IQWiG Reports – Commission No. A16-35

Nivolumab (melanoma) –

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 (Melanom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 September 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf)
BRAF V600 mut	BRAF V600 mutant
BRAF V600 wt	BRAF V600 wild type
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
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)
ITT	intention to treat
IV	intravenous
LDH	lactate dehydrogenase
ORR	objective response rate
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
ULN	upper limit of normal
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 8 June 2016.

Research questions

The aim of this report was to assess the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in adult patients with advanced (unresectable or metastatic) melanoma. The research questions shown in Table 2 resulted from the appropriate comparator therapy (ACT) specified by the G-BA.

Table 2: Research questions of the benefit assessment of nivolumab + ipilimumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Treatment-naive patients with BRAF V600 mutant tumour	Vemurafenib
2	Treatment-naive patients with BRAF V600 wild type tumour	Ipilimumab
3	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee

Deviating from the ACT specified by the G-BA, the company defined ipilimumab as comparator therapy for all patients in the therapeutic indication (adult patients with advanced [unresectable or metastatic] melanoma) irrespective of their BRAF V600 mutation status and pretreatment status.

It additionally also investigated the research questions of the present benefit assessment based on the respective ACT specified by the G-BA.

The present assessment was conducted in comparison with the ACT specified by the G-BA.

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

Result for research question 1: treatment-naive patients with BRAF V600 mutant tumour

There were no data on the comparison with the ACT specified by the G-BA for the assessment of the added benefit of nivolumab + ipilimumab in the treatment of treatment-naive patients with BRAF V600 mutant (mut) tumour. Hence there was no hint of an added benefit of nivolumab + ipilimumab in comparison with the ACT vemurafenib; an added benefit is therefore not proven.

Result for research question 2: treatment-naive patients with BRAF V600 wild type tumour

Study pool and study characteristics

The 2 studies CA209-067 and CA209-069 were available for the benefit assessment.

Both studies were randomized, double-blind, active-controlled, parallel-group studies. Both studies included treatment-naive patients with unresectable or metastatic BRAF V600 wild type (wt) or BRAF V600 mut melanoma (stage III or IV). Patients had to be in good general condition (corresponding to an Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1).

In the CA209-067 study, 314 patients were randomized to the nivolumab + ipilimumab arm and 315 patients to the ipilimumab arm. In this research question, only patients with BRAF V600 wt tumour were relevant for the benefit assessment. These were 213 patients in the nivolumab + ipilimumab arm and 218 patients in the ipilimumab arm. The company presented analyses of the patients with BRAF V600 wt tumour. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question 2 and were used for the benefit assessment.

In the CA209-069 study, 95 patients were randomized to the nivolumab + ipilimumab arm and 47 patients to the ipilimumab arm. The subpopulation relevant for the research question in this research question comprised patients with a BRAF V600 wt tumour. These were 72 patients in the nivolumab + ipilimumab arm and 37 patients in the ipilimumab arm. The company presented analyses of the patients with BRAF V600 wt tumour. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question 2 and were used for the benefit assessment.

In the first 12 weeks, the patients in the nivolumab + ipilimumab arm of both studies received 1 mg/kg body weight nivolumab intravenously (IV) every 3 weeks and additionally 3 mg/kg body weight ipilimumab every 3 weeks for 4 doses in total. Subsequently, nivolumab at a dose of 3 mg/kg body weight every 2 weeks was continued until the end of the randomized study treatment.

The patients in the ipilimumab arm of both studies received 3 mg/kg body weight ipilimumab IV every 3 weeks for 4 doses in the first 12 weeks. Placebo for nivolumab was additionally

administered. After the first study phase, placebo for nivolumab every 2 weeks was continued until the end of the randomized study treatment.

Overall survival and progression-free survival (PFS) were the primary outcomes of the study of the CA209-067 study; objective response rate (ORR) was the primary outcome of the CA209-069 study.

Analysis and data cut-offs

For the CA209-067 study, the planned analysis of the PFS was conducted at the database closure on 17 February 2015, after all patients had been observed for at least 9 months. Except overall survival, the results available for the benefit assessment were based on this data cut-off. For overall survival, results were available on the data cut-off on 10 November 2015, after all patients had been observed for at least 18 months. No data were available for further outcomes at this data cut-off.

For the CA209-069 study, the planned analysis for the ORR was conducted with the data cut-off on 4 September 2014, after all patients had been observed for at least 6 months. Except overall survival, the results available for the benefit assessment were based on this data cut-off. For overall survival, results from the data cut-off on 30 January 2015 (minimum observation period of 12 months for all patients) and from the data cut-off on 25 February 2016 (minimum observation period of 24 months for all patients) were available. No data were available for further outcomes at these later data cut-offs.

Risk of bias

The risk of bias at study level was rated as low for the 2 studies CA209-067 and CA209-069.

The risk of bias for the outcome “overall survival” was rated as low.

For the outcomes “symptoms”, “health status” and “health-related quality of life”, usable data were only available from the CA209-067 study. Due to potentially informative censoring and the inadequate implementation of the intention-to-treat (ITT) principle, the risk of bias for these outcomes was rated as high.

The risk of bias for the outcomes “serious adverse events (SAEs)”, “severe adverse events (AEs)” (Common Terminology Criteria for Adverse Events [CTCAE] grade 3-4) and “discontinuation due to AEs” was also rated as high due to potentially informative censoring.

Only the CA209-069 study provided data for the following outcomes: eye disorders, skin and subcutaneous tissue disorders and colitis. The risk of bias was rated as high due to the different proportions of patients who discontinued and the different reasons for discontinuation.

Results

Mortality

The meta-analysis of both studies showed a statistically significant difference in favour of nivolumab + ipilimumab for the outcome "overall survival".

In addition, there was an indication of an effect modification by the characteristic "sex" for this outcome. For women, there was an indication of added benefit of nivolumab + ipilimumab. For men, there was proof of added benefit of nivolumab + ipilimumab for the outcome "overall survival".

Morbidity

Only the CA209-067 study provided usable data for the outcome "symptoms" measured with the symptom scales of the questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

No statistically significant difference between the treatment arms was shown for the following outcomes: **fatigue, pain, dyspnoea, insomnia, impaired appetite, constipation** and **diarrhoea**. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven.

No statistically significant difference between the treatment arms was shown for the outcome "**nausea** and **vomiting**". However, there was proof of an effect modification by the characteristic "metastasis stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

Health status

For the outcome "health status" (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]), usable data were only available from the CA209-067 study.

There was no statistically significant difference between the treatment groups for the outcome "health status" (EQ-5D VAS). There was no hint of an added benefit of nivolumab + ipilimumab; an added benefit for the outcome "health status" is therefore not proven.

Health-related quality of life

Only the CA209-067 study provided usable data for the outcome "health-related quality of life" measured with the functional scales of the EORTC QLQ-C30 questionnaire.

No statistically significant difference between the treatment arms was shown for the outcomes **"role functioning", "emotional functioning"** and **"social functioning"**. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven.

For the outcome **"cognitive functioning"**, there was a statistically significant result to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

There was no statistically significant difference between the treatment groups for the outcome **"physical functioning"**. However, there was proof of an effect modification by the characteristic "metastasis stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M0/M1a/M1b. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M1c, there was a statistically significant difference in favour of nivolumab + ipilimumab; hence there was a hint of an added benefit.

There was no statistically significant difference between the treatment groups for the outcome **"global health status"** from the EORTC. However, there was an indication of an effect modification by the characteristic "metastasis stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

Side effects

Serious adverse events

The meta-analysis of both studies showed a statistically significant difference to the disadvantage of nivolumab + ipilimumab for the outcome "SAEs". This resulted in an indication of greater harm from nivolumab + ipilimumab in comparison with ipilimumab.

Severe adverse events (CTCAE grade 3–4)

The meta-analysis of both studies showed a statistically significant effect to the disadvantage of nivolumab + ipilimumab for the outcome "severe AEs" (CTCAE grade 3–4). In addition, there was proof of an effect modification by the characteristic "metastasis stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This resulted in an indication of greater harm from nivolumab + ipilimumab.

Discontinuation due to adverse events

Each of the studies CA209-067 and CA209-069 showed a statistically significant effect to the disadvantage of nivolumab + ipilimumab for the outcome "discontinuation due to AEs". In spite of important heterogeneity, the results were clearly in the same direction. Hence there was an indication of greater harm.

Eye disorders

Only the CA209-069 study provided data for the outcome "eye disorders". A statistically significant difference to the disadvantage of nivolumab + ipilimumab, which was no more than marginal, was shown for the outcome. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit for this outcome is not proven.

Skin and subcutaneous tissue disorders (severe adverse events [CTCAE grade 3–4]) and colitis (discontinuation due to adverse events)

Only the CA209-069 study provided data for the outcomes "skin and subcutaneous tissue disorders" (severe AEs [CTCAE grade 3–4]) and colitis (discontinuation due to AEs). A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown for these outcomes. There was a hint of greater harm from nivolumab + ipilimumab in each case.

Result for research question 3: pretreated patients

There were no data on the comparison with the ACT specified by the G-BA for the assessment of the added benefit of nivolumab + ipilimumab in the treatment of pretreated patients. Hence there was no hint of an added benefit of nivolumab + ipilimumab in comparison with the ACT individual treatment; 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 in combination with ipilimumab in comparison with the ACT are 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].

Research question 1: treatment-naive patients with BRAF V600 mutant tumour

Since no data were available for the assessment of the added benefit of nivolumab + ipilimumab in treatment-naive patients with BRAF V600 mut tumour, an added benefit of nivolumab + ipilimumab is not proven.

Research question 2: treatment-naive patients with BRAF V600 wild type tumour

In the overall consideration, there were positive and negative effects for nivolumab + ipilimumab in comparison with ipilimumab. The negative effects were of major importance particularly in the category "side effects". Beyond that, the true extent of side effects remains unclear because the company presented only data on the early data cut-offs (9 months for the CA209-067 study; 6 months for the CA209-069 study). The results on overall survival were based on data cut-offs that were conducted much later (18 months for the CA209-067 study; 24 months for the CA209-069 study). It was not comprehensible that the company's dossier did not contain the results for the side effects at the later data cut-offs because the events were continued to be recorded. Hereinafter, the results on the added benefit are described separately for men and women.

For men, there was proof of major added benefit on the side of positive effects for the outcome "overall survival" and, in one subgroup, a hint of an added benefit in the category "health-related quality of life". The positive effects were accompanied by indications and hints of negative effects in the categories "health-related quality of life", "morbidity", "serious/severe side effects" and "non-serious/non-severe side effects". The negative effects varied in their extent and partly only applied to individual subgroups. For the total patient population, however, greater harm of major extent was shown for SAEs, attaining high rates of SAEs. Overall, the negative effects were not so large as to completely outweigh the survival advantage of nivolumab + ipilimumab. They resulted in a downgrading of the extent of added benefit from "major" to "considerable", however. In addition, the certainty of conclusions due to the uncertainty caused by the missing data on AEs at the data cut-offs used for the effects for overall survival was downgraded from "proof" to "indication". In summary, there is an indication of considerable added benefit for men with advanced (unresectable or metastatic) treatment-naive BRAF V600 wt melanoma.

For women, there is an indication of a non-quantifiable added benefit on the side of positive effects for the outcome "overall survival" and, in only one subgroup, a hint of an added benefit in the category "health-related quality of life". In contrast, there were indications and hints of negative effects in the categories "health-related quality of life", "serious/severe side effects" and "non-serious/non-severe side effects". The negative effects varied in their extent (at most "major") and partly only applied to individual subgroups. Overall, the negative effects were not so large as to completely outweigh the survival advantage of nivolumab + ipilimumab. They resulted in a downgrading of the possible extent of added benefit from at most "major" to at most "considerable", however. The certainty of conclusions due to the uncertainty caused by the missing data on AEs at the data cut-offs used

for the effects for overall survival was downgraded from “indication” to “hint”. In summary, there is a hint of a non-quantifiable added benefit, which can be at most “considerable”, for women with advanced (unresectable or metastatic) treatment-naive BRAF V600 wt melanoma.

Result for research question 3: pretreated patients

Since no data were available for the assessment of the added benefit of nivolumab + ipilimumab in pretreated patients, an added benefit of nivolumab + ipilimumab is not proven.

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

Table 3: Nivolumab + ipilimumab – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Subgroup	Extent and probability of added benefit
1	Treatment-naive patients with BRAF V600 mutant tumour	Vemurafenib	Added benefit not proven	
2	Treatment-naive patients with BRAF V600 wild type tumour	Ipilimumab	Men	Indication of considerable added benefit
			Women	Hint of a non-quantifiable added benefit (at most “considerable”)
3	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy	Added benefit not proven	

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee

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 in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in comparison with the ACT in adult patients with advanced (unresectable or metastatic) melanoma.

For the benefit assessment, the 3 research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of nivolumab + ipilimumab

Research question	**Therapeutic indication**	**Appropriate comparator therapy**[a]
1	Treatment-naive patients with BRAF V600 mutant tumour	Vemurafenib
2	Treatment-naive patients with BRAF V600 wild type tumour	Ipilimumab
3	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee		

Deviating from the ACT specified by the G-BA, the company defined ipilimumab as comparator therapy for all patients in the therapeutic indication (adult patients with advanced [unresectable or metastatic] melanoma) irrespective of their BRAF V600 mutation status and pretreatment status (see Section 2.7.1 of the full dossier assessment).

It additionally also investigated the research questions of the present benefit assessment based on the respective ACT specified by the G-BA.

The present assessment was conducted in comparison with the ACT specified by the G-BA.

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: treatment-naive patients with BRAF V600 mutant tumour

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: 13 April 2016)
- bibliographical literature search on nivolumab + ipilimumab (last search on 5 April 2016)
- search in trial registries for studies on nivolumab + ipilimumab (last search on 6 April 2016)
- bibliographical literature search on the ACT (last search on 12 April 2016)
- search in trial registries for studies on the ACT (last search on 13 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 23 June 2016)
- search in trial registries for studies on the ACT (last search on 23 June 2016)

No additional study was identified from the check.

2.3.2 Results on added benefit

There were no data on the comparison with the ACT specified by the G-BA for the assessment of the added benefit of nivolumab + ipilimumab in the treatment of treatment-naive patients with BRAF V600 mut tumour. Hence there was no hint of an added benefit of nivolumab + ipilimumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of nivolumab + ipilimumab in treatment-naive patients with BRAF V600 mut tumour, an added benefit of nivolumab + ipilimumab in comparison with vemurafenib is not proven in these patients.

2.3.4 List of included studies

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

2.4 Research question 2: treatment-naive patients with BRAF V600 wild type tumour

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on nivolumab (status: 13 April 2016)
- bibliographical literature search on nivolumab + ipilimumab (last search on 5 April 2016)
- search in trial registries for studies on nivolumab + ipilimumab (last search on 6 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 23 June 2016)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CA209-067	Yes	Yes	No
CA209-069	Yes	Yes	No
a: Study for which the company was sponsor. BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of nivolumab + ipilimumab in comparison with ipilimumab in treatment-naive patients with BRAF V600 wt tumour consisted of the studies CA209-067 and CA209-069 and concurred with that of the company.

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-067	RCT, double-blind, parallel	Treatment-naive adults with unresectable or metastatic (BRAF V600 mut or BRAF V600 wt) melanoma, stage III or stage IV according to the AJCC, ECOG status 0 or 1	Nivolumab + ipilimumab (N = 314) ipilimumab (N = 315) nivolumab (N = 316)[b] Relevant subpopulation thereof[c]: nivolumab + ipilimumab (N = 213) ipilimumab (N = 218)	Screening: within 28 days before randomization Treatment: ▪ Nivolumab + ipilimumab: 4 doses, then nivolumab until progression (or after progression for as long as the investigator considers the treatment to be beneficial to the patient) or until intolerance ▪ Ipilimumab: 4 doses (12 weeks) Follow-up: until death or discontinuation of study participation (at most up to 5 years)	137 centres in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom, USA 6/2013–ongoing Data cut-off 18 months for overall survival: 10 Nov 2015 Data cut-off for other outcomes: 31 Dec 2014[d]	Primary: PFS, overall survival Secondary: symptoms, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-069	RCT, double-blind, parallel	Treatment-naive adults with unresectable or metastatic (BRAF V600 mut or BRAF V600 wt) melanoma, stage III or stage IV according to the AJCC, ECOG PS 0 or 1	Nivolumab + ipilimumab (N = 95) ipilimumab (N = 47) Relevant subpopulation thereof[c]: nivolumab + ipilimumab (n = 72) ipilimumab (n = 37)	Screening: within 28 days before randomization Treatment: ▪ Nivolumab + ipilimumab: 4 doses, then nivolumab until progression (or after progression for as long as the investigator considers the treatment to be beneficial to the patient) or until intolerance ▪ Ipilimumab: 4 doses[e] (12 weeks) Follow-up: until death or discontinuation of study participation (at most up to 5 years)	21 centres in France and USA 8/2013–ongoing Data cut-off 24 months for overall survival: 25 Feb 2016 Data cut-off 12 months: 30 Jan 2015 Data cut-off 6 months: 4 Sep 2014	Primary: objective response rate Secondary: overall survival, symptoms, 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: This study arm is not relevant for the assessment and is not shown in the next tables.
c: Patients with BRAF V600 wt tumour, information on tumour classification, as for randomization, using IVRS.
d: Date of the last observation, database closure on 17 February 2015.
e: After documented progression or discontinuation of study medication, the patients in the ipilimumab arm had the opportunity to switch to nivolumab monotherapy.
AE: adverse event; AJCC: American Joint Committee on Cancer; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 mut: BRAF V600 mutant; BRAF V600 wt: BRAF V600 wild type; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IVRS: interactive voice response system; N: number of randomized patients; n: relevant subpopulation; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study	Intervention	Comparison	Prior and concomitant medication
CA209-067	Week 1-12:		**Pretreatment** ▪ no pretreatment with systemic treatment in advanced stage (III or IV) ▪ adjuvant or neoadjuvant treatment in the advanced stage (III or IV) had to be completed at least 6 weeks before randomization **Concomitant treatment** ▪ palliative radiotherapy or surgery if progression had occurred and the randomized study medication has been continued beyond progression **Non-permitted concomitant treatment** ▪ immunosuppressants (except for the treatment of an AE) ▪ systemic corticosteroids > 10 mg/day prednisone equivalent (except for the treatment of an AE); corticosteroids with minimal systemic absorption were allowed ▪ other antineoplastic treatment
	nivolumab 1 mg/kg BW IV + ipilimumab 3 mg/kg BW IV, every 3 weeks for 4 doses	ipilimumab 3 mg/kg BW IV + nivolumab placebo IV, every 3 weeks for 4 doses	
	From week 13:		
	nivolumab 3 mg/kg BW IV, every 2 weeks	placebo IV, every 2 weeks	
	no dose adjustments allowed for nivolumab, ipilimumab and placebo		
CA209-069	Weeks 1–12:		**Pretreatment** ▪ no pretreatment with systemic therapy for unresectable or metastatic melanoma ▪ adjuvant or neoadjuvant treatment in the advanced stage (III or IV) had to be completed at least 6 weeks before randomization **Concomitant treatment** ▪ palliative radiotherapy or surgery if progression had occurred and the randomized study medication has been continued beyond progression **Non-permitted concomitant treatment** ▪ immunosuppressants (except for the treatment of an AE) ▪ systemic corticosteroids > 10 mg/day prednisone equivalent; corticosteroids with minimal systemic absorption were allowed ▪ other antineoplastic treatment
	nivolumab 1 mg/kg BW IV + ipilimumab 3 mg/kg BW IV, every 3 weeks for 4 doses	ipilimumab 3 mg/kg BW IV + nivolumab placebo IV, every 3 weeks for 4 doses	
	From week 13:		
	nivolumab 3 mg/kg BW IV, every 2 weeks	placebo IV, every 2 weeks	

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; BW: body weight; IV: intravenous; RCT: randomized controlled trial; vs.: versus

The CA209-067 study was a randomized, double-blind, active-controlled, 3-arm parallel group study. It was conducted in Australia/New Zealand, Europe, Israel and North America.

The study included treatment-naive patients with unresectable or metastatic BRAF V600 wt or BRAF V600 mut melanoma (stage III or IV). Patients had to be in good general condition (corresponding to an ECOG PS of 0 or 1).

Randomization of the patients was stratified by programmed cell death ligand 1 (PD-L1) status, BRAF mutation status and metastasis stage. 314 patients were randomized to the nivolumab + ipilimumab arm and 315 patients to the ipilimumab arm. Only patients with BRAF V600 wt tumour were relevant for the benefit assessment. These were 213 patients in the nivolumab + ipilimumab arm and 218 patients in the ipilimumab arm. The company presented analyses of the patients with BRAF V600 wt tumour. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question 2 and were used for the benefit assessment. Figure 1 shows the design of study CA209-067.

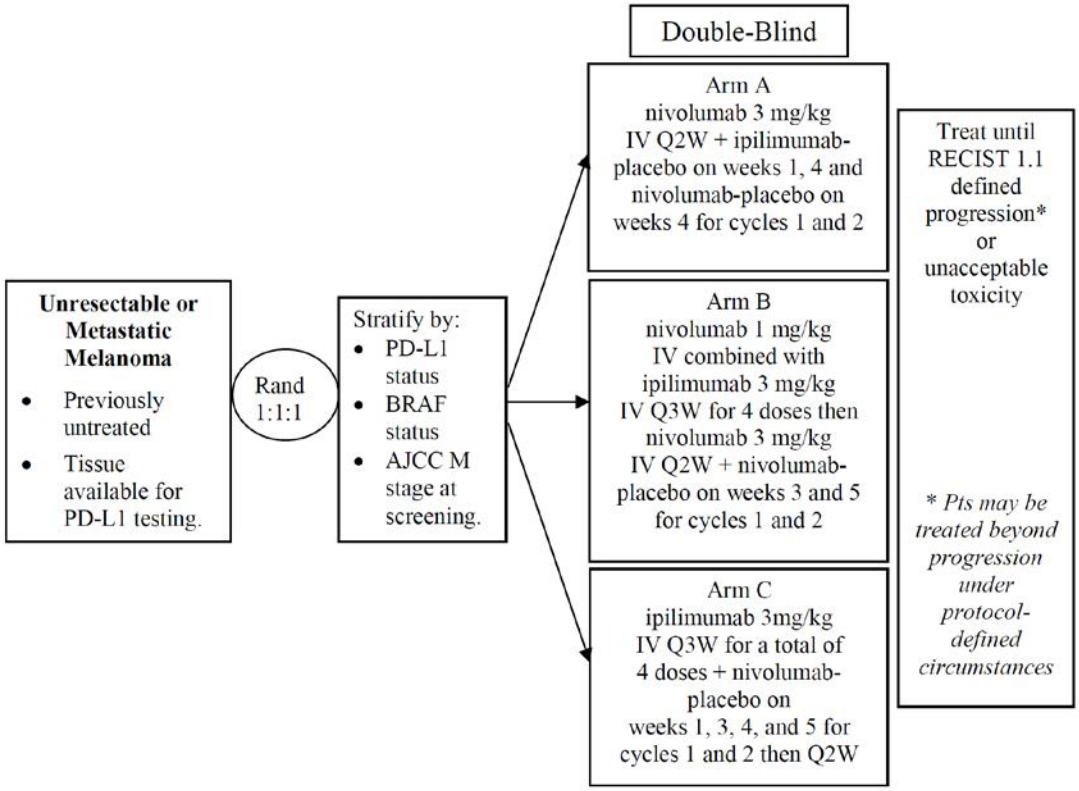

Figure 1: Design of study CA209-067

The CA209-069 study was a randomized, double-blind, active-controlled parallel group study. It was conducted in France and the USA. The study included treatment-naive patients with unresectable or metastatic BRAF V600 wt or BRAF V600 mut melanoma (stage III or IV). Randomization of the patients was stratified by BRAF mutation status.

The patients were randomized in a ratio of 2:1, 95 patients to the nivolumab + ipilimumab arm and 47 patients to the ipilimumab arm. The subpopulation relevant for the research

question comprised patients with a BRAF V600 wt tumour. These were 72 patients in the nivolumab + ipilimumab arm and 37 patients in the ipilimumab arm. The company presented analyses of the patients with BRAF V600 wt tumour. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question 2 and were used for the benefit assessment. Figure 2 shows the design of study CA209-069.

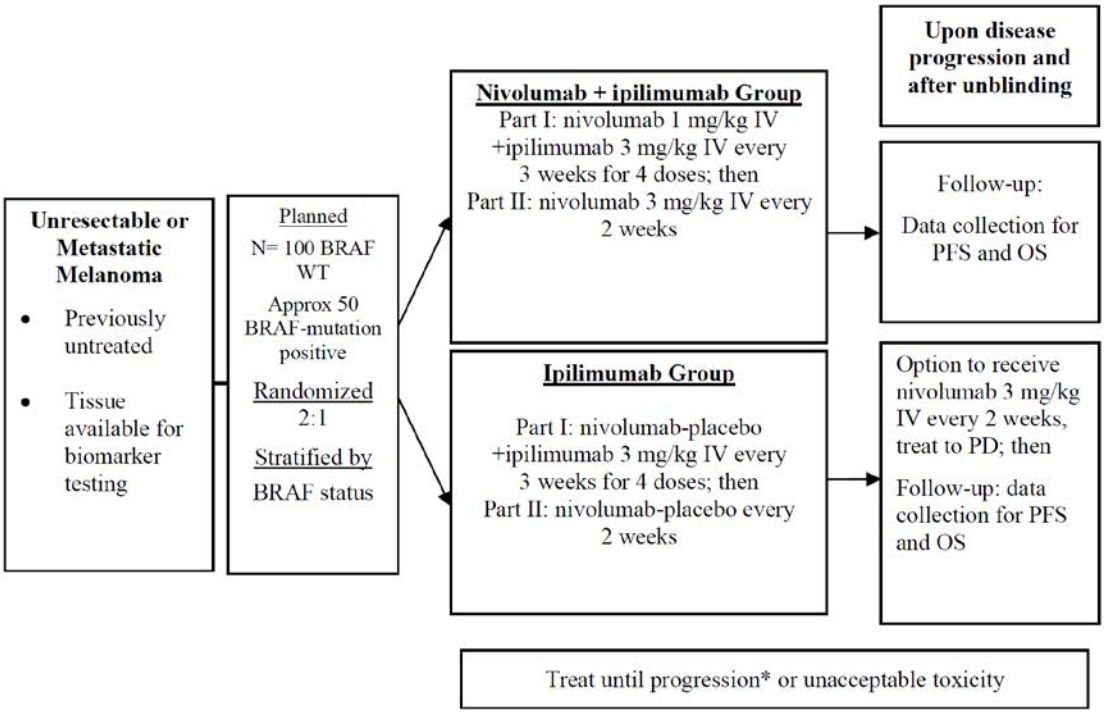

Figure 2: Design of study CA209-069

In the first 12 weeks, the patients in the nivolumab + ipilimumab arm of both studies received 1 mg/kg body weight nivolumab IV every 3 weeks and additionally 3 mg/kg body weight ipilimumab every 3 weeks for 4 doses in total. Subsequently, nivolumab at a dose of 3 mg/kg body weight every 2 weeks was continued until the end of the randomized study treatment. This concurs with the requirements of the Summary of Product Characteristics (SPC) [3].

The patients in the ipilimumab arm of both studies received 3 mg/kg body weight ipilimumab IV every 3 weeks for 4 doses in the first 12 weeks. Placebo for nivolumab was additionally administered. The use of ipilimumab concurred with the requirements of the SPC [4]. After the first study phase, placebo for nivolumab every 2 weeks was continued until the end of the randomized study treatment.

In both studies, no dose adjustments were allowed in the intervention or in the comparator arm.

The patients in both studies could receive concomitant treatments in addition to the study medication. Immunosuppressants, systemic corticosteroids and other antineoplastic treatments were not allowed.

In both studies, the randomized study treatment was continued until at least one of the following stopping criteria occurred:

- withdrawal of the patient's consent or patient's request to discontinue the randomized study treatment
- safety concerns (e.g. non-acceptable toxicity)
- occurrence of progression; however, the randomized study treatment could be continued after progression occurred if the patient tolerated this treatment and the investigator considered this treatment to be beneficial for the patient

On occurrence of progression and at the end of the study treatment, patient and investigator were unblinded in both studies.

In study CA209-067, there were no restrictions regarding the subsequent therapies after completion of the randomized treatment phase. Treatment switching from the ipilimumab arm to the nivolumab + ipilimumab arm was not allowed. 17.8% of the patients in the nivolumab + ipilimumab arm and 49.1% of the patients in the ipilimumab arm received subsequent systemic therapy after progression. None of the patients in the relevant subpopulation from the ipilimumab arm received nivolumab as subsequent systemic therapy.

In study CA209-069, there was also no restriction regarding the subsequent therapies after completion of the randomized treatment phase. Treatment switching from the ipilimumab arm to the nivolumab + ipilimumab arm was not allowed. However, patients were allowed to switch from the ipilimumab arm to nivolumab monotherapy after disease progression. At the 24-month data cut-off from 25 February 2016, 54% of the patients from the ipilimumab arm were receiving treatment with nivolumab.

Overall survival and PFS were the primary outcomes of the study of the CA209-067 study; ORR was the primary outcome of the CA209-069 study.

Analysis and data cut-offs

CA209-067

For the CA209-067 study, the company had planned separate time points of analysis for both primary outcomes. PFS was to be analysed after all patients had been observed for at least 9 months. The primary analysis of PFS was conducted at the database closure on 17 February 2015. Except overall survival, the results available for the benefit assessment were based on this data cut-off. Originally, overall survival was to be analysed only after all patients had been observed for at least 28 months. An earlier data cut-off from 10 November 2015 available for the benefit assessment resulted from an unplanned interim analysis requested by

the European Medicines Agency (EMA) in the framework of the approval process of nivolumab + ipilimumab. At this time point, the company presented results on overall survival after all patients had been observed for at least 18 months. No data were available for other outcomes at this data cut-off.

The time point for the primarily planned analysis of overall survival after 28 months has not been reached yet.

CA209-069

The preplanned final analysis for the ORR with data cut-off on 4 September 2014 was planned for the time point after all patients had been observed for at least 6 months. At this time point, the company presented also data for all other outcomes.

In addition, the company presented results on overall survival at the data cut-off on 30 January 2015. This derived from an addendum to the final clinical study report (CSR). At this time point, all patients had been observed for at least 12 months. The company additionally presented further results on overall survival at the data cut-off 25 February 2016; all patients had been observed for at least 24 months at this time point. These 2 data cut-offs had not been prespecified in the protocol.

Planned duration of follow-up

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

Table 8: Planned duration of follow up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study **Outcome category** **Outcome**	**Planned follow-up**
CA209-067	
Overall survival	Until death, discontinuation of participation in the study or end of study[a]
Morbidity	
EORTC QLQ-C30 (symptom scales)[b]	First follow-up visit: 30 ± 7 days after end of treatment[c] Second follow-up visit: 70 to 84 days after the first follow-up visit
EQ-5D VAS	First and second follow-up visit, then every 3 months for one year, and then every 6 months until death, discontinuation of participation in the study or end of study
Health-related quality of life	
EORTC QLQ-C30 (functional scales)[d]	First follow-up visit: 30 ± 7 days after end of treatment[c] Second follow-up visit: 70 to 84 days after the first follow-up visit
Side effects	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 70 to 84 days after the first follow-up visit[e]
CA209-069	
Mortality	
Overall survival	Until death, discontinuation of participation in the study or end of study[f]
Morbidity	
EORTC QLQ-C30 (symptom scales)[b]	Recorded only in the first 6 months after the start of treatment
EQ-5D VAS	Recorded only in the first 6 months after the start of treatment
Health-related quality of life	
EORTC QLQ-C30 (functional scales)[d]	Recorded only in the first 6 months after the start of treatment
Side effects	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 70 to 84 days after the first follow-up visit[e]

a: The follow-up observation for overall survival can be conducted up to 5 years after the first analysis of survival. The study ends with the final analysis of overall survival.
b: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0.
c: 30 ± 7 days after the last dose of the study medication or on the day of study discontinuation ± 7 days if this was ≥ 37 days after the last dose.
d: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0.
e: Later toxicities were documented also beyond the second follow-up visit.
f: The follow-up observation for overall survival can be conducted up to 5 years after the final analysis of the primary outcome.
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The studies CA209-067 and CA209-069 differed in some aspects regarding the planned duration of follow-up for the outcomes of the category “morbidity and health-related quality

of life". In the CA209-069 study, the outcomes from the questionnaires EORTC QLQ-C30 and EQ-5D (VAS) were only recorded within the first 6 months after the start of treatment, whereas in the CA209-067 study, data were continued to be recorded during the entire study treatment and also after the first follow-up visit (about 30 days).

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

Table 9: Characteristics of the study populations – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study Characteristics Category	**Nivolumab + ipilimumab**	**Ipilimumab**
CA209-067	**N = 213**	**N = 218**
Age [years], mean (SD)	61 (14)	63 (12)
Sex [F/M], %	33/67	33/67
Ethnicity, n (%)		
White	211 (99.1)	208 (95.4)
Other	2 (0.9)	10 (4.6[a])[b]
Metastases at the start of the study, n (%)		
M0	7 (3.3)	11 (5.0)
M1a	22 (10.3)	23 (10.6)
M1b	57 (26.8)	52 (23.9)
M1c	127 (59.6)	132 (60.6)
Extent of metastases (number of locations), n (%)		
< 3	ND	ND
≥ 3	ND	ND
PD-L1 status with threshold value ≥ 5%[c], n (%)		
Positive	44 (20.7)	44 (20.2)[d]
Negative/non-quantifiable	169 (79.3[a])	174 (79.8[a])
Time since first diagnosis [years], median [min; max]	ND	ND
Baseline LDH serum level, n (%)		
≤ ULN	130 (61.0)	130 (59.6)
> ULN	82 (38.5)	83 (38.1)
Not reported	1 (0.5)	5 (2.3)
History of brain metastases, n (%)		
Yes	9 (4.2)	10 (4.6)
No	204 (95.8)	208 (95.4)
ECOG Performance Status, n (%)		
0	151 (70.9)	150 (68.8)
1	61 (28.6)	68 (31.2)
2	0 (0)	0 (0)
Not reported	1 (0.5)	0 (0)
Disease stage according to the AJCC at the start of the study, n (%)		
III	10 (4.7)	15 (6.9)
IV	203 (95.3)	203 (93.1)

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (continued)

Study Characteristics Category	**Nivolumab + ipilimumab**	**Ipilimumab**
CA209-067	**N = 213**	**N = 218**
9-month data cut-off		
Study discontinuations, n (%)	ND	ND
Treatment discontinuations, n (%)	ND	ND
18-month data cut-off		
Study discontinuations, n (%)	ND	ND
Treatment discontinuations, n (%)	ND	ND
CA209-069	N = 72	N = 37
Age [years], mean (SD)	65 (10)	67 (9)
Sex [F/M], %	33/67	38/62
Ethnicity, n (%)		
White	69 (95.8)	37 (100)
Other	3 (4.2[a])	0 (0)
Metastases at the start of the study, n (%)		
M0	6 (8.3)	5 (13.5)
M1a	9 (12.5)	7 (18.9)
M1b	22 (30.6)	8 (21.6)
M1c	34 (47.2)	16 (43.2)
Not reported	1 (1.4)	1 (2.7)
Extent of metastases (number of locations), n (%)		
< 3	48 (66.7)[a]	28 (75.7)[a]
≥ 3	24 (33.3)[a]	9 (24.3)[a]
PD-L1 status with threshold value ≥ 5%[c], n (%)		
Positive	19 (26.4)	8 (21.6)
Negative/non-quantifiable	53 (73.6[a])	29 (78.4[a])
Time since first diagnosis [years], median [min; max]	1.71 [0.1; 23.5]	1.40 [0.1; 20.4]
Baseline LDH serum level, n (%)		
≤ ULN	57 (79.2)	30 (81.1)
> ULN	15 (20.8)	7 (18.9)
Not reported		
History of brain metastases, n (%)		
Yes	4 (5.6)	0 (0)
No	67 (93.1)	37 (100)
Not reported	1 (1.4)	0 (0)

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (continued)

Study Characteristics Category	**Nivolumab + ipilimumab**	**Ipilimumab**
CA209-069	N = 72	N = 37
ECOG Performance Status, n (%)		
0	62 (86.1)	30 (81.1)
1	9 (12.5)	7 (18.9)
2	1 (1.4)	0 (0)
Disease stage according to the AJCC at the start of the study, n (%)		
III	8 (11.1)	8 (21.6)
IV	64 (88.9)	29 (78.4)
6-month data cut-off:		
Study discontinuations, n (%)	13 (18.3[e])	13 (35.1)
Treatment discontinuations, n (%)	54 (76.1[e])	20 (54.1)
12-month data cut-off:		
Study discontinuations, n (%)	15 (21.1[e])	16 (43.2)
Treatment discontinuations, n (%)	57 (80.3[e])	25 (67.6)
24-month data cut-off:		
Study discontinuations, n (%)	ND	ND
Treatment discontinuations, n (%)	ND	ND

a: Institute's calculation.
b: Includes one person with unreported ethnicity.
c: Proportion of PD-L1-positive cells.
d: Inconsistencies with the information provided in the dossier [5] on nivolumab monotherapy where a positive PD-L1 status was reported for 92 (42.8%) of the patients in the ipilimumab arm (BRAF V600 wt). In the total population (information provided in M5), the proportion in the nivolumab + ipilimumab and in the ipilimumab arms is also reported to be > 40%.
e: Percentage based on the number of randomized and treated patients: N = 71.
AJCC: American Joint Committee on Cancer; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; ECOG: Eastern Cooperative Oncology Group; F: female; LDH: lactate dehydrogenase; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of patients with BRAF V600 wt tumour; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; ULN: upper limit of normal; vs.: versus

The patient characteristics in both studies were largely comparable. In the CA209-067 study, the proportion of patients with metastasis stage M1c at the start of the study was somewhat higher (about 60%) than in the CA209-069 study (about 45%). In both studies, most patients had an ECOG PS of 0, and the vast majority of the patients had stage IV disease.

No data were available on the number of patients who discontinued the study or the treatment for the relevant subpopulation of study CA209-067. In the CA209-069 study, the number of patients who discontinued the study at the 6-month and 12-month data cut-offs was lower in

the nivolumab + ipilimumab arm than in the ipilimumab arm. The number of treatment discontinuations, however, was higher in each case in the nivolumab + ipilimumab arm than in the ipilimumab arm.

Table 10 shows the mean/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, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study **Data cut-off** **Duration of the study phase** **Outcome category**	**Nivolumab + ipilimumab**	**Ipilimumab**
CA209-067	N = 212	N = 215
Data cut-off: 17 February 2015 (9 months[a])		
Treatment duration [months]		
Median [min; max]	2.8 [< 0.1; 18.8]	3.3 [< 0.1; 18.6]
Mean (SD)	5.7 (5.4)	5.2 (4.6)
Observation period [months]		
Overall survival		
Median [min; max]	12.4 [< 0.1; 18.8]	12.2 [0.3; 18.6]
Mean (SD)	11.0 (4.5)	10.6 (4.5)
Morbidity, health-related quality of life, side effects	ND	ND
Data cut-off: 10 November 2015 (18 months[a])		
Treatment duration [months]	ND	ND
Observation period [months]	ND	ND
CA209-069	N = 71	N = 37
Data cut-off: 4 September 2014 (6 months[a])		
Treatment duration [months]	ND[b]	ND[b]
Observation period [months]	ND	ND
Data cut-off: 30 January 2015 (12 months[a])		
Treatment duration [months]		
Median [min; max]	2.1 [< 0.1; 10.2]	2.8 [0.7; 8.8]
Mean (SD)	3.5 (3.0)	3.7 (2.5)
Observation period [months]		
Overall survival		
Median [min; max]	7.6 [0.2; 10.2]	6.9 [1.3; 10.1]
Mean (SD)	6.9 (2.3)	6.6 (2.2)
Morbidity, health-related quality of life, side effects	ND	ND
Data cut-off: 25 February 2016 (24 months[a])		
Treatment duration [months]	ND	ND
Observation period [months]	ND	ND

a: Minimum observation period for all patients.

b: Median time (months) until treatment discontinuation and 95% CI estimated from the Kaplan-Meier curve: 2.14 [2.07; 3.71] vs. 2.76 [2.07; 4.86].

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; max: maximum; min: minimum; n: number of patients in the category; N: number of treated patients with BRAF V600 wt tumour; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In study CA209-067, the median treatment duration was somewhat longer in the ipilimumab arm (3.3 months) than in the nivolumab + ipilimumab arm (2.8 months). The median observation period for overall survival in both study arms was about 12 months at the data cut-off on 17 February 2015 (minimum observation period of 9 months for all patients).

In study CA209-069, the median treatment duration was also somewhat longer in the ipilimumab arm (2.8 months) than in the nivolumab + ipilimumab arm (2.1 months). The median observation period for overall survival in both study arms was about 7 months at the data cut-off on 30 January 2015 (minimum observation period of 12 months for all patients) and was therefore notably shorter than in study CA209-067 (about 12 months after a minimum observation period of 9 months for all patients).

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

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			
CA209-067	Yes	Yes	Yes[a]	Yes[a]	Yes	Yes	Low
CA209-069	Yes	Yes	Yes[b]	Yes[b]	Yes	Yes	Low

a: After progression and treatment discontinuation, about 20% of the patients in the nivolumab + ipilimumab arm and about 30% of the patients in the ipilimumab arm were unblinded.
b: After progression and treatment discontinuation, about 30% of the patients in the nivolumab + ipilimumab arm and about 60% of the patients in the ipilimumab arm were unblinded.
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; RCT: randomized controlled trial; vs.: versus

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

2.4.2 Results on added benefit

2.4.2.1 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 scales of the EORTC QLQ-C30
  - health status, measured with the EQ-5D VAS
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3-4)
  - discontinuation due to AEs
  - eye disorders (System Organ Class [SOC])
  - skin and subcutaneous tissue disorders ([SOC]; severe AEs [CTCAE grade 3–4])
  - colitis (Preferred Term [PT], discontinuation due to AEs)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 E) (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, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study / Data cut-off	Overall survival	Symptoms (EORTC)[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC)[b]	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3-4)	Eye disorders	Skin and subcutaneous tissue disorders (CTCAE grade 3–4)	Colitis (discontinuation due to AEs)
CA209-067										
17 Feb 2015 (9 months)	No	**Yes**[c]	**Yes**[c]	**Yes**[c]	**Yes**	**Yes**	**Yes**	No	No	No
10 Nov 2015 (18 months)	**Yes**	No	No	No	No	No	No	No	No	No
CA209-069										
4 Sep 2014 (6 months)	**Yes**	No[d]	No[d]	No[d]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
30 Jan 2015 (12 months)	**Yes**	No	No	No	No	No	No	No	No	No
25 Feb 2016 (24 months)	**Yes**	No	No	No	No	No	No	No	No	No

a: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0.
b: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0.
c: Usable data up to the time point 67 weeks.
d: The proportion of analysed patients was below 70% at all time points.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Table 12 shows that the company presented analyses of all patient-relevant outcomes (except overall survival for study CA209-067) only for the first data cut-offs of the 2 studies CA209-067 and CA209-069. As Table 8 shows, in study CA209-067 data were still continuously recorded after the first data cut-off for all patient-relevant outcomes; in study CA209-069, besides mortality, side effects were continued to be recorded. It is therefore incomprehensible that the company's dossier only contained analyses of overall survival and not analyses of the other patient-relevant outcomes for the later data cut-offs of the studies. These data are required for a complete benefit assessment, however.

2.4.2.2 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, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Study		Outcomes									
	Study level	Overall survival	Symptoms (EORTC)[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC)[b]	SAEs[c]	Discontinuation due to AEs[c]	Severe AEs (CTCAE grade 3–4)[c]	Eye disorders[d]	Skin and subcutaneous tissue disorders (CTCAE grade 3–4)[d]	Colitis (discontinuation due to AEs)[d]
CA209-067[e]	L	L	H[f, g]	H[f]	H[f, g]	H[g]	H[g]	H[g]	–[h]	–[h]	–[h]
CA209-069[i]	L	L	–[j]	–[j]	–[j]	H[g]	H[g]	H[g]	H[k]	H[k]	H[k]

a: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0.
b: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0.
c: Analysis without recording of progression of the underlying disease. 100-day follow-up (discontinuation due to AEs: 30-day follow-up)
d: 30-day follow-up in study CA209-069.
e: Data cut-off for overall survival from 10 November 2015. For all other outcomes from 17 February 2015.
f: No adequate implementation of the ITT principle.
g: Potential informative censoring.
h: No usable data available, information only for the total study population.
i: Data cut-off for overall survival from 25 February 2016. For all other outcomes from 4 September 2014.
j: No usable data available, no adequate implementation of the ITT principle.
k: Different proportions of discontinuations and different reasons for discontinuation.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; ITT: intention to treat; L: low; QLQ-C30: Quality of Life Questionnaire Core-30; 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.

For the outcomes “symptoms”, “health status” and “health-related quality of life”, usable data were only available from the CA209-067 study. Due to potentially informative censoring and the inadequate implementation of the ITT principle, the risk of bias for these outcomes was rated as high. This concurs with the company’s assessment.

The risk of bias for the outcomes “SAEs”, “severe AEs” (CTCAE grade 3-4) and “discontinuation due to AEs” was also rated as high due to potentially informative censoring. This deviates from the company’s assessment, which rated the risk of bias as low.

Only the CA209-069 study provided data for the specific AEs (eye disorders, skin and subcutaneous tissue disorders and colitis). The risk of bias was rated as high due to the different proportions of patients who discontinued and the different reasons for discontinuation. The company did not present these outcomes in its Module 4 E and, accordingly, made no statement on the risk of bias (see Section 2.7.2.4.2 of the full dossier assessment for more details on the risk of bias).

2.4.2.3 Results

Table 14, Table 15 and Table 16 summarize the results on the comparison of nivolumab + ipilimumab in treatment-naive patients with advanced (unresectable or metastatic) BRAF V600 wt tumour.

Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations. The Kaplan-Meier curves on overall survival are presented in Appendix A of the full dossier assessment; the tables showing the overviews of the most common AEs (information for the relevant subpopulation was only available for study CA209-069) are presented in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Outcome category Outcome Study	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab HR [95% CI]; p-value
Mortality					
Overall survival					
CA209-067					
10 Nov 2015 (18-month data cut-off)	213	NA [NA; NA] 81 (38.0)	218	18.6 [15.08; NA] 117 (53.7)	0.65 [0.49; 0.86]; 0.003
CA209-069					
25 Feb 2016 (24-month data cut-off)	72	NA [NA; NA] 23 (31.9)	37	24.8 [10.3; NA] 18 (48.6)	0.58 [0.31; 1.08] 0.084
Total[a]					0.64 [0.49; 0.82]; < 0.001
Supplementary presentation: further data cut-offs of study 069					
4 Sep 2014 (6-month data cut-off)	*72*	*NA [NA; NA]* *13 (18.1)*	*37*	*NA [NA; NA]* *11 (29.7)*	*0.60 [0.27; 1.35]* *0.213*
30 January 2015 (12-month data cut-off)	*72*	*NA [NA; NA]* *15 (20.8)*	*37*	*NA [NA; NA]* *14 (37.8)*	*0.54 [0.26; 1.11]* *0.090*
Morbidity					
Symptoms (EORTC QLQ-C30 – time to deterioration)[b]					
CA209-067[c]					
Fatigue	213	1.9 [1.4; 2.6] 132 (62.0)	218	2.3 [1.4; 2.5] 143 (65.6)	0.94 [0.74; 1.20] 0.631
Nausea and vomiting	213	9.1 [4.2; NA] 89 (41.8)	218	NA [6.8; NA] 79 (36.2)	1.14 [0.84; 1.54] 0.403
Pain	213	5.4 [2.9; 6.9] 107 (50.2)	218	3.5 [2.4; 4.5] 119 (54.6)	0.80 [0.62; 1.04] 0.102
Dyspnoea	213	13.2 [5.4; NA] 85 (39.9)	218	NA [5.7; NA] 79 (36.2)	1.08 [0.80; 1.47] 0.602
Insomnia	213	6.3 [3.7; NA] 90 (42.3)	218	12.0 [5.0; NA] 83 (38.1)	1.08 [0.80; 1.45] 0.620
Impaired appetite	213	5.4 [3.3; 10.4] 103 (48.4)	218	9.2 [4.9; NA] 89 (40.8)	1.27 [0.95; 1.68] 0.104
Constipation	213	NA [11.5; NA] 67 (31.5)	218	18.5 [8.7; 18.5] 70 (32.1)	0.90 [0.64; 1.26] 0.528

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (continued)

Outcome category Outcome Study	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab HR [95% CI]; p-value
Diarrhoea	213	NA [6.9; NA] 73 (34.3)	218	15.9 [8.9; NA] 73 (33.5)	0.94 [0.68; 1.30] 0.697
CA209-069				No usable data[d]	
Health-related quality of life					
EORTC QLQ-C30 - time to deterioration[e]					
CA209-067[c]					
Physical functioning	213	5.1 [3.9; 6.9] 104 (48.8)	218	4.5 [2.7; 7.6] 110 (50.5)	0.93 [0.71; 1.21] 0.576
Role functioning	213	2.8 [2.3; 3.9] 122 (57.3)	218	3.5 [2.4; 4.5] 124 (56.9)	0.98 [0.76; 1.26] 0.877
Emotional functioning	213	NA [13.2; NA] 67 (31.5)	218	NA [10.8; NA] 69 (31.7)	0.98 [0.70; 1.38] 0.907
Cognitive functioning	213	5.5 [4.2; 8.4] 104 (48.8)	218	15.9 [6.8; NA] 81 (37.2)	1.35 [1.01; 1.80] 0.045
Social functioning	213	3.5 [2.4; 5.1] 114 (53.5)	218	4.3 [3.1; 7.6] 107 (49.1)	1.14 [0.88; 1.48] 0.332
Global health status	213	3.5 [2.6; 4.7] 113 (53.1)	218	4.2 [3.1; 5.7] 111 (50.9)	1.22 [0.94; 1.59] 0.141
CA209-069				No usable data[d]	
Side effects[f]					
AEs (supplementary information)					
CA209-067[g]	212	0.25 [0.20; 0.30] 210 (99.1)	215	0.36 [0.30; 0.46] 213 (99.1)	–
CA209-069[h]	71	0.20 [0.10; 0.30] 71 (100)	37	0.26 [0.07; 0.43] 36 (97.3)	–
SAEs					
CA209-067[g]	212	2.10 [1.74; 2.60] 153 (72.2)	215	5.95 [4.50; 12.65] 111 (51.6)	1.82 [1.42; 2.33] < 0.001
CA209-069[h]	71	2.60 [1.71; 4.37] 47 (66.2)	37	7.62 [2.86; NA] 19 (51.4)	1.58 [0.93; 2.70] 0.088
Total[i]					1.77 [1.42; 2.22]; < 0.001

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (continued)

Outcome category Outcome Study	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab HR [95% CI]; p-value
Severe AEs (CTCAE grade 3–4)[j]					
CA209-067[g]	212	2.00 [1.64; 2.53] 158 (74.5)	215	4.30 [2.79; 6.18] 127 (59.1)	1.60 [1.27; 2.02] < 0.001
CA209-069[h]	71	1.94 [1.41; 2.76] 56 (78.9)	37	4.37 [2.60; 9.43] 21 (56.8)	2.15 [1.29; 3.59] 0.003
Total[i]					1.69 [1.35; 2.12]; < 0.001
Discontinuation due to AEs					
CA209-067[g]	212	15.18 [7.06; NA] 85 (40.1)	215	NA [NA; NA] 36 (16.7)	2.71 [1.83; 4.00] < 0.001
CA209-069[h]	71	4.57 [2.83; NA] 32 (45.1)	37	NA [NA; NA] 3 (8.1)	6.59 [2.02; 21.54] < 0.001
Total[i]				Heterogeneity: I^2 = 48.8%; p = 0.162	

a: Calculated from the meta-analysis of the 18-month data cut-off of study CA209-067 and the 24-month data cut-off of study CA209-069.
b: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0. An increase in score by at least 10 points compared with baseline is considered as deterioration.
c: The last usable time point for study CA209-067 was week 67. Patients without data for at least one documentation time after the start of the study were censored on day 1. Hence, 182 of 213 (85.4%) patients in the nivolumab + ipilimumab arm and 179 of 218 (82.1%) patients in the ipilimumab arm were actually analysed.
d: The proportion of analysed patients was below 70% at all time points.
e: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0. A decrease in score by at least 10 points compared with baseline is considered as deterioration.
f: AEs up to 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.
g: AEs at the data cut-off 17 February 2015 (9-month data cut-off).
h: AEs at the data cut-off 4 September 2014 (6-month data cut-off).
i: Calculated from meta-analysis.
j: Patients with the highest severity grade 5 who have had a grade 3 or 4 AE before are also considered.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; 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; vs.: versus

Table 15: Results (morbidity – health status) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Outcome category Outcome Study	Nivolumab + ipilimumab			Ipilimumab			Nivolumab + ipilimumab vs. ipilimumab
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI][c]; p-value
Morbidity							
Health status (EQ-5D VAS)							
CA209-067[d]	182	73.1 (19.5)	-6.5 (1.4)	178	75.4 (18.8)	-5.6 (1.4)	-0.9 [-3.7; 1.9]; 0.532
CA209-069	No usable data[e]						

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the ITT population.
c: A positive change in comparison with the start of the study indicates improvement.
d: The last usable time point for study CA209-067 was week 67.
e: The proportion of analysed patients was below 70% at all time points.

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 16: Results (specific AEs) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Outcome category Outcome Study	Nivolumab + ipilimumab N	 Patients with event n (%)	Ipilimumab N	 Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab RR [95% CI]; p-value
Side effects[a]					
Eye disorders					
CA209-067		ND		ND	ND
CA209-069	71	17 (23.9)	37	2 (5.4)	4.43 [1.08; 18.15][b]; 0.017[c]
Skin and subcutaneous tissue disorders (CTCAE grade 3–4)					
CA209-067		ND		ND	ND
CA209-069	71	8 (11.3)	37	0 (0)	–[d]; 0.040[c]
Colitis (discontinuation due to AEs)					
CA209-067		ND		ND	ND
CA209-069	71	12 (16.9)	37	1 (2.7)	–[d]; 0.032[c]

a: Information for study CA209-069 with 30-day follow-up after treatment discontinuation, at the 6-month data cut-off.
b: Institute's calculation.
c: Institute's calculation, unconditional exact test (CSZ method according to [6]).
d: Effect estimate and 95% CI not meaningfully interpretable.
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus

At most proof of an added benefit can be derived from the results of the 2 studies CA209-067 and CA209-069 (see Section 2.4.2.2 and Section 2.7.2.8 of the full dossier assessment).

Mortality

Overall survival

Study CA209-069 showed no statistically significant difference between the treatment groups for the outcome "overall survival". For the CA209-067 study and the meta-analysis of both studies, in contrast, a statistically significant difference in favour of nivolumab + ipilimumab was shown.

In addition, there was an indication of an effect modification by the characteristic "sex" for this outcome (see Section 2.4.2.4). For women, there was an indication of added benefit of nivolumab + ipilimumab. For men, there was proof of added benefit of nivolumab + ipilimumab for the outcome "overall survival".

This assessment deviates from that of the company, which derived proof of added benefit for the outcome "all-cause mortality" on the basis of the total population and did not consider the effect modification by sex.

Morbidity

Symptoms (EORTC)

Only the CA209-067 study provided usable data for the outcome "symptoms" measured with the symptom scales of the EORTC QLQ-C30 questionnaire.

No statistically significant difference between the treatment arms was shown for the following outcomes: **fatigue, pain, dyspnoea, insomnia, impaired appetite, constipation** and **diarrhoea**. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven.

No statistically significant difference between the treatment arms was shown for the outcome "**nausea** and **vomiting**". However, there was proof of an effect modification by the characteristic "metastases at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

This deviates from the company's assessment, which derived a hint of a minor added benefit for the total population only for the outcome "pain". It did not consider the effect modification for the outcome "nausea and vomiting".

Health status (EQ-5D VAS)

For the outcome "health status" (EQ-5D VAS), usable data were only available from the CA209-067 study.

There was no statistically significant difference between the treatment groups for the outcome "health status" (EQ-5D VAS). There was no hint of an added benefit of nivolumab + ipilimumab; an added benefit for the outcome "health status" is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

Health-related quality of life (EORTC)

Only the CA209-067 study provided usable data for the outcome "health-related quality of life" measured with the functional scales of the EORTC QLQ-C30 questionnaire.

No statistically significant difference between the treatment arms was shown for the outcomes **"role functioning", "emotional functioning"** and **"social functioning"**. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven.

For the outcome **"cognitive functioning"**, there was a statistically significant result to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

There was no statistically significant difference between the treatment groups for the outcome **"physical functioning"**. However, there was proof of an effect modification by the characteristic "metastasis stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M0/M1a/M1b. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M1c, there was a statistically significant difference in favour of nivolumab + ipilimumab; hence there was a hint of an added benefit.

There was no statistically significant difference between the treatment groups for the outcome **"global health status"** from the EORTC. However, there was an indication of an effect modification by the characteristic "metastasis stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

The results deviate from those of the company, which saw neither added benefit nor lesser benefit of nivolumab + ipilimumab for the outcome "health-related quality of life".

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 2.7.2.4.3 of the full dossier assessment).

Serious adverse events

Study CA209-069 showed no statistically significant difference between the treatment groups for the outcome "SAEs". For the CA209-067 study and the meta-analysis of both studies, in contrast, a statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown. This resulted in an indication of greater harm from nivolumab + ipilimumab in comparison with ipilimumab.

This deviates from the company's assessment, which derived proof of greater harm.

Severe adverse events (CTCAE grade 3-4)

Each of the studies CA209-067 and CA209-067 as well as the meta-analysis showed a statistically significant effect to the disadvantage of nivolumab + ipilimumab for the outcome "severe AEs" (CTCAE grade 3–4). In addition, there was proof of an effect modification by the characteristic "metastasis stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This resulted in an indication of greater harm from nivolumab + ipilimumab.

This deviates from the company's assessment, which derived proof of greater harm on the basis of the total population. It did not consider the effect modification by the characteristic "metastasis stage at the start of the study".

Discontinuation due to adverse events

Each of the studies CA209-067 and CA209-069 showed a statistically significant effect to the disadvantage of nivolumab + ipilimumab for the outcome "discontinuation due to AEs". In spite of important heterogeneity, the results were clearly in the same direction. Hence there was an indication of greater harm.

This deviates from the company's assessment, which derived proof of greater harm.

Eye disorders

Only the CA209-069 study provided data for the outcome "eye disorders". A statistically significant difference to the disadvantage of nivolumab + ipilimumab, which was no more than marginal, was shown for the outcome (see Section 2.4.3.1). Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit for this outcome is not proven.

The company did not use this outcome in its assessment.

Skin and subcutaneous tissue disorders (severe adverse events [CTCAE grade 3–4]) and colitis (discontinuation due to adverse events)

Only the CA209-069 study provided data for the outcomes "skin and subcutaneous tissue disorders" (severe AEs [CTCAE grade 3–4]) and colitis (discontinuation due to AEs). A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown for the outcomes. There was a hint of greater harm from nivolumab + ipilimumab in each case.

The company did not use these outcomes in its assessment.

2.4.2.4 Subgroups and other effect modifiers

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

- metastasis stage at the start of the study (M0/M1a/M1b versus M1c)
- age group II (< 65 years/≥ 65 years to < 75 years/≥ 75 years)
- sex (male versus female)
- ethnicity I (white versus African American versus Asian versus other)
- brain metastases (yes versus no)
- lactate dehydrogenase (LDH) I serum level (≤ upper limit of normal [ULN] versus **≥** ULN)
- PD-L1 status II (< 5% versus > 5%)

All subgroup characteristics and cut-off values mentioned were predefined in the studies CA209-067 and CA209-069.

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.

The subgroup results of nivolumab + ipilimumab in comparison with ipilimumab are summarized in Table 17. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

Table 17: Subgroups (mortality, morbidity; health-related quality of life, side effects) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab

Outcome Characteristic Study Subgroup	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab HR [95% CI]	p-value
Mortality						
Overall survival						
Sex						
CA209-067						
Male	143	NA [NA; NA] 49 (34.3)	145	18.5 [12.8; NA] 79 (54.5)	0.55 [0.38; 0.78]	< 0.001
Female	70	NA [10.7; NA] 32 (45.7)	73	20.2 [14.1; NA] 38 (52.1)	0.91 [0.57; 1.46]	0.692
CA209-069						
Male	48	NA [NA; NA] 13 (27.1)	23	NA [5.4; NA] 11 (47.8)	0.54 [0.24; 1.21]	0.130
Female	24	NA [17.0; NA] 10 (41.7)	14	24.8 [5.1; NA] 7 (50.0)	0.65 [0.25; 1.72]	0.387
Total					Interaction:	0.106
Male					0.55 [0.39; 0.76]	< 0.001
Female					0.85 [0.56; 1.30]	0.461
Morbidity						
Symptoms (EORTC QLQ-C30 – time to deterioration)[a]						
Nausea and vomiting						
Metastases at the start of the study						
CA209-067					Interaction:	0.004
M0/M1a/M1b	87	5.6 [2.8; NA] 43 (49.4)	89	NA [NA; NA] 25 (28.1)	1.97 [1.20; 3.23]	0.007
M1c	126	NA [3.7; NA] 46 (36.5)	129	7.1 [3.1; NA] 54 (41.9)	0.78 [0.52; 1.16]	0.213

(continued)

Table 17: Subgroups (mortality, morbidity; health-related quality of life, side effects) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (continued)

Outcome Characteristic Study Subgroup	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab HR [95% CI]	p-value
Health-related quality of life						
EORTC QLQ-C30 - time to deterioration[b]						
Physical functioning						
Metastases at the start of the study						
CA209-067					Interaction:	0.016
M0/M1a/M1b	87	4.5 [2.7; 6.3] 47 (54.0)	89	8.9 [3.8; NA] 40 (44.9)	1.42 [0.93; 2.18]	0.106
M1c	126	5.6 [3.9; NA] 57 (45.2)	129	2.6 [2.4; 4.9] 70 (54.3)	0.70 [0.49; 0.99]	0.046
Global health status						
Metastases at the start of the study						
CA209-067					Interaction:	0.054
M0/M1a/M1b	87	2.6 [2.0; 3.6] 53 (60.9)	89	4.6 [2.9; 8.7] 46 (51.7)	1.73 [1.15; 2.58]	0.008
M1c	126	5.3 [2.8; 9.6] 60 (47.6)	129	3.8 [2.4; 5.8] 65 (50.4)	0.96 [0.67; 1.36]	0.813

(continued)

Table 17: Subgroups (mortality, morbidity; health-related quality of life, side effects) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (continued)

Outcome Characteristic Study Subgroup	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median survival time in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab HR [95% CI]	p-value
Side effects						
Severe AEs (CTCAE grade 3-4)						
Metastases at the start of the study						
CA209-067						
M0/M1a/M1b	86	1.9 [1.5; 2.5] 69 (80.2)	86	12.7 [3.4; NA] 42 (48.8)	2.29 [1.55; 3.37]	< 0.001
M1c	126	2.1 [1.6; 2.8] 89 (70.6)	129	2.9 [2.2; 5.2] 85 (65.9)	1.27 [0.94; 1.71]	0.122
CA209-069						
M0/M1a/M1b	36	1.7 [0.8; 5.2] 27 (75.0)	20	8.5 [2.6; 9.4] 10 (50.0)	2.49 [1.17; 5.32]	0.015
M1c	34	2.2 [1.5; 2.8] 28 (82.4)	16	3.9 [1.3; NA] 10 (62.5)	1.94 [0.93; 4.04]	0.073
Total					Interaction:	0.025
M0/M1a/M1b					2.33 [1.65; 3.29]	< 0.001
M1c					1.37 [1.00; 1.87]	0.052

a: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0. An increase in score by at least 10 points compared with baseline is considered as deterioration.
b: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0. A decrease in score by at least 10 points compared with baseline is considered as deterioration.
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; 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; vs.: versus

Mortality

Overall survival

For the studies CA209-067 and CA209-069 jointly, an indication (interaction test: p = 0.106) of an effect modification by the characteristic “sex” was shown for the outcome “overall survival”.

Both studies showed a numerical difference in favour of nivolumab + ipilimumab for women, but neither the individual studies nor the meta-analysis showed a statistically significant difference between the treatment groups. The result was statistically significant in the meta-analysis of the total populations of both studies. Since there was only an indication and no proof of an effect modification, the added benefit of nivolumab + ipilimumab in women is not principally called into question, but subject to greater uncertainty. The certainty of conclusions was therefore downgraded from "proof" to "indication". In the present data situation, the extent of added benefit for women cannot be determined using the overall estimator of the study or the effect estimate of the subgroup. Hence there is an indication of a non-quantifiable added benefit of nivolumab + ipilimumab for women. Study CA209-069 showed no statistically significant difference between the treatment groups for men. In the CA209-067 study and the meta-analysis of both studies, in contrast, a statistically significant difference in favour of nivolumab + ipilimumab was shown for the outcome "overall survival". There was proof of added benefit of nivolumab + ipilimumab.

This deviates from the company's assessment, which did not use the effect modification by the characteristic "sex" in its assessment.

Morbidity

Symptoms (EORTC)

Proof (p = 0.004) of an effect modification by the characteristic "metastasis stage at the start of the study" was shown for the outcome **"nausea and vomiting"** for study CA209-067.

No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

This deviates from the company's assessment, which did not use the effect modification by the characteristic "metastasis stage at the start of the study" in its assessment.

Health-related quality of life

Health-related quality of life (EORTC)

There was proof (p = 0.016) of an effect modification by the characteristic "metastasis stage at the start of the study" for the outcome **"physical functioning"**.

No statistically significant difference between the treatment arms was shown for patients with metastasis stage M0/M1a/M1b. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M1c, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

There was an indication (p = 0.054) of an effect modification by the characteristic "metastasis stage at the start of the study" for the outcome **"global health status"**.

No statistically significant difference between the treatment arms was shown for patients with metastasis stage M1c. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. For patients with metastasis stage M0/M1a/M1b, there was a statistically significant difference to the disadvantage of nivolumab + ipilimumab. This led to a hint of lesser benefit of nivolumab + ipilimumab.

This deviates from the company's assessment, which did not use the effect modification by the characteristic "metastasis stage at the start of the study" in its assessment.

Side effects

Severe adverse events (CTCAE grade 3–4)

Proof (p = 0.025) of an effect modification by the characteristic "metastasis stage at the start of the study" was shown for the outcome "severe AEs" (CTCAE grade 3–4) for the studies CA209-067 and CA209-069 jointly.

For patients with metastasis stage M1c, the meta-analysis showed no statistically significant result. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven. Each of both studies CA209-067 and CA209-069 as well as the meta-analysis showed a statistically significant difference to the disadvantage of nivolumab + ipilimumab for patients with metastasis stage M0/M1a/M1b. This resulted in an indication of greater harm from nivolumab + ipilimumab.

This deviates from the company's assessment, which did not use the effect modification by the characteristic "metastasis stage at the start of the study" in its assessment.

2.4.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for research question 2 (treatment-naive patients with BRAF V600 wt tumour) 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.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Sections 2.4.2.3 and 2.4.2.4 resulted in the following assessment of nivolumab + ipilimumab in comparison with ipilimumab:

- proof of added benefit for the outcome "overall survival" for men
- an indication of an added benefit for the outcome "overall survival" for women
- a hint of lesser benefit for the outcome "nausea and vomiting" for patients with M0/M1a/M1b metastasis stage at the start of the study
- a hint of added benefit for the outcome "physical functioning" for patients with M1c metastasis stage at the start of the study
- a hint of lesser benefit for each of the outcomes "cognitive functioning" and "global health status" (the latter only for patients with M0/M1a/M1b metastasis stage at the start of the study)
- an indication of greater harm for each of the outcomes "SAEs", "discontinuation due to AEs" and "severe AEs" (CTCAE grade 3–4) (the latter only for patients with M0/M1a/M1b metastasis stage at the start of the study)
- a hint of greater harm for each of the outcomes "skin and subcutaneous tissue disorders" severe AEs (CTCAE grade 3–4) and "colitis" (discontinuation due to AEs)

The extent of the respective added benefit at outcome level was estimated from these results (see Table 18).

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

The outcome "discontinuation due to AEs" was allocated to the category "non-serious/non-severe side effects" because the company's dossier contained no information on the severity of the events. Eye disorders were allocated to the category "non-serious/non-severe side effects" because they were mainly CTCAE grade I-II events.

The outcomes "SAEs", "severe AEs" (CTCAE grade 3–4), "skin and subcutaneous tissue disorders" (severe AEs [CTCAE grade 3–4]) were per se allocated to the outcome category "serious/severe AEs", as was the outcome "colitis" because mainly severe AEs (CTCAE grade 3–4) occurred.

Table 18: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. ipilimumab** **Median time to event or proportion of events or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 18.6 to 24.8 months[c] HR: 0.64 [0.49; 0.82] p < 0.001	
Sex		
Men	NA vs. NA to 18.5 months[c] HR: 0.55 [0.39; 0.76] P < 0.001 probability: "proof"	Outcome category: all-cause mortality $CI_u < 0.85$ added benefit, extent: "major"
Women	NA vs. 20.2 to 24.8 months[c] HR: 0.85 [0.56; 1.39] p = 0.461 probability: "indication"	Outcome category: all-cause mortality added benefit, extent: "non-quantifiable"
Morbidity		
EORTC QLQ-C30 symptom scales: time to deterioration of symptoms		
Fatigue[d]	1.9 vs. 2.3 months HR: 0.94 [0.74; 1.20] p = 0.631	Lesser benefit/added benefit not proven
Nausea and vomiting[d]		
Metastases at the start of the study		
M0/M1a/M1b	5.6 months vs. NA HR: 1.97 [1.20; 3.23] HR: 0.51 [0.31; 0.83][e] p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ lesser benefit, extent: "minor"
M1c	NA vs. 7.1 months HR: 0.78 [0.52; 1.16] p = 0.213	Lesser benefit/added benefit not proven
Pain[d]	5.4 vs. 3.5 months HR: 0.80 [0.62; 1.04] p = 0.102	Lesser benefit/added benefit not proven
Dyspnoea[d]	13.2 months vs. NA HR: 1.08 [0.80; 1.47] p = 0.602	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (continued)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. ipilimumab** **Median time to event or proportion of events or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Insomnia[d]	6.3 vs. 12.0 months HR: 1.08 [0.80; 1.45] p = 0.620	Lesser benefit/added benefit not proven
Impaired appetite[d]	5.4 vs. 9.2 months HR: 1.27 [0.95; 1.68] p = 0.104	Lesser benefit/added benefit not proven
Constipation[d]	NA vs. 18.5 months HR: 0.90 [0.64; 1.26] p = 0.528	Lesser benefit/added benefit not proven
Diarrhoea[d]	NA vs. 15.9 months HR: 0.94 [0.68; 1.30] p = 0.697	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)[d]	mean: -6.5 vs. -5.6 MD: -0.9 [-3.7; 1.9] p = 0.532	Lesser benefit/added benefit not proven
Health-related quality of life		
Functional scales and global health status of the EORTC QLQ-C30: time to deterioration		
Physical functioning[d] Metastases at the start of the study M0/M1a/M1b	4.5 vs. 8.9 months HR: 1.42 [0.93; 2.18] p = 0.106	Lesser benefit/added benefit not proven
M1c	5.6 vs. 2.6 months HR: 0.70 [0.49; 0.99] p = 0.046 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Role functioning[d]	2.8 vs. 3.5 months HR: 0.98 [0.76; 1.26] p = 0.877	Lesser benefit/added benefit not proven
Emotional functioning[d]	NA HR: 0.98 [0.70; 1.38] p = 0.907	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (continued)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. ipilimumab** **Median time to event or proportion of events or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Cognitive functioning[d]	5.5 vs. 15.9 months HR: 1.35 [1.01; 1.80] HR: 0.74 [0.56; 0.99][e] p = 0.045 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
Social functioning[d]	3.5 vs. 4.3 months HR: 1.14 [0.88; 1.48] p = 0.332	Lesser benefit/added benefit not proven
Global health status[d]	3.5 vs. 4.2 months HR: 1.22 [0.94; 1.59] p = 0.141	
Metastases at the start of the study		
M0/M1a/M1b	2.6 vs. 4.6 months HR: 1.73 [1.15; 2.58] HR: 0.58 [0.39; 0.87][e] p = 0.008 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ lesser benefit; extent: "considerable"
M1c	5.3 vs. 3.8 months HR: 0.96 [0.67; 1.36] p = 0.813	Lesser benefit/added benefit not proven
Side effects		
SAEs	2.1 to 2.6 vs. 5.95 to 7.62 months[c] HR: 1.77 [1.42; 2.22] HR: 0.56 [0.45; 0.70][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"

(continued)

Table 18: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. ipilimumab** **Median time to event or proportion of events or mean change** **Effect estimates [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Severe AEs (CTCAE grade 3-4)		
Metastases at the start of the study		
M0/M1a/M1b	1.7 to 1.9 months vs. 8.5 to 12.7 months[c] HR: 2.33 [1.65; 3.29] HR: 0.43 [0.30; 0.61][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
M1c	2.1 to 2.2 months vs. 2.9 to 3.9 months[c] HR: 1.37 [1.00; 1.87] p = 0.052	Greater/lesser harm not proven
Discontinuation due to AEs[f]	4.57 to 15.18 months vs. NA[c] heterogeneous results; there was a statistically significant effect to the disadvantage of nivolumab + ipilimumab in both studies probability: "indication"	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"
Eye disorders[g]	Proportion: 23.9% vs. 5.4% RR: 4.43 [1.08; 18.15] RR: 0.23 [0.06; 0.93][e] p = 0.017[h]	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven
Skin and subcutaneous tissue disorders[g] (severe AEs [CTCAE grade 3–4])	Proportion: 11.3% vs. 0% RR: NC[i] p = 0.040 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"
Discontinuation due to colitis[g] (severe AEs CTCAE grade 3–4)	Proportion: 16.9% vs. 2.7% RR: NC[i] p = 0.032 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"

(continued)

Table 18: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (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: Minimum and maximum medians of the time to event in each treatment arm in the studies included.
d: Only data from the CA209-067 study were available.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: No common effect estimate can be provided due to heterogeneous data.
g: Only data from the CA209-069 study were available.
h: Greater/lesser harm is not proven because the effect size is only marginal.
i: Effect estimate and CI not meaningfully interpretable.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 19 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of nivolumab + ipilimumab in comparison with ipilimumab for treatment-naive patients with BRAF V600 wt tumour

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Men proof of an added benefit – extent: "major" ▫ Women indication of an added benefit – extent: "non-quantifiable"	
	Morbidity[a] ▪ Symptoms (EORTC QLQ-C30) ▫ Nausea and vomiting - Metastases at the start of the study, M0/M1a/M1b: hint of lesser benefit – extent: "minor"
Health-related quality of life[a] ▪ Functional scales of the EORTC (QLQ-C30) ▫ Physical functioning - metastases at the start of the study, M1c: hint of an added benefit – extent: "minor"	Health-related quality of life[a] ▪ Functional scales of the EORTC (QLQ-C30) ▫ Cognitive functioning: hint of lesser benefit – extent: "minor" ▫ Global health status - metastases at the start of the study, M0/M1a/M1b: hint of lesser benefit – extent: "considerable"
	Serious/severe side effects ▪ SAEs: indication of greater harm – extent: "major" ▪ Severe AEs (CTCAE grade 3-4) ▫ metastases at the start of the study, M0/M1a/M1b: indication of greater harm – extent: "major" ▪ skin and subcutaneous tissue disorders[b]: hint of greater harm – extent: "non-quantifiable" ▪ discontinuation due to colitis[b]: hint of greater harm – extent: "non-quantifiable"
	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: indication of greater harm – extent: "non-quantifiable"
a: Only data from the CA209-067 study were available. b: Only data from the CA209-069 study were available. AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; SAE: serious adverse event; vs.: versus	

In the overall consideration, there were positive and negative effects for nivolumab + ipilimumab in comparison with ipilimumab. The negative effects were of major importance particularly in the category "side effects". Beyond that, the true extent of side effects remains unclear because the company presented only data on the early data cut-offs

(9 months for the CA209-067 study; 6 months for the CA209-069 study). The results on overall survival were based on data cut-offs that were conducted much later (18 months for the CA209-067 study; 24 months for the CA209-069 study). It was not comprehensible that the company's dossier did not contain the results for the side effects at the later data cut-offs because the events were continued to be recorded. Hereinafter, the results on the added benefit are described separately for men and women.

For men, there was proof of major added benefit on the side of positive effects for the outcome "overall survival" and, in one subgroup, a hint of an added benefit in the category "health-related quality of life". The positive effects were accompanied by indications and hints of negative effects in the categories "health-related quality of life", "morbidity", "serious/severe side effects" and "non-serious/non-severe side effects". The negative effects varied in their extent and partly only applied to individual subgroups. For the total patient population, however, greater harm of major extent was shown for SAEs, attaining high rates of SAEs. Overall, the negative effects were not so large as to completely outweigh the survival advantage of nivolumab + ipilimumab. They resulted in a downgrading of the extent of added benefit from "major" to "considerable", however. In addition, the certainty of conclusions due to the uncertainty caused by the missing data on AEs at the data cut-offs used for the effects for overall survival was downgraded from "proof" to "indication". In summary, there is an indication of considerable added benefit for men with advanced (unresectable or metastatic) treatment-naive BRAF V600 wt melanoma.

For women, there is an indication of a non-quantifiable added benefit on the side of positive effects for the outcome "overall survival" and, in one subgroup, a hint of an added benefit in the category "health-related quality of life". In contrast, there were indications and hints of negative effects in the categories "health-related quality of life", "serious/severe side effects" and "non-serious/non-severe side effects". The negative effects varied in their extent (at most "major") and partly only applied to individual subgroups. Overall, the negative effects were not so large as to completely outweigh the survival advantage of nivolumab + ipilimumab. They resulted in a downgrading of the possible extent of added benefit from at most "major" to at most "considerable", however. The certainty of conclusions due to the uncertainty caused by the missing data on AEs at the data cut-offs used for the effects for overall survival was downgraded from "indication" to "hint". In summary, there is a hint of a non-quantifiable added benefit, which can be at most "considerable", for women with advanced (unresectable or metastatic) treatment-naive BRAF V600 wt melanoma.

2.4.4 List of included studies

CA209-067

Bristol-Myers Squibb. A phase 3, randomized, double- blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma [online]. In: EU Clinical Trials Register. [Accessed: 29.06.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005371-13.

Bristol-Myers Squibb. Phase 3 study of nivolumab or nivolumab plus ipilimumab versus ipilimumab alone in previously untreated advanced melanoma (CheckMate 067): full text view [online]. In: ClinicalTrials.gov. 24.06.2016 [Accessed: 29.06.2016]. URL: https://ClinicalTrials.gov/show/NCT01844505.

Bristol-Myers Squibb. Nivolumab program: studys CA209; core safety statistical analysis plan for multiple indications; version # 4 [unpublished].

Bristol-Myers Squibb. A phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma: study CA209067; statistical analysis plan for clinical study report; version # 3.0 [unpublished]. 2014.

Bristol-Myers Squibb. A phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma: study CA209067; interim clinical study report [unpublished]. 2015.

Bristol-Myers Squibb. A phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma: study CA209067; clinical protocol [unpublished]. 2015.

Bristol-Myers Squibb. A phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma: study CA209067; addendum 01 for interim clinical study report; PD-L1 results using a validated IHC assay [unpublished]. 2015.

Bristol-Myers Squibb. Nivolumab (Opdivo): Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms bei Erwachsenen in Kombination mit Ipilimumab; study CA209-067; Zusatzanalysen [unpublished]. 2016.

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373(1): 23-34.

Larkin JMG, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD et al. Supplementary appendix to "Combined nivolumab and ipilimumab or monotherapy in untreated melanoma" (N Engl J Med 2015; 373(1): 23-34) [online]. [Accessed: 15.08.2016]. URL: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1504030/suppl_file/nejmoa1504030_appendix.pdf.

CA209-069

Bristol-Myers Squibb. Study of nivolumab (BMS-936558) plus ipilimumab compared with ipilimumab alone in the treatment of previously untreated, unresectable, or metastatic melanoma (CheckMate 069): full text view [online]. In: ClinicalTrials.gov. 08.01.2016 [Accessed: 29.06.2016]. URL: https://ClinicalTrials.gov/show/NCT01927419.

Bristol-Myers Squibb. Study of nivolumab (BMS-936558) plus ipilimumab compared with ipilimumab alone in the treatment of previously untreated, unresectable, or metastatic melanoma (CheckMate 069): study results [online]. In: ClinicalTrials.gov. 08.01.2016 [Accessed: 29.06.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01927419.

Bristol-Myers Squibb. Nivolumab program: studys CA209; core safety statistical analysis plan for multiple indications; version # 4 [unpublished].

Bristol-Myers Squibb. A phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma: study CA209069; final clinical study report [unpublished]. 2014.

Bristol-Myers Squibb. A phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma: study CA209069; addendum 1 to clinical study report [unpublished]. 2015.

Bristol-Myers Squibb. A phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma: study CA209069; addendum 2 to clinical study report [unpublished]. 2015.

Bristol-Myers Squibb. Nivolumab (Opdivo): Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms bei Erwachsenen in Kombination mit Ipilimumab; study CA209-069; Zusatzanalysen [unpublished]. 2016.

Bristol-Myers Squibb. A phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma: study CA209069; addendum 1 to clinical study report [unpublished]. 2015.

Bristol-Myers Squibb. A phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma: study CA209069; addendum 2 to clinical study report [unpublished]. 2015.

Bristol-Myers Squibb. Nivolumab (Opdivo): Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms bei Erwachsenen in Kombination mit Ipilimumab; study CA209-069; Zusatzanalysen [unpublished]. 2016.

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2.5 Research question 3: pretreated patients

Research question 3 concerns the comparison of nivolumab + ipilimumab with the ACT (treatment of physician's choice) in pretreated patients.

2.5.1 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: 13 April 2016)
- bibliographical literature search on nivolumab + ipilimumab (last search on 5 April 2016)
- search in trial registries for studies on nivolumab + ipilimumab (last search on 6 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 23 June 2016)

No relevant study was identified from the check.

2.5.2 Results on added benefit

There were no data on the comparison with the ACT specified by the G-BA for the assessment of the added benefit of nivolumab + ipilimumab in the treatment of pretreated patients. Hence there was no hint of an added benefit of nivolumab + ipilimumab in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of nivolumab + ipilimumab in pretreated patients, an added benefit of nivolumab + ipilimumab in comparison with individual treatment is not proven.

2.5.4 List of included studies

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

2.6 Extent and probability of added benefit – summary

Table 20 presents a summary of the extent and probability of the added benefit of nivolumab + ipilimumab.

Table 20: Nivolumab + ipilimumab – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Subgroup	Extent and probability of added benefit
1	Treatment-naive patients with BRAF V600 mutant tumour	Vemurafenib	Added benefit not proven	
2	Treatment-naive patients with BRAF V600 wild type tumour	Ipilimumab	Men	Indication of considerable added benefit
			Women	Hint of a non-quantifiable added benefit (at most "considerable")
3	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy	Added benefit not proven	

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee

This deviates from the company's approach, which derived proof of considerable added benefit for the total population of adult patients with advanced (unresectable or metastatic) melanoma irrespective of the BRAF V600 mutation status and the pretreatment status.

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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