-based chemotherapy or third-line treatment after therapy with an EGFR or ALK-TKI (in case of confirmed activating EGFR mutation or ALK translocation of their tumour) and a platinum-based chemotherapy. The patients had to have a good general condition (corresponding to ECOG PS 0 or 1). The population investigated in the study corresponded to the therapeutic indication of nivolumab in the present research question. Since no patients with ECOG PS 2 were included in the CA209-057 study, no conclusions can be derived from the available data for these patients.

The patients were stratified by prior maintenance treatment (yes vs. no) and line of treatment (second vs. third line) and randomly allocated to nivolumab or docetaxel in a ratio of 1:1. A total of 582 patients were randomized, 292 patients to the nivolumab arm and 290 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]. In the course of the CA209-057 study, the docetaxel dose was first reduced to 55 mg/m^2 in 25.4% of the patients in the docetaxel arm, and, in a further step, to 37.5 mg/m^2 in 3.4% of the patients. This had no consequence for the assessment, however.

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 central nervous system (CNS) lesions. Restrictions beyond that referred to therapy with antineoplastic treatments, among other things. No relevant differences that cannot 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 continued until withdrawal of consent, occurrence of unacceptable AEs, disease progression (measured with the Response Evaluation Criteria in

Solid Tumours [RECIST] version 1.1) or if, in the physician's opinion, further treatment would not be in the patient's best interest. In the nivolumab arm, continued treatment after disease progression was possible. Following the interim analysis, the Data Monitoring Committee decided to offer all patients in the docetaxel arm the opportunity to receive nivolumab treatment in the framework of an extension phase.

There were no restrictions regarding the subsequent therapies after completion of the randomized treatment phase. 42.1% of the patients in the nivolumab arm and 49.7% of the patients in the docetaxel arm received subsequent anticancer therapy.

Analyses and data cut-offs

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** **Outcome**	**Planned follow-up**
CA209-057	
Mortality	
Overall survival	At 3-month intervals until death, lost to follow-up, or discontinuation of study participation, up to a maximum of 5 years
Morbidity	
Symptoms (LCSS)	Up to 100 days after treatment discontinuation
Health status (EQ-5D VAS)	Every third month in the first 12 months, then every 6 months[a]
Side effects	Up to 30 days and 100 days after treatment discontinuation[a]
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	

Overall survival and health status (using to the EQ-5D VAS) were recorded until the end of participation in the study. The outcome "symptoms" (LCSS) was continued to be recorded until 100 days after treatment discontinuation; the side effects were also continued to be observed for 100 days.

Overall survival was the primary outcome of the CA209-057 study. An interim analysis was planned after 380 events; and the final analysis was planned after 442 events. The data cut-off for the interim analysis was 18 March 2015. Since a statistically significant difference in favour of nivolumab was shown for overall survival already at this time point, the Data Monitoring Committee offered all patients in the docetaxel arm the opportunity to receive treatment with nivolumab in the framework of an extension phase.

The present benefit assessment was conducted on the basis of the data cut-off on 18 March 2015; the data cut-off on 1 July 2015 was additionally used for the outcome "overall survival". At the time point of the data cut-off on 18 March 2015, about 15% of the patients in the nivolumab arm were still receiving the randomized study treatment, and no patient remained on the randomized study treatment in the docetaxel arm.

Characteristics of the study populations

Table 9 shows the characteristics of patients in the studies included in the assessment.

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

Study **Characteristics** **Category**	**Nivolumab**	**Docetaxel**
CA290-057	N[a] = 292	N[a] = 290
Age [years], mean (SD)	61 (9)	62 (10)
Sex [F/M], %	48/52	42/58
Ethnicity, n (%)		
White	267 (91.4)	266 (91.7)
Black/African American	7 (2.4)	9 (3.1)
Other	18 (6.2)	15 (5.2)
Region, n (%)		
USA/Canada	105 (36.0)	110 (37.9)
Europe	135 (46.2)	134 (46.2)
Rest of the world	52 (17.8)	46 (15.9)
Disease stage, n (%)		
IIIB	20 (6.8)	24 (8.3)
IV	272 (93.2)	266 (91.7)
ECOG Performance Status, n (%)		
0	84 (28.8)	95 (32.8)
1	208 (71.2)	193 (66.6)
> 1	0 (0)	1 (0.3)
Not reported	0 (0)	1 (0.3)
PD-L1 status with threshold value ≥ 5%[b], n (%)		
Positive	95 (32.5)	86 (29.7)
Negative	136 (46.6)	138 (47.6)
Non-quantifiable	61 (20.9)	66 (22.8)
EGFR mutation status, n (%)		
Positive	44 (15.1)	38 (13.1)
Not confirmed	168 (57.5)	172 (59.3)
Unknown	80 (27.4)	80 (27.6)
ALK translocation status, n (%)		
Positive	13 (4.5)	8 (2.8)
Not confirmed	113 (38.7)	130 (44.8)
Unknown	166 (56.8)	152 (52.4)
CNS metastases, n (%)		
Yes	34 (11.6)	34 (11.7)
No	258 (88.4)	256 (88.3)

(continued)

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

Study Characteristics Category	Nivolumab	Docetaxel
CA290-057	N[a] = 292	N[a] = 290
Smoking status, n (%)		
Current/former smoker	231 (79.1)	227 (78.3)
Never-smoker	58 (19.9)	60 (20.7)
Unknown	3 (1.0)	3 (1.0)
Disease duration: time between diagnosis and randomization [years], median [min; max]	0.8 [0.2; 8.4]	0.8 [0.0; 8.5]
Line of treatment[c], n (%)		
Second line	255 (87.3)	254 (87.6)
Third line	37 (12.7)	36 (12.4)
Type of prior platinum-based regimen, n (%)		
Carboplatin	192 (65.8)	207 (71.4)
Cisplatin	125 (42.8)	107 (36.9)
Treatment discontinuation, n (%)	244 (85.0)[d]	268 (100)[d]
Study discontinuation, n (%)	ND	ND

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: Proportion of PD-L1-positive cells.
c: According to IVRS.
d: Information for the treated patients (nivolumab: N = 287, docetaxel: N = 268). The most common reason for treatment discontinuation was disease progression (nivolumab 67.6%; docetaxel 66.8%).
ALK: anaplastic lymphoma kinase; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; F: female; IVRS: interactive voice response system; M: male; max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were largely evenly distributed between both study arms. There were somewhat more men than women in both arms. Most patients were white and originated from Europe and the USA/Canada. Almost 80% of the patients were current or former smokers.

The median disease duration of the patients was about 9 months. More than 90% of the patients in both arms had disease stage IV and an ECOG PS of 0 or 1. About 30% of the patients had a positive PD-L1 status (threshold value ≥ 5% positive cells). The majority of the patients (about 87%) were receiving their second line of treatment.

Table 10 shows the treatment duration of the patients and the observation 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**	**Docetaxel**
CA290-057[a]	N = 292	N = 290
Treatment duration [months][a]		
Median [min; max]	2.6 [< 0.1; 24.0]	2.3 [< 0.1; 15.9]
Mean (SD)	5.7 (6.6)	3.3 (3.0)
Observation period [months][b]		
Median [min; max][b]	12.2 [0.2; 25.3]	9.8 [0.3; 26.4]
Mean (SD)[b]	11.5 (7.4)	10.5 (6.3)
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND
Median	5.9[c]	5.6[c]
Mean	9.0[c]	6.6[c]

a: Information for the treated patients (nivolumab: N = 287, docetaxel: N = 268).
b: It is unclear which outcome the observation period refers to.
c: Institute's calculation on the basis of the treatment duration and the planned follow-up (100 days).
max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration was about the same in both study arms. The mean treatment duration, in contrast, differed notably between the study arms (5.7 months in the nivolumab arm versus 3.3 months in the docetaxel arm, see also Figure 1 in Appendix A of the full dossier assessment).

The mean observation period was about the same in both study arms (approximately 11 months); however, it was not clear from the documents in the dossier which outcomes the observation period referred to. The Institute's calculation on the basis of the treatment duration and the planned observation period showed a considerably longer mean observation period for the outcomes on side effects in the nivolumab in comparison with the docetaxel arm (9 months vs. 6.6 months).

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			
CA209-057	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. Restrictions resulting from the open-label study design and the different observation periods in the treatment arms are described in Section 2.6.2.4.2 of the full dossier assessment and in Section 2.3.2.2 under 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 questions of the LCSS questionnaire
  - health status measured with the VAS of the EQ-5D questionnaire
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade 3-4)
  - alopecia (Preferred Term [PT])
  - blood and lymphatic system disorders (CTCAE grade 3–4) (System Organ Class [SOC])

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 C) (see Section 2.6.2.4.3 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)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Alopecia	Blood and lymphatic system disorders (CTCAE grade 3–4)
Study CA209-057	Yes	No[a]	No[a]	No[b]	Yes	Yes	Yes	Yes	Yes

a: No usable data available, see Section 2.6.2.4.3 of the full dossier assessment.
b: Outcome not recorded (the LCSS symptom score is allocated to morbidity; the LCSS total score and the GTIC [mean value of the LCSS items 7 to 9] are not validated for health-related quality of life; see Section 2.6.2.4.3 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; GTIC: global three-item composite index; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event; 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: nivolumab vs. docetaxel

Study	Study level	Outcomes								
		Overall survival	Symptoms (LCSS)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Alopecia	Blood and lymphatic system disorders (CTCAE grade 3–4)
Study CA209-057	L	L	-[a]	-[a]	-[b]	H[c]	H[c, d]	L[e]	H[d,f]	H[f]

a: No usable data available, see Section 2.6.2.4.3 of the full dossier assessment.
b: Outcome not recorded (the LCSS symptom score is allocated to morbidity; the LCSS total score and the GTIC [mean value of the LCSS items 7 to 9] are not validated for quality of life; see Section 2.6.2.4.3 of the full dossier assessment).
c: Potential informative censoring.
d: Outcome has subjective components in open-label study design.
e: Low risk of bias despite potential informative censoring because the majority of severe AEs occurred very early (see Section 2.6.2.4.2 of the full dossier assessment).
f: Different mean observation periods.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; GTIC: global three-item composite index; 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 outcomes “overall survival” and “severe AEs” (CTCAE grade 3–4) was classed as low. This concurs with the company’s assessment.

Due to the small proportion of analysed patients, there were no usable data for the outcomes “symptoms” (LCSS) and “health status” (EQ-5D VAS). The risk of bias for these outcomes was therefore not assessed. This deviates from the approach of the company, which rated the risk of bias for these outcomes as high and used the results for the assessment of the added benefit.

Due to the potential informative censoring, the risk of bias was rated as high for the outcomes “SAEs”, “discontinuation due to AEs”, and “specific AEs”. The subjective components in an open-label study design were another reason to assess the risk of bias as high for the outcomes “discontinuation due to AEs” and “alopecia” (see also Section 2.6.2.4.2 of the full dossier assessment).

This deviated from the company to some extent. The company rated the risk of bias as low for the outcomes “SAEs” and “severe AEs” (CTCAE grade 3–4). It rated the risk of bias as high for the outcome “discontinuation due to AEs”. It did not present the outcomes “alopecia” and

"blood and lymphatic system disorders" (CTCAE grade 3–4) in Module 4 C and therefore did not describe the risk of bias.

2.3.2.3 Results

Table 14 and Table 15 summarize the results on the comparison of nivolumab with docetaxel in patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are suitable for chemotherapy or treatment with a TKI. The results are based on the data cut-off on 18 March 2015. Data from the data cut-off on 1 July 2015 were additionally available for the outcome "overall survival"; these are also shown. Since there was no information on the number of patients in the docetaxel arm who were already treated with nivolumab at this time point, the results from the data cut-off on 18 March 2015 were primarily used for the interpretation of the outcome "overall survival". Due to the different mean observation periods, analyses on the basis of survival time analyses were used for the outcomes on side effects. Such analyses were not available for specific AEs (alopecia and blood and lymphatic system disorders [CTCAE grade 3–4]), however, and the relative risks on the basis of the naive proportions (proportion of patients with event) were estimated.

Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The Kaplan-Meier curves on overall survival are presented in Appendix A and the tables with overviews of the most common AEs are presented in Appendix B of the full dossier assessment.

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

Study Outcome category	Nivolumab		Docetaxel		Nivolumab vs. docetaxel
Outcome Time point	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]; p-value[c]
CA209-057					
Mortality					
Overall survival					
First data cut-off 18 March 2015	292	12.19 [9.66; 14.98] 190 (65.1)	290	9.36 [8.05; 10.68] 223 (76.9)	0.73 [0.60; 0.89]; 0.002
Second data cut-off 1 July 2015	292	12.21 [9.66; 15.08] 206 (70.5)	290	9.36 [8.05; 10.68] 236 (81.4)	0.72 [0.60; 0.88]; 0.001
Morbidity					
Symptoms (LCSS)	No usable data[d]				
Health status (EQ-5D VAS)	No usable data[d]				
Health-related quality of life					
There are no usable data					
Side effects[e]					
AEs (supplementary information)	287	0.26 [0.20; 0.26] 280 (97.6)	268	0.10 [0.10; 0.13] 265 (98.9)	
SAEs	287	11.96 [8.02; 19.02] 132 (46.0)	268	6.05 [4.99; 8.80] 136 (50.7)	0.78 [0.61; 1.00] 0.049
Severe AEs (CTCAE grade 3–4)	287	6.21 [3.88; 12.29] 156 (54.4)	268	0.66 [0.39; 1.25] 202 (75.4)	0.43 [0.35; 0.53] < 0.001
Discontinuation due to AEs	287	NA [NA; NA] 36 (12.5)	268	15.70 [8.97; NA] 55 (20.5)	0.47 [0.31; 0.73] < 0.001

a: Calculated with a log-log transformation (according to Brookmeyer and Crowley).
b: Cox model stratified by prior maintenance treatment (yes vs. no) and line of treatment (second-line vs. third-line treatment) as documented in the IVRS.
c: Log-rank test stratified by prior maintenance treatment (yes vs. no) and line of treatment (second-line vs. third-line treatment) as documented in the IVRS.
d: No validated MID and proportion of the patients included in the MMRM analysis too small.
e: AEs until 100 days after the end of treatment except treatment discontinuation due to AEs (up to 30 days after the end of treatment), without events associated with 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; MMRM: mixed-effects model repeated measures; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Table 15: Results (specific AEs) – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome category Outcome	Nivolumab		Docetaxel		Nivolumab vs. docetaxel
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
CA209-057					
Side effects[b]					
Alopecia	287	11 (3.8)	268	70 (26.1)	0.15 [0.08; 0.27][c]; < 0.001
Blood and lymphatic system disorders (CTCAE grade 3–4)	287	12 (4.2)	268	114 (42.5)	0.10 [0.06; 0.17][c] < 0.001

a: Institute's calculation, unconditional exact test (CSZ method according to [5]).
b: AEs until 100 days after the end of treatment.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

A statistically significant advantage of nivolumab was shown for the outcome "overall survival" in both data cut-offs.

However, the Kaplan-Meier curves of both data cut-offs (see Figure 2 and Figure 3 in Appendix A of the full dossier assessment) cross after 7 months. This contradicts the preconditions for a Cox proportional hazards model. The survival time curve of the nivolumab arm was slightly below the one of the docetaxel arm in the time period until 6 months, and was then notably above it. Since the distance between the curves was notably smaller in the first 6 months than in the later period of time, and, in addition, the curves crossed before the median survival time, the result of the effect estimate was not regarded to have an important bias.

In addition, there was proof of an effect modification by the characteristic "PD-L1 status" for this outcome (see Section 2.3.2.4). There was no hint of an added benefit of nivolumab for PD-L1-negative patients; an added benefit is therefore not proven. For PD-L1-positive patients, there was an indication of an added benefit of nivolumab for the outcome "overall survival".

This deviates from the company's assessment, which, on the basis of the total population, derived proof of an added benefit and presented the effect modification by the PD-L1 status, but did not use it for the derivation of the added benefit.

Morbidity

Symptoms (LCSS)

The dossier contained no usable data for the outcome "symptoms" recorded with the LCSS (see Section 2.6.2.4.3 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.

Health status (EQ-5D VAS)

The dossier contained no usable data for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.6.2.4.3 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.

Health-related quality of life

The dossier contained no suitable data for the outcome "health-related quality of life" (see Section 2.6.2.4.3 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.

Side effects

Analyses excluding progression events were used for the outcomes "SAEs", "severe AEs" (CTCAE grade 3–4), and "discontinuation due to AEs". The follow-up observation for side effects was conducted for 100 days, and for the outcome "discontinuation due to AEs" for 30 days (see also Section 2.6.2.4.3 of the full dossier assessment).

Serious adverse events

A statistically significant advantage of nivolumab was shown for the outcome "SAEs". In addition, there was an indication of an effect modification by the characteristic "PD-L1 status" for this outcome (see Section 2.3.2.4). There was no hint of an added benefit of nivolumab for PD-L1-negative patients; an added benefit for these patients is therefore not proven. For PD-L1-positive patients, there was a hint of lesser harm from nivolumab in comparison with docetaxel for the outcome "SAEs".

This deviates from the company's assessment, which derived an indication of an added benefit on the basis of the total population.

Severe adverse events (CTCAE grade 3–4)

A statistically significant advantage of nivolumab was shown for the outcome "severe AEs" (CTCAE grade 3–4). Hence there was an indication of lesser harm from nivolumab than from docetaxel.

This deviates from the company's assessment, which derived proof of an added benefit.

Discontinuation due to adverse events

A statistically significant advantage of nivolumab was shown for the outcome "discontinuation due to AEs". The risk of bias for this outcome was rated as high. Hence there was a hint of lesser harm from nivolumab than from docetaxel.

This deviates from the company's assessment, which derived an indication of an added benefit.

Alopecia

A statistically significant advantage of nivolumab was shown for the outcome "alopecia". The risk of bias for this outcome was rated as high. Hence there was a hint of lesser harm from nivolumab than from docetaxel.

The company did not use this outcome in its assessment.

Blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant advantage of nivolumab was shown for the outcome "blood and lymphatic system disorders". The risk of bias for this outcome was rated as high. For this outcome, this assessment was solely due to the different observation periods. Due to the known direction of bias to the disadvantage of nivolumab, the high risk of bias with a statistically significant advantage of nivolumab did not lead to a downgrading of the certainty of results. Hence there was an indication of lesser harm from nivolumab than from docetaxel.

The company did not use this outcome in its assessment.

2.3.2.4 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 years to < 75 years, ≥ 75 years)
- sex (male, female)
- ethnicity (white, African American, Asian, other)
- line of treatment (second line, third line, other)

- CNS metastases (yes/no)
- PD-L1 status (≥ 5%) (positive, negative)

All subgroup characteristics and cut-off values mentioned were predefined in the CA209-057 study.

Only the results on subgroups and outcomes are presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic. 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. Furthermore, subgroups are not shown if there were no statistically significant and relevant results in the total population or in one of the subgroups.

Table 16, Table 17, Table 18, and Table 19 summarize the subgroup results on nivolumab in comparison with docetaxel. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

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

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median survival time in months [95% CI][a] Patients with event n (%)	docetaxel N	docetaxel Median survival time in months [95% CI][a] Patients with event n (%)	Nivolumab vs. docetaxel HR [95% CI]	Nivolumab vs. docetaxel p-value[b]
Study CA209-057						
Overall survival (data cut-off 18 March 2015)						
Region						
USA/Canada	105	16.8 [10.8; 20.6] 64 (61.0)	110	8.0 [6.7; 10.1] 89 (80.9)	0.52 [0.37; 0.72]	< 0.001
Europe	135	10.3 [6.5; 15.5] 88 (65.2)	134	9.3 [7.5; 10.8] 107 (79.9)	0.81 [0.61; 1.07]	0.136
Rest of the world	52	11.1 [6.2; 14.3] 38 (73.1)	46	14.5 [10.3; NA] 27 (58.7)	1.49 [0.91; 2.45]	0.108
					Interaction:	0.002[c]
CNS metastases						
Yes	34	7.6 [4.5; 11.1] 30 (88.2)	34	7.3 [4.4; 10.6] 27 (79.4)	1.04 [0.62; 1.76]	0.876
No	258	13.1 [10.3; 172] 160 (62.0)	256	10.0 [8.5; 11.1] 196 (76.6)	0.71 [0.58; 0.88]	0.002
					Interaction:	0.186[c]
PD-L1 status (≥ 5%)[d]						
Positive	95	18.2 [15.2; NA] 46 (48.4)	86	8.1 [6.5; 10.1] 68 (79.1)	0.43 [0.30; 0.63]	< 0.001
Negative	136	9.7 [6.9; 12.6] 99 (72.8)	138	10.1 [8.1; 11.9] 100 (72.5)	1.01 [0.77; 1.34]	0.928
					Interaction:	< 0.001[c]
Line of treatment						
Second line	256	12.8 [10.0; 16.2] 164 (64.1)	259	9.3 [8.0; 10.7] 204 (78.8)	0.69 [0.56; 0.85]	< 0.001
Third line	35	8.2 [2.8; 15.5] 25 (71.4)	31	10.1 [5.9; NA] 19 (61.3)	1.34 [0.73; 2.43]	0.336
Other	1	14.7 [NA; NA] 1 (100.0)	0	0		
					Interaction:	0.027[d]

(continued)

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

a: Calculated with a log-log transformation (according to Brookmeyer and Crowley).
b: Cox model with values at the start of the study as covariate.
c: Cox model with values at the start of the study as covariate, and treatment, subgroup characteristic and the interaction term treatment*subgroup characteristic for the assessment of the significance of the interaction between treatment and subgroup characteristic.
d: Proportion of PD-L1-positive cells.
CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 17: Subgroups (severe AEs [CTCAE grade 3–4]) – RCT, direct comparison: nivolumab vs. docetaxel

Study	**Nivolumab**		**Docetaxel**		**Nivolumab vs. docetaxel**	
Outcome / **Characteristic** / **Subgroup**	**N**	**Median time to first AE in months [95% CI][a] Patients with event n (%)**	**N**	**Median time to first AE in months [95% CI][a] Patients with event n (%)**	**HR [95% CI][b]**	**p-value[b]**
Study CA209-057						
Severe AEs (CTCAE grade 3-4)						
Ethnicity						
White	262	6.7 [3.9; 13.1] 141 (53.8)	244	1.1 [0.5; 1.8] 179 (73.4)	0.46 [0.37; 0.57]	< 0.001
African American	7	1.3 [0.2; 10.0] 5 (71.4)	9	0.3 [0.1; 0.4] 8 (88.9)	0.26 [0.07; 0.94]	0.035
Asian	9	NA [0.4; NA] 4 (44.4)	8	0.3 [< 0.1; 0.3] 8 (100.0)	0.14 [0.04; 0.49]	0.001
Other	9	3.8 [0.2; NA] 6 (66.7)	7	0.3 [0.2; 0.5] 7 (100.0)	0.31 [0.10; 0.98]	0.042
					Interaction:	0.065[c]

a: Calculated with a log-log transformation (according to Brookmeyer and Crowley).
b: Cox model with values at the start of the study as covariate.
c: Cox model with values at the start of the study as covariate, and 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 patients with (at least one) event; N: number; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 18: Subgroups (SAEs) – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median time to first AE in months [95% CI][a] Patients with event n (%)	Docetaxel N	Docetaxel Median time to first AE in months [95% CI][a] Patients with event n (%)	Nivolumab vs. docetaxel HR [95% CI][b]	Nivolumab vs. docetaxel p-value[b]
Study CA209-057						
SAEs						
PD-L1 status (≥ 5%)[c]						
Positive	93	13.2 [9.6; NA] 43 (46.2)	79	5.0 [3.8; 9.0] 44 (55.7)	0.57 [0.37; 0.88]	0.011
Negative	134	13.7 [5.3; 21.0] 58 (43.3)	128	7.1 [5.2; NA] 59 (46.1)	0.88 [0.61; 1.27]	0.499
					Interaction:	0.110[d]

a: Calculated with a log-log transformation (according to Brookmeyer and Crowley).
b: Cox model with values at the start of the study as covariate.
c: Proportion of PD-L1-positive cells.
d: Cox model with values at the start of the study as covariate, and treatment, subgroup characteristic and the interaction term treatment*subgroup characteristic for the assessment of the significance of the interaction between treatment and subgroup characteristic.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number; NA: not achieved; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 19: Subgroups (discontinuation due to AEs) – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median time to first AE in months [95% CI][a] Patients with event n (%)	Docetaxel N	Docetaxel Median time to first AE in months [95% CI][a] Patients with event n (%)	Nivolumab vs. docetaxel HR [95% CI][b]	Nivolumab vs. docetaxel p-value[b]
Study CA209-057						
Discontinuation due to AEs						
Region						
USA/Canada	104	NA [NA; NA] 11 (10.6)	94	8.8 [4.5; NA] 18 (19.1)	0.39 [0.18; 0.84]	0.014
Europe	131	NA [NA; NA] 16 (12.2)	130	9.0 [7.1; NA] 29 (22.3)	0.40 [0.21; 0.75]	0.003
Rest of the world	52	NA [13.7; NA] 9 (17.3)	44	15.7 [NA; NA] 8 (18.2)	0.98 [0.37; 2.61]	0.966
					Interaction:	0.094[c]

a: Calculated with a log-log transformation (according to Brookmeyer and Crowley).
b: Cox model with values at the start of the study as covariate.
c: Cox model with values at the start of the study as covariate, and 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; HR: hazard ratio; n: number of patients with (at least one) event; N: number; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

For the outcome "overall survival", there was proof of an effect modification by the characteristics "region" and "PD-L1 status" and indications of an effect modification by the characteristics "CNS metastases" and "line of treatment". Since no information on possible dependencies between the subgroup characteristics was available, the subgroup results could not be fully interpreted. Due to the mechanism of action of nivolumab, only the subgroup results for the characteristic "PD-L1 status" were used for the present benefit assessment (for the corresponding Kaplan-Meier curves, see Figure 4 and Figure 5 in Appendix A of the full dossier assessment).

No statistically significant difference between the treatment arms was shown for PD-L1-negative patients. Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel; an added benefit is therefore not proven. A statistically significant advantage of nivolumab was shown for PD-L1-positive patients; hence there was an indication of an added benefit of nivolumab.

The effect modification for the outcome "overall survival" by the characteristic "PD-L1 status" presented in Table 16 refers to a threshold value of ≥ 5% for PD-L1-positive cells. The subgroup results for the characteristic "PD-L1" for the outcome "overall survival" with a threshold value of ≥ 1% and ≥ 10% PD-L1-positive cells are shown as additional information in Table 26 in Appendix A of the full dossier assessment. Whereas only an indication of an effect modification was shown for the threshold value of ≥ 1% ($p = 0.065$), proof of an effect modification was also shown for the threshold value of ≥ 10% ($p < 0.001$). No statistically significant difference between the treatment groups was shown for PD-L1-negative patients for any of the threshold values considered, with the effect estimate remaining constant in each case. A statistically significant advantage of nivolumab was shown for PD-L1-positive patients. This confirmed the association between PD-L1 status and overall survival.

The company presented the effect modification based on PD-L1 status, but did not use the results for the derivation of the added benefit for the outcome "overall survival".

Side effects

Severe adverse events (CTCAE grade 3–4)

There was an indication of an effect modification by the characteristic "ethnicity" for the outcome "severe AEs (CTCAE grade 3–4)". A statistically significant advantage of nivolumab was shown for whites, African Americans, Asians, and others. Hence there was an indication of lesser harm from nivolumab than from docetaxel for all ethnicities. Since about 90% of the patients in the CA209-057 study were white and this ethnicity was decisive for the health care area of the present benefit assessment, hereinafter only the results on the basis of the total population are considered for the outcome "severe AEs" (CTCAE grade 3–4).

The company did not use the effect modification by the characteristic "ethnicity" for this outcome and derived proof of an added benefit on the basis of the total population.

Serious adverse events

There was an indication of an effect modification by the characteristic "PD-L1 status" for the outcome "SAEs". No statistically significant difference between the treatment arms was shown for PD-L1-negative patients. Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel; an added benefit is therefore not proven for these patients. A statistically significant advantage of nivolumab was shown for PD-L1-positive patients. The risk of bias for this outcome was rated as high. This resulted in a hint of lesser harm from nivolumab in comparison with docetaxel.

This deviates from the assessment of the company, which considered the effect modification by the characteristic "PD-L1 status", but derived an indication of an added benefit of nivolumab on the basis of the total population.

Discontinuation due to adverse events

There was an indication of an effect modification by the characteristic "region" for the outcome "discontinuation due to AEs". A statistically significant advantage of nivolumab was shown for USA/Canada and Europe. Hence there was a hint of lesser harm from nivolumab. There was no statistically significant difference between the treatment arms for the rest of the world. Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel; an added benefit is therefore not proven. Since Germany is the decisive geographical region for the health care area of the present benefit assessment and the effect of patients from Europe concurred with the effect of the total population, hereinafter only the results on the basis of the total population are considered for the outcome "discontinuation due to AEs".

The company did not use the effect modification by the characteristic "region" for this outcome and derived an indication of an added benefit on the basis of the total population.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for research question 1 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 Sections 2.3.2.2 and 2.3.2.4 resulted in the following assessments for nivolumab in comparison with docetaxel in patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are suitable for chemotherapy or treatment with a TKI:

- an indication of an added benefit for the outcome "overall survival" for PD-L1-positive patients
- a hint of lesser harm for the outcome "SAEs" for PD-L1-positive patients
- indications of lesser harm for the outcomes "severe AEs" (CTCAE grade 3–4) and "blood and lymphatic system disorders" (CTCAE grade 3–4)
- hints of lesser harm for the outcomes "discontinuation due to AEs" and "alopecia"

Determination of the outcome category for the outcomes of the category "side effects"

The outcomes "SAEs", "severe AEs" (CTCAE grade 3–4), and "blood and lymphatic system disorders" (CTCAE grade 3–4) were per se allocated to the outcome category "serious/severe side effects". The same applies to the outcome "discontinuation due to AEs" because the

proportion of events due to severe AEs (CTCAE grade 3–4) was above 50%. The outcome "alopecia" was allocated to the outcome category "non-serious/non-severe side effects" because the severity grade of the events was not clear from the documents in the company's dossier.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 20).

Table 20: Extent of added benefit at outcome level: nivolumab vs. docetaxel

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. docetaxel** **Median time to event or proportion of events or MD** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival PD-L1 status (≥ 5%)[c]		
Positive	Median: 18.2 vs. 8.1 months HR: 0.43 [0.30; 0.63] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Negative	Median: 9.7 vs. 10.1 months HR: 1.01 [0.77; 1.34] p = 0.928	Lesser benefit/added benefit not proven
Morbidity		
No data available		
Health-related quality of life		
No data available		
Side effects		
SAEs PD-L1 status (≥ 5%)[c]		
Positive	Median: 13.2 vs. 5.0 months HR: 0.57 [0.37; 0.88] p = 0.011 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Negative	Median: 13.7 vs. 7.1 months HR: 0.88 [0.61; 1.27]; p = 0.499	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	Median: 6.2 vs. 0.7 months HR: 0.43 [0.35; 0.53] p < 0.00 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs	Median: NA vs. 15.7 months HR: 0.47 [0.31; 0.73] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Alopecia	Proportion of events: 3.8% vs. 26.1% RR: 0.15 [0.08; 0.27] p = < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Blood and lymphatic system disorders (CTCAE grade 3–4)	Proportion of events: 4.2% vs. 42.5% RR: 0.10 [0.06; 0.17] p = < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"

(continued)

Table 20: Extent of added benefit at outcome level: nivolumab vs. docetaxel (continued)

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: Proportion of PD-L1-positive cells. 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; MD: mean difference; NA: not achieved; PD-L1: programmed cell death ligand 1; RR: relative risk; SAE: serious adverse event

2.3.3.2 Overall conclusion on added benefit

Table 21 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 21: Positive and negative effects from the assessment of nivolumab in comparison with docetaxel

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ PD-L1 status (≥ 5%)[a] positive indication of an added benefit – extent: “major”	–
Serious/severe side effects ▪ SAEs ▫ PD-L1 status (≥ 5%)[a] positive hint of lesser harm – extent: “considerable” ▪ severe AEs (CTCAE grade 3–4): indication of lesser harm – extent: “major” ▪ discontinuation due to AEs: hint of lesser harm – extent: “major” ▪ blood and lymphatic system disorders (CTCAE grade 3–4): indication of lesser harm – extent: “major”	
Non-serious/non-severe side effects ▪ alopecia: hint of lesser harm – extent: “considerable”	
a: Proportion of PD-L1-positive cells. AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; PD-L1: programmed cell death ligand 1; SAE: serious adverse event	

Only positive effects for nivolumab in comparison with docetaxel resulted in the overall assessment. There is an indication of a major added benefit for the outcome “overall survival”, which only applies to patients with positive PD-L1 status, however. In addition, a hint and indications of lesser harm with the extent “major” were determined in the outcome category “serious/severe side effects”. For the outcome “SAEs”, there is additionally a hint of lesser harm with the extent “considerable” for patients with a positive PD-L1 status.

Furthermore, there is a hint of lesser harm with the extent “considerable” in the category “non-serious/non-severe side effects”.

In summary, there is an indication of a major added benefit for patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are suitable for chemotherapy or treatment with a TKI.

2.3.4 List of included studies

Bristol-Myers Squibb. Study of BMS-936558 (nivolumab) compared to docetaxel in previously treated metastatic non-squamous NSCLC (CheckMate057): study results [online]. In: ClinicalTrials.gov. 29.01.2016 [Accessed: 23.05.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01673867.

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Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373(17): 1627-1639.

Bristol-Myers Squibb. An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated metastatic nonsquamous non-small cell lung cancer (NSCLC): study CA209057; final clinical study report [unpublished]. 2015.

Bristol-Myers Squibb. An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated metastatic non-squamous non-small cell lung cancer (NSCLC) [online]. In: EU Clinical Trials Register. [Accessed: 19.04.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-002472-14.

Bristol-Myers Squibb. An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated metastatic non-squamous non-small cell lung cancer (NSCLC) [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 19.04.2016]. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

Bristol-Myers Squibb. An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated metastatic nonsquamous non-small cell lung cancer: study CA209057; core safety statistical analysis plan for multiple indications [unpublished].

2.4 Research question 2: patients who are unsuitable for chemotherapy or treatment with a TKI

2.4.1 Information retrieval and study pool

The company presented no study for the assessment of the added benefit of nivolumab in comparison with BSC in patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are unsuitable for chemotherapy or treatment with a TKI. 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 2.6.2.3.2 of the full dossier assessment). Overall, there were therefore no relevant data for the assessment of the added benefit of nivolumab for these patients.

2.4.2 Results on added benefit

There were no data for the assessment of the added benefit of nivolumab in patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are unsuitable for chemotherapy or treatment with a TKI (in particular, these may be patients with ECOG PS 4, 3 and possibly 2). Hence there was no hint of an added benefit of nivolumab 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 usable data for the assessment of the added benefit of nivolumab in patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are unsuitable for chemotherapy or treatment with a TKI, an added benefit of nivolumab is not proven for these patients.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 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 22.

Table 22: Nivolumab – extent and probability of added benefit

Therapeutic indication[a]	**ACT**[b]	**Extent and probability of added benefit**
Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	▪ **docetaxel** or pemetrexed or ▪ gefitinib or erlotinib (only for patients with confirmed activating EGFR mutation who have not been pretreated with gefitinib or erlotinib) or ▪ crizotinib (only for patients with confirmed ALK translocation)	Indication of major added benefit
Patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed, gefitinib, erlotinib, and crizotinib is not indicated[c]	BSC[d]	Added benefit not proven

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: Presentation of the respective 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.
c: 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).
d: 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; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

This deviates from the approach of the company, which derived proof of a major added benefit for patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are suitable for chemotherapy or treatment with a TKI.

The company derived a hint of a non-quantifiable added benefit for patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are unsuitable for chemotherapy or treatment with a TKI.

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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