IQWiG Reports – Commission No. A17-27

Nivolumab (melanoma) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

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: 13 September 2017). 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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[2] Due to legal data protection regulations, employees have the right not to be named.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
BRAF	rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf)
BRAF V600 wt	BRAF V600 wild type
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 15 June 2017.

The company already submitted a dossier for the drug to be evaluated in the present therapeutic indication on 8 June 2016 for the early benefit assessment. In this procedure, on 15 December 2016, the G-BA limited its decision until 15 June 2017. The reason for the limitation of the decision was a change in the appropriate comparator therapy (ACT) from ipilimumab to nivolumab or pembrolizumab for the subpopulation of treatment-naive patients with advanced (unresectable or metastatic) melanoma with rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf) wild type (BRAF V600 wt) tumour.

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 treatment-naive adult patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour. The research question shown in Table 2 resulted from the ACT specified by the G-BA.

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

Subindication	**ACT**[a]
Treatment-naive adult patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour	**Nivolumab** or pembrolizumab

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); BRAF V600 wt: BRAF V600 wild type; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT and chose nivolumab from the options presented. The assessment therefore refers to the comparison of the combination therapy (nivolumab + ipilimumab) with nivolumab monotherapy. In this constellation, it is not possible to draw a conclusion on the drug nivolumab alone. This is all the more so since the dosages used in the induction phase differed between combination therapy and monotherapy.

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

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

Results

One relevant study (CA209-067) was available for the benefit assessment.

Study pool and patient characteristics

The CA209-067 study was a randomized, double-blind, active-controlled, 3-arm parallel group study. The nivolumab + ipilimumab arm and the nivolumab arm of the study were relevant for the present assessment. The study included patients with unresectable or metastatic melanoma (stage III or IV according to the American Joint Committee on Cancer [AJCC] classification), known BRAF V600 mutation status and good general condition (corresponding to an Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1).

Overall, 316 patients were randomized to the nivolumab arm, and 314 patients to the nivolumab + ipilimumab arm of the study. Randomization was stratified according to the factors programmed cell death ligand 1 (PD-L1) status, BRAF V600 mutation status and metastasis stage. The analyses on the subpopulation of the patients with BRAF V600 wt tumour who received either nivolumab + ipilimumab combination therapy (N = 213) or nivolumab monotherapy (N = 216) were used for the present benefit assessment.

In each case, treatment of the patients was in compliance with the specifications of the Summaries of Product Characteristics (SPCs). In the 12-week induction phase, patients in the intervention group of the study received nivolumab 1 mg/kg body weight in combination with ipilimumab 3 mg/kg body weight every 3 weeks. The comparator group received nivolumab 3 mg/kg body weight every 2 weeks. In the maintenance phase, both groups received nivolumab 3 mg/kg body weight every 2 weeks.

Patients were treated until progression or unacceptable persistent toxicity.

Primary outcomes of the study were progression-free survival (PFS) and overall survival. Secondary outcomes were symptoms, health-related quality of life and side effects.

The present assessment was based on the prespecified final analysis on overall survival at month 28 at database closure on 13 September 2016.

Risk of bias

The risk of bias at study level was rated as low. The risk of bias at outcome level was rated as low for all outcomes except for the outcome “overall survival”. There were no usable data for specific AE outcomes.

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival". There was no hint of an added benefit of nivolumab + ipilimumab in comparison with nivolumab; an added benefit is therefore not proven.

Morbidity

Symptoms (measured with the symptom scales of the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30])

No statistically significant difference was shown between the treatment groups for the outcome "symptoms", measured with the symptom scales of the EORTC QLQ-C30 questionnaire, for the scales of pain, insomnia and constipation. This resulted in no hint of an added benefit of nivolumab + ipilimumab for any of these outcomes; an added benefit for these outcomes is therefore not proven.

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for each of the scales of fatigue, nausea and vomiting, dyspnoea, decreased appetite and diarrhoea. However, the 95% confidence interval (CI) of the standardized mean difference (Hedges' g) was fully outside the irrelevance range of −0.2 to 0.2 only for the diarrhoea scale. Hence only the effect for the diarrhoea scale was interpreted as relevant. This resulted in a hint of lesser benefit of nivolumab + ipilimumab in comparison with nivolumab for the outcome "diarrhoea". For the outcomes "fatigue", "nausea and vomiting", "dyspnoea" and "decreased appetite", there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit for these outcomes is therefore not proven.

Health status

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for health status measured with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (EORTC QLQ-C30)

For the outcome "health-related quality of life", measured with the EORTC QLQ-C30 functional scales, a statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for the scales of global health status, physical functioning, role functioning, emotional functioning, and social functioning. However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2 for any of these scales. Hence a relevant effect cannot be inferred for any of the scales. The scale on cognitive functioning showed no statistically

significant difference between the treatment groups. Overall, there was no hint of an added benefit of nivolumab + ipilimumab for the outcome "health-related quality of life"; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs) and severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4)

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for each of the outcomes "SAEs" and "severe AEs (CTCAE grade 3–4)". This resulted in a hint of greater harm of nivolumab + ipilimumab in comparison with nivolumab for each of these outcomes.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for the outcome "discontinuation due to AEs". In addition, there was an effect modification by the characteristic "age" for this outcome. A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown both for patients < 65 years and for patients ≥ 65 years of age. This resulted in a hint of greater harm of nivolumab + ipilimumab for each of both age categories with differences in the extent.

Further outcomes

There were no usable data for specific AE outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

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

In the overall consideration, there were only negative effects for nivolumab + ipilimumab in the outcome categories "morbidity" and "side effects".

There was a hint of lesser benefit with non-quantifiable extent for the outcome "diarrhoea" (measured with the EORTC QLQ-C30). In the outcome category "side effects", there was a hint of greater harm of major extent for each of the outcomes "SAEs" and "severe AEs

[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].

(CTCAE grade 3–4)". For the outcome "discontinuation due to AEs", there was a hint of greater harm of major extent for patients < 65 years and a hint of greater harm of considerable extent for patients ≥ 65 years of age.

In summary, there is a hint of lesser benefit of nivolumab + ipilimumab in comparison with nivolumab for treatment-naive patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour.

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

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

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Treatment-naive adult patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour[b]	**Nivolumab** or pembrolizumab	Hint of lesser benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The study underlying the benefit assessment included patients with an ECOG PS of 0 or 1. It is unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); BRAF V600 wt: BRAF V600 wild type; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on the 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 treatment-naive adult patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour.

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

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

Subindication	**ACT**[a]
Treatment-naive adult patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour	**Nivolumab** or pembrolizumab
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); BRAF V600 wt: BRAF V600 wild type; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT and chose nivolumab from the options presented (see Section 2.7.1 of the full dossier assessment). The assessment therefore refers to the comparison of the combination therapy (nivolumab + ipilimumab) with nivolumab monotherapy. In this constellation, it is not possible to draw a conclusion on the drug nivolumab alone. This is all the more so since the dosages used in the induction phase differed between combination therapy and monotherapy.

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

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

2.3 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: 21 March 2017)
- bibliographical literature search on nivolumab (last search on 21 March 2017)
- search in trial registries for studies on nivolumab (last search on 21 March 2017)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 5 July 2017)

The check identified no additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: nivolumab + ipilimumab vs. nivolumab

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
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab + ipilimumab vs. nivolumab

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 melanoma, stage III or IV according to the AJCC, ECOG PS of 0 or 1 and known BRAF mutation status[b]	Nivolumab + ipilimumab (N = 314) ipilimumab (N = 315)[c] nivolumab (N = 316) Relevant subpopulation thereof[d]: nivolumab + ipilimumab (n = 213) nivolumab (n = 216)	Screening: within 28 days before randomization Treatment: ▪ nivolumab + ipilimumab: 2 6-week cycles (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 ▪ nivolumab: until progression (or after progression for as long as the investigator considers the treatment to be beneficial to the patient) or until intolerance Follow-up observation: until death or discontinuation of study participation (at most up to 5 years after primary analysis of overall survival)	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 9 months for final PFS analysis: 17 Feb 2015 ▪ interim data cut-off 18 months for interim analysis of overall survival: 10 Nov 2015 ▪ final data cut-off 28 months for overall survival: 13 Sep 2016	Primary: PFS, overall survival Secondary: symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: The BRAF mutation status was tested according to local standards of the individual study centres.
c: The arm is not relevant for the assessment and is not shown in the following tables.
d: Patients with BRAF V600 wt tumour according to IVRS.

AE: adverse event; 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 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, nivolumab + ipilimumab vs. nivolumab

Study	Intervention	Comparison	Prior and concomitant medication
CA209-067	Cycles 1 and 2 (6 weeks each):		**Pretreatment** ▪ no pretreatment with systemic treatment in the 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, in weeks 1 and 4 + nivolumab placebo in week 3 and 5 of a cycle	nivolumab 3 mg/kg BW IV, every 2 weeks + ipilimumab placebo in week 1 and 4, and nivolumab placebo in week 4	
	From cycle 3:		
	nivolumab 3 mg/kg BW IV, every 2 weeks	nivolumab 3 mg/kg BW IV, every 2 weeks	
	No dose adjustments allowed for nivolumab, ipilimumab and placebo		

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

The CA209-067 study was a randomized, double-blind, active-controlled, 3-arm parallel group study. The nivolumab + ipilimumab arm and the nivolumab arm of the study were relevant for the present assessment. The study included patients with unresectable or metastatic melanoma (stage III or IV according to the AJCC classification), known BRAF V600 mutation status and good general condition (ECOG PS of 0 or 1). Hence there were no data for patients with an ECOG PS of > 1.

Overall, 316 patients were randomized to the nivolumab arm, and 314 patients to the nivolumab + ipilimumab arm of the study. Randomization was stratified according to the factors PD-L1 status, BRAF V600 mutation status and metastasis stage. The company presented analyses for the total population and for the subpopulation of patients with BRAF V600 wt tumour. The analyses on the subpopulation of the patients with BRAF V600 wt tumour who received either nivolumab + ipilimumab combination therapy (N = 213) or nivolumab monotherapy (N = 216) were used for the present benefit assessment (see Section 2.7.2.2 of the full dossier assessment).

Treatment of patients in both relevant study arms was conducted according to the regimen described in Table 7 and was in compliance with the recommendations of the SPCs [3,4]. In the 12-week induction phase, patients in the intervention group of the study received

nivolumab 1 mg/kg body weight in combination with ipilimumab 3 mg/kg body weight every 3 weeks. The comparator group received nivolumab 3 mg/kg body weight every 2 weeks. In the maintenance phase, both groups received nivolumab 3 mg/kg body weight every 2 weeks. No dose adjustments were allowed in the study. Immunosuppressants, systemic corticosteroids and other antineoplastic treatments were not allowed to be given as concomitant medication.

Patients were treated until progression or unacceptable persistent toxicity. Under certain conditions, patients could continue treatment beyond progression at the investigator's discretion.

Patients were unblinded on occurrence of progression and at the end of the study treatment.

There were no limitations regarding subsequent therapy after progression. Switching to the treatment of the other study arm was not allowed. 27% of the patients with BRAF V600 wt tumour in the nivolumab + ipilimumab arm received subsequent systemic therapy. With 9%, dacarbazine was the most common subsequent therapy for these patients. 39% of the patients with BRAF V600 wt tumour in the nivolumab monotherapy arm received subsequent systemic therapy, with ipilimumab being the most common subsequent therapy (26.9%).

Primary outcomes of the study were PFS and overall survival. Secondary outcomes were symptoms, health-related quality of life and side effects.

The present assessment was based on the prespecified final analysis on overall survival at month 28 at database closure on 13 September 2016. Follow-up observation is conducted for the outcome "overall survival".

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, nivolumab + ipilimumab vs. nivolumab

Study **Outcome category** **Outcome**	**Planned follow-up**
CA209-067	
Mortality	
Overall survival	Until death, discontinuation of participation in the study or end of study[a]
Morbidity	
EORTC QLQ-C30 (symptoms)[b]	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 84 ± 7 days after the first follow-up visit
EQ-5D VAS	First and second follow-up visit, then every 3 months for 1 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 (functions)[c]	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 84 ± 7 days after the first follow-up visit
Side effects	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 84 ± 7 days after the first follow-up visit[d]

a: The follow-up observation for overall survival can be conducted up to 5 years after the final analysis of overall survival.
b: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0.
c: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0.
d: Later toxicities were documented also beyond the second follow-up visit.
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 planned duration of follow-up observation for the outcome "overall survival" was conducted until death, discontinuation of participation in the study or end of study. The study is currently in the planned follow-up phase, which can last until at most 5 years after the final analysis of overall survival. The proportion of censored patients in the available final analysis on overall survival in patients with BRAF V600 wt tumour is 54.9% in the combination arm and 52.3% in the monotherapy arm. At the time point of database closure, the majority of censored patients were in the follow-up phase.

There were 2 follow-up visits for the follow-up observation on the outcome categories of morbidity, health-related quality of life (both recorded with the EORTC QLQ-C30) and on side effects. The first follow-up visit was planned for 30 ± 7 days after discontinuation of treatment. The second follow-up visit was planned for 84 ± 7 days after the first one.

Health status measured with the EQ-5D VAS was to be recorded at the first and second follow-up visit, then every 3 months for 1 year, and then every 6 months until death, discontinuation of participation in the study or end of study.

The planned observation periods for the outcomes on EORTC QLQ-C30 (morbidity, health-related quality of life) and on side effects were systematically shortened because they were recorded for the period of treatment with the study medication (plus 30 or 114 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

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

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

Study Characteristics Category	**Nivolumab + ipilimumab**	**Nivolumab**
CA209-067	N = 213	N = 216
Age [years], mean (SD)	61 (14)	62 (13)
Sex [F/M], %	33/67	35/65
Ethnicity, n (%)		
White	211 (99.1)	210 (97.2)
Other[a]	2 (0.9)	6 (2.8)[b]
Metastases at the start of the study[c], n (%)		
M0	7 (3.3)	17 (7.9)
M1a	22 (10.3)	21 (9.7)
M1b	57 (26.8)	51 (23.6)
M1c	127 (59.6)	127 (58.8)
PD-L1 status with threshold value ≥ 5%[d], n (%)		
Positive	44 (20.7)	60 (27.8)
Negative/non-quantifiable	169 (79.3)[b]	156 (72.2)[b]
Time since first diagnosis [years], median [min; max]	ND[e]	ND[e]
Baseline LDH serum level, n (%)		
≤ ULN	130 (61.0)	132 (61.1)
> ULN	82 (38.5)	79 (36.6)
Not reported	1 (0.5)	5 (2.3)
History of brain metastases, n (%)		
Yes	9 (4.2)	6 (2.8)
No	204 (95.8)	210 (97.2)
ECOG Performance Status, n (%)		
0	151 (70.9)	154 (71.3)
1	61 (28.6)	61 (28.2)
2	0 (0)	1 (0.5)
Not reported	1 (0.5)	0 (0)
Disease stage according to the AJCC at the start of the study, n (%)		
III	10 (4.7)	21 (9.7)
IV	203 (95.3)	195 (90.3)
Treatment discontinuation, n (%)	ND[f]	ND[f]
Study discontinuation, n (%)	ND[g]	ND[g]

(continued)

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

a: The category "other" includes patients of Asian and Polynesian origin and patients whose origin is not further described.
b: Institute's calculation.
c: M0: no distant metastases; M1a: metastases to skin, subcutis, or extra-regional lymph nodes; M1b: lung metastasis/metastases; M1c: distant metastasis/metastases to other sites, distant metastasis/metastases to any site combined with an elevated serum LDH level.
d: Proportion of PD-L1-positive cells in biopsy.
e: Median [min; max] for total population: nivolumab + ipilimumab 1.87 [0.1; 32.5] vs. nivolumab 2.18 [0.1; 35.4].
f: Treatment discontinuations in total population n (%): nivolumab + ipilimumab 269 (85.9%) vs. nivolumab 249 (79.6%).
g: Study discontinuations in total population n (%): nivolumab + ipilimumab 132 (42.2%) vs. nivolumab 146 (46.6%).

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 between both considered arms of the CA209-067 study were sufficiently balanced. The mean age of the included patients with BRAF V600 wt tumour was 61 years; 2 thirds of them were male. About 98% of the patients were of Caucasian origin. Over 99% of the patients had an ECOG PS of 0 or 1, and over 90% were in disease stage IV.

Information on treatment and study discontinuations was only available for the total population, but not for the relevant subpopulation of patients with BRAF V600 wt tumour. In the total population, more patients discontinued treatment in the combination therapy arm than in the monotherapy arm. The main reason for discontinuation in the combination therapy arm was side effects, and the main reason for discontinuation in the monotherapy arm was disease progression. The proportion of patients who discontinued the study in relation to the total population was numerically somewhat higher in the nivolumab arm than in the nivolumab + ipilimumab arm.

Table 10 shows the mean/median treatment duration of the patients and the mean/median observation 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. nivolumab

Study **Duration of the study phase** **Outcome category**	**Nivolumab + ipilimumab**	**Nivolumab**
CA209-067	N = 213	N = 216
Treatment duration [months]		
Median [min; max]	2.78 [0.0; 35.9]	7.85 [0.0; 36.0]
Mean (SD)	9.08 (11.26)	13.36 (12.27)
Observation period [months]		
Overall survival		
Median [min; max]	30.16 [0.1; 37.4[a]][b]	29.50 [0.0; 36.1][b]
Mean (SD)	22.05 (12.45)[b]	21.90 (12.18)[b]
Morbidity, health-related quality of life, side effects[c]	ND	ND

a: Analysis contains censored values.
b: Information refers to patient population who have received at least 1 dose of the study medication: nivolumab + ipilimumab N = 212 and nivolumab N = 215.
c: Side effects were observed for 30 (all AE outcomes) and 100 days (all AE outcomes except discontinuation due to AEs) after the end of treatment.
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

While the observation duration on the outcome "overall survival" was comparable – the median was about 30 months – the treatment duration differed notably between the treatment groups. The median treatment duration in the nivolumab arm was almost 3 times as long as in the nivolumab + ipilimumab arm. The difference in treatment durations was caused by differences in treatment discontinuations in the course of the study (see Table 9 for the proportions of patients who discontinued the treatment).

The dossier contained no information on observation periods of other individual outcomes. It can be assumed that the differences in treatment durations in outcomes with time points of observations that are linked to the treatment duration led to differences in observation periods (see Section 2.7.2.4.2 of the full dossier assessment).

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. nivolumab

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

a: After progression and treatment discontinuation, about 30% of the patients in the total study population were unblinded in the nivolumab + ipilimumab arm and about 55% in the nivolumab arm.

BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); BRAF V600 wt: BRAF V600 wild type; RCT: randomized controlled trial; vs.: versus

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

2.4 Results on added benefit

2.4.1 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 EORTC QLQ-C30 symptom scales
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3–4)
  - discontinuation due to AEs
  - if applicable, further specific 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. nivolumab

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30[a])	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30[b])	SAEs[c]	Severe AEs (CTCAE grade 3–4)[c]	Discontinuation due to AEs[c]	Specific AEs
CA209-067	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]

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 and 100 days of follow-up after the end of treatment (discontinuation due to AEs: 30 days of follow-up).
d: No usable data (see Section 2.7.2.4.3 of the full dossier assessment).

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; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 13 describes 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. nivolumab

Study		Outcomes							
	Study level	Overall survival	Symptoms (EORTC QLQ-C30[a])	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30[b])	SAEs[c]	Severe AEs (CTCAE grade 3–4)[c]	Discontinuation due to AEs[c]	Specific AEs
CA209-067	L	N	H[d,e]	H[d]	H[d,e]	H[f]	H[f]	H[f]	-[g]

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 and 100 days of follow-up after the end of treatment (discontinuation due to AEs: 30 days of follow-up).
d: No adequate implementation of the ITT principle: 1) high proportion of patients, or large difference between the treatment groups, who were not considered in the analysis; 2) response to the questionnaires in the course of the study decreased notably earlier in the nivolumab + ipilimumab arm than in the comparator arm, with potentially informative reasons for these decreases (see Section 2.7.2.4.2 of the full dossier assessment).
e: In contrast to the first assessment (A16-35), the analyses presented did not include any event time analyses. Selective outcome reporting can therefore not be excluded.
f: Potentially informative censoring.
g: No usable data 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: 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 at outcome level was rated as low for all outcomes except for the outcome "overall survival". For the outcomes on symptoms, health status and health-related quality of life, this was due to the inadequate implementation of the intention-to-treat principle. The risk of bias of the outcomes on side effects was rated as high because of potentially informative censoring (see Section 2.7.2.4.2 of the full dossier assessment).

For the outcomes of the outcome category "side effects", this deviates from the assessment of the company, which derived a low risk of bias for each of these outcomes.

There were no usable data for specific AE outcomes (see Section 2.7.2.4.3 of the full dossier assessment).

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of nivolumab + ipilimumab with nivolumab in treatment-naive adult patients with advanced (unresectable or metastatic) melanoma and BRAF V600 wt tumour. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. Kaplan-Meier curves on overall survival and side effect outcomes can be found in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment.

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

Study **Outcome category**	**Nivolumab + ipilimumab**		**Nivolumab**		**Nivolumab + ipilimumab vs. nivolumab**
Outcome	**N**	**Median survival time in months [95% CI][a]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI][a]** **Patients with event n (%)**	**HR[b] [95% CI][c]; p-value[d]**
CA209-067					
Mortality					
Overall survival					
Data cut-off 13 Sep 2016 (28 months)	213	NA [27.60; NA] 96 (45.1)	216	NA [23.46; NA] 103 (47.7)	0.94 [0.71; 1.24]; 0.640
Side effects[e]					
AEs (supplementary information)	212	0.23 [0.16; 0.30] 210 (99.1)	215	0.36 [0.26; 0.46] 212 (98.6)	–
SAEs	212	2.10 [1.74; 2.60] 157 (74.1)	215	21.52 [16.76; NA] 89 (41.4)	2.93 [2.24; 3.82]; < 0.001
Severe AEs (CTCAE grade 3–4)	212	1.97 [1.64; 2.50] 167 (78.8)	215	10.61 [7.43; 17.94] 119 (55.3)	2.36 [1.86; 2.99]; < 0.001
Discontinuation due to AEs	212	15.05 [7.06; NA] 93 (43.9)	215	NA [NA; NA] 29 (13.5)	RR: 3.25 [2.24; 4.71]; < 0.001[f]

a: Calculated with log-log transformation according to Brookmeyer and Crowley.
b: Unless stated otherwise.
c: Calculated with Cox model, stratified by PD-L1 and metastasis status at the start of the study.
d: Calculated with log-rank test, stratified by PD-L1 and metastasis status at the start of the study.
e: Recording until 100 days after the end of treatment (in case of treatment discontinuation due to AEs until 30 days after the end of treatment) and without recording of events due to progression of the underlying disease.
f: Institute's calculation; p-value: unconditional exact test (CSZ method according to [5]).

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; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

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

Study Outcome category Outcome	Nivolumab + ipilimumab			Nivolumab			Nivolumab + ipilimumab vs. nivolumab
	N[a]	Values at start of study, mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at start of study, mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value
CA209-067							
Morbidity							
Symptoms (EORTC QLQ-C30)[c]							
Fatigue	161	24.9 (22.2)	11.8 (1.6)	188	22.8 (21.4)	5.9 (1.4)	5.9 [2.3; 9.5]; 0.001 Hedges' g 0.34 [0.13; 0.56]
Nausea and vomiting	161	4.0 (9.8)	4.5 (1.0)	188	4.7 (11.6)	0.3 (0.9)	4.2 [1.6; 6.8]; 0.002 Hedges' g 0.34 [0.12; 0.55]
Pain	161	20.8 (24.9)	3.7 (1.7)	188	18.6 (23.3)	1.8 (1.5)	1.9 [–1.8; 5.6]; 0.319
Dyspnoea	161	13.5 (22.8)	7.2 (1.3)	188	13.8 (23.3)	2.4 (1.2)	4.8 [1.7; 7.9]; 0.003 Hedges' g 0.32 [0.11; 0.54]
Insomnia	161	23.8 (24.6)	–1.2 (1.5)	188	22.2 (23.9)	–3.8 (1.4)	2.6 [–1.0; 6.1]; 0.159
Decreased appetite	161	13.7 (23.1)	7.3 (1.6)	188	10.6 (21.6)	–0.1 (1.5)	7.4 [3.5; 11.3]; < 0.001 Hedges' g 0.40 [0.19; 0.61]
Constipation	161	10.4 (19.8)	2.3 (1.3)	188	9.4 (21.0)	–0.3 (1.2)	2.6 [–0.3; 5.6]; 0.081
Diarrhoea	161	5.4 (14.9)	4.1 (0.9)	188	3.7 (10.5)	–1.2 (0.8)	5.3 [3.2; 7.5]; < 0.001 Hedges' g 0.52 [0.31; 0.74]
Health status (EQ-5D VAS)[d]	161	73.2 (19.7)	–4.6 (1.2)	187	75.0 (18.9)	–1.0 (1.1)	–3.6 [–6.5; –0.7]; 0.015 Hedges' g –0.26 [–0.47; –0.05]

(continued)

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

Study Outcome category Outcome	Nivolumab + ipilimumab			Nivolumab			Nivolumab + ipilimumab vs. nivolumab
	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value
CA209-067							
Health-related quality of life							
Global health status and functional scales (EORTC QLQ-C30)[d]							
Global health status	161	69.5 (22.5)	–7.7 (1.3)	188	75.0 (19.3)	–3.5 (1.2)	−4.2 [−7.3; −1.2]; 0.006 Hedges' g −0.29 [−0.50; −0.08]
Physical functioning	161	83.8 (20.6)	–8.0 (1.3)	188	86.7 (18.6)	–4.2 (1.2)	–3.9 [–6.7; –1.1]; 0.006 Hedges' g −0.29 [−0.50; −0.08]
Role functioning	161	83.2 (24.9)	–13.3 (1.9)	188	83.8 (24.0)	–6.6 (1.7)	–6.7 [–10.9; –2.5]; 0.002 Hedges' g –0.33 [–0.55; –0.12]
Emotional functioning	161	74.6 (19.1)	1.6 (1.2)	188	79.3 (18.1)	4.5 (1.1)	–2.9 [–5.6; –0.2]; 0.034 Hedges' g –0.23 [–0.44; –0.02]
Cognitive functioning	161	89.4 (15.2)	–5.4 (1.1)	188	91.6 (14.1)	–3.4 (1.0)	–2.0 [–4.3; 0.3]; 0.095
Social functioning	161	82.9 (22.7)	–5.4 (1.5)	188	84.0 (22.7)	–1.7 (1.4)	–3.7 [–7.2; –0.2]; 0.039 Hedges' g –0.22 [–0.43; –0.01]

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 with data until week 151.
c: A negative change from the start until the end of the study indicates improvement; a negative effect estimate indicates an advantage for the intervention.
d: A positive change from the start until the end of the study indicates improvement; a positive effect estimate indicates an advantage for the intervention.

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

Based on the available data, at most an indication, e.g. of an added benefit, can be derived for the outcome "overall survival", and at most a hint for the other outcomes due to the high risk of bias.

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival". There was no hint of an added benefit of nivolumab + ipilimumab in comparison with nivolumab; an added benefit is therefore not proven.

This assessment deviates from that of the company, which derived an indication of a non-quantifiable added benefit for overall survival on the basis of the data of the total population.

Morbidity

Symptoms (EORTC QLQ-C30)

No statistically significant difference was shown between the treatment groups for the outcome "symptoms", measured with the symptom scales of the EORTC QLQ-C30, for the scales of pain, insomnia and constipation. This resulted in no hint of an added benefit of nivolumab + ipilimumab for any of these outcomes; an added benefit for these symptom scales is therefore not proven.

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for each of the scales of fatigue, nausea and vomiting, dyspnoea, decreased appetite and diarrhoea. However, the 95% CI of the standardized mean difference (Hedges' g) was fully outside the irrelevance range of −0.2 to 0.2 only for the diarrhoea scale. Hence only the effect for the diarrhoea scale was interpreted as relevant. This resulted in a hint of lesser benefit of nivolumab + ipilimumab in comparison with nivolumab for the outcome "diarrhoea". For the outcomes "fatigue", "nausea and vomiting", "dyspnoea" and "decreased appetite", there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit for these outcomes is therefore not proven.

This deviates from the assessment of the company, which determined no added benefit for any of these outcomes based on the analyses on the total population.

Health status

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for health status measured with the EQ-5D VAS. However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit of nivolumab + ipilimumab; an added benefit is therefore not proven.

Based on the analyses on the total population, the company reached the same conclusion.

Health-related quality of life

Health-related quality of life (EORTC QLQ-C30)

For the outcome "health-related quality of life", measured with the EORTC QLQ-C30 functional scales, a statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for the scales of global health status, physical functioning, role functioning, emotional functioning, and social functioning. However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2 for any of these scales. It can therefore not be inferred that the effect is relevant. The scale on cognitive functioning showed no statistically significant difference between the treatment groups. Overall, there was no hint of an added benefit of nivolumab + ipilimumab for any of the outcomes on health-related quality of life; an added benefit is therefore not proven.

Based on the analyses on the total population, the company reached the same conclusion.

Side effects

Analyses without events due to progression of the underlying disease were used for the outcomes "SAEs", "severe AEs (CTCAE grade 3–4)", and "discontinuation due to AEs". Follow-up observation was until 100 days after the end of treatment for SAEs and severe AEs (CTCAE grade 3–4) and 30 days after the end of treatment for discontinuation due to AEs.

SAEs and severe AEs (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for each of the outcomes "SAEs" and "severe AEs (CTCAE grade 3–4)". This resulted in a hint of greater harm of nivolumab + ipilimumab in comparison with nivolumab for each of these outcomes.

This assessment deviates from that of the company. Based on the analyses on the total population, the company derived an indication of greater harm.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab was shown for the outcome "discontinuation due to AEs". In addition, there was an effect modification by the characteristic "age" for this outcome (see Section 2.4.4). A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown both for patients < 65 years and for patients ≥ 65 years of age. This resulted in a hint of greater harm of nivolumab + ipilimumab for each of both age categories with differences in the extent.

This deviates from the assessment of the company, which did not consider any subgroup results for this outcome and derived an indication of greater harm based on the analyses on the total population.

2.4.4 Subgroups and other effect modifiers

The following prespecified subgroup characteristics were considered in the benefit assessment:

- metastasis at the start of the study (M0/M1a/M1b/M1c)
- age group (< 65 years/≥ 65 years to < 75 years/≥ 75 years)
- sex (female/male)
- ethnicity (white/African American/Asian/other)
- brain metastases (yes/no)
- lactate dehydrogenase (LDH) serum level (≤ upper limit of normal [ULN]/> ULN)
- programmed cell death ligand 1(PD-L1) status (< 5%/≥ 5%)

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

For some subgroup characteristics, patient-reported outcomes (EORTC QLQ-C30, EQ-5D VAS) were not usable for the benefit assessment. In addition, these outcomes showed a high risk of bias already in the total subpopulation with BRAF V600 wt tumour (see Section 2.7.2.4.2 of the full dossier assessment), resulting in general uncertainty of the interaction tests. Overall, the subgroup results on these outcomes are therefore not presented.

The subgroup results of nivolumab + ipilimumab in comparison with nivolumab are summarized in Table 16. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

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

Study Outcome	Nivolumab + ipilimumab		Nivolumab		Nivolumab + ipilimumab vs. nivolumab	
Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]	p-value[a]
CA209-067						
Discontinuation due to AEs						
Age [years]						
< 65	112	53 (47.3)	119	7 (5.9)	8.04 [3.82; 16.94]	< 0.001
≥ 65[b]	100[c]	40 (40.0)[c]	96[c]	22 (22.9)[c]	1.75 [1.13; 2.71]	0.010
Total					Interaction:	0.002[d]

a: Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test [CSZ method according to [5]]), unless stated otherwise.
b: Subgroups of ≥ 65 years to < 75 years and of ≥ 75 years summarized because no interaction was found in pairwise comparison.
c: Institute's calculation.
d: Institute's calculation, p-value from Q test for heterogeneity, relating to the original 3 subgroups.
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; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

The results of the CA209-067 study showed an effect modification by the characteristic "age" for the outcome "discontinuation due to AEs". Of the 3 age groups considered, the categories of ≥ 65 years to < 75 years and ≥ 75 years of age were summarized because no interaction was found in pairwise comparison.

A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown for patients < 65 years and for patients ≥ 65 years of age. This resulted in a hint of greater harm of nivolumab + ipilimumab in comparison with nivolumab for each of both age categories with differences in the extent.

This assessment deviates from that of the company. The company also identified proof of interaction by the subgroup characteristic "age", but did not consider the subgroup results in the derivation of the added benefit.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in a hint of lesser benefit for the EORTC QLQ-C30 symptom scale “diarrhoea” for treatment-naive adult patients with advanced (unresectable or metastatic) melanoma and BRAF V600 wt tumour. In addition, there was a hint of greater harm for each of the outcomes “SAEs” and “severe AEs (CTCAE grade 3–4)”. A hint of greater harm from nivolumab + ipilimumab was shown for the outcome “discontinuation due to AEs” for each of both age categories considered (< 65 and ≥ 65 years).

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

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. nivolumab** **Median time to event or proportion of events or mean change** **Effect estimate [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	NA vs. NA HR: 0.94 [0.71; 1.24] p = 0.640	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	11.8 vs. 5.9 MD: 5.9 [2.3; 9.5] p = 0.001 Hedges' g: 0.34 [0.13; 0.56]	Lesser benefit/added benefit not proven[c]
Nausea and vomiting	4.5 vs. 4.7 MD: 4.2 [1.6; 6.8] p = 0.002 Hedges' g: 0.34 [0.12; 0.55]	Lesser benefit/added benefit not proven[c]
Pain	3.7 vs. 1.8 MD: 1.9 [–1.8; 5.6] p = 0.319	Lesser benefit/added benefit not proven
Dyspnoea	7.2 vs. 2.4 MD: 4.8 [1.7; 7.9] p = 0.003 Hedges' g: 0.32 [0.11; 0.54]	Lesser benefit/added benefit not proven[c]
Insomnia	–1.2 vs. –3.8 MD: 2.6 [–1.0; 6.1] p = 0.159	Lesser benefit/added benefit not proven
Decreased appetite	7.3 vs. –0.1 MD: 7.4 [3.5; 11.3] p < 0.001 Hedges' g: 0.40 [0.19; 0.61]	Lesser benefit/added benefit not proven[c]
Constipation	2.3 vs. –0.3 MD: 2.6 [–0.3; 5.6] p = 0.081	Lesser benefit/added benefit not proven
Diarrhoea	4.1 vs. –1.2 MD: 5.3 [3.2; 7.5] p < 0.001 Hedges' g: 0.52 [0.31; 0.74] Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications lesser benefit, extent: "non-quantifiable"
Health status (EQ-5D VAS)	–4.6 vs. –1.0 MD: –3.6 [–6.5; –0.7] p = 0.015 Hedges' g: –0.26 [–0.47; –0.05]	Lesser benefit/added benefit not proven[c]

(continued)

Table 17: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. nivolumab (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. nivolumab** **Median time to event or proportion of events or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
Global health status and functional scales (EORTC QLQ-C30)		
Global health status	–7.7 vs. –3.5 MD: –4.2 [–7.3; –1.2] p = 0.006 Hedges' g: –0.29 [–0.50; –0.08]	Lesser benefit/added benefit not proven[c]
Physical functioning	–8.0 vs. –4.2 MD: –3.9 [–6.7; –1.1] p = 0.006 Hedges' g; −0.29 [−0.50; −0.08]	Lesser benefit/added benefit not proven[c]
Role functioning	–13.3 vs. –6.6 MD: –6.7 [–10.9; –2.5] p = 0.002 Hedges' g: –0.33 [–0.55; –0.12]	Lesser benefit/added benefit not proven[c]
Emotional functioning	1.6 vs. 4.5 MD: –2.9 [–5.6; –0.2] p = 0.034 Hedges' g: –0.23 [–0.44; –0.02]	Lesser benefit/added benefit not proven[c]
Cognitive functioning	–5.4 vs. –3.4 MD: –2.0 [–4.3; 0.3] p = 0.095	Lesser benefit/added benefit not proven
Social functioning	−5.4 vs. −1.7 −3.7 [−7.2; −0.2] p = 0.039 Hedges' g: –0.22 [–0.43; –0.01]	Lesser benefit/added benefit not proven[c]
Side effects		
SAEs	2.10 vs. 21.52 months HR: 2.93 [2.24; 3.82] HR: 0.34 [0.26; 0.45][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ greater harm, extent: "major"
Severe AEs (CTCAE grade 3–4)	1.97 vs. 10.61 months HR: 2.36 [1.86; 2.99] HR: 0.42 [0.33; 0.54][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ greater harm, extent: "major"

(continued)

Table 17: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. nivolumab (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. nivolumab** **Median time to event or proportion of events or mean change** **Effect estimate [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Discontinuation due to AEs		
Age [years]		
< 65	47.3% vs. 5.9% RR: 8.04 [3.82; 16.94] RR: 0.12 [0.06; 0.26][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 greater harm, extent: "major"
≥ 65	40.0% vs. 22.9% RR: 1.75 [1.13; 2.71] RR: 0.57 [0.37; 0.88][d] p = 0.010 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.90 greater harm, extent: "considerable"

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

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; LDH: lactate dehydrogenase; MD: mean difference; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; ULN: upper limit of normal; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 18: Positive and negative effects from the assessment of nivolumab + ipilimumab in comparison with nivolumab

Positive effects	**Negative effects**
–	Outcome category: non-serious/non-severe symptoms/late complications: ▪ Diarrhoea (EORTC QLQ-C30): hint of lesser benefit – extent: “non-quantifiable”
	Outcome category: serious/severe side effects: ▪ SAEs: hint of greater harm – extent: “major” ▪ severe AEs (CTCAE grade 3 –4): hint of greater harm – extent: “major” ▪ discontinuation due to AEs: ▫ < 65 years: hint of greater harm – extent: “major” ▫ ≥ 65 years: hint of greater harm – extent: “considerable”
AE: adverse event; 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	

In the overall consideration, there were only negative effects for nivolumab + ipilimumab in the outcome categories “morbidity” and “side effects”.

There was a hint of lesser benefit with non-quantifiable extent for the outcome “diarrhoea” (measured with the EORTC QLQ-C30). In the outcome category “side effects”, there was a hint of greater harm of major extent for each of the outcomes “SAEs” and “severe AEs (CTCAE grade 3–4)”. For the outcome “discontinuation due to AEs”, there was a hint of greater harm of major extent for patients < 65 years and a hint of greater harm of considerable extent for patients ≥ 65 years of age.

In summary, there is a hint of lesser benefit of nivolumab + ipilimumab in comparison with nivolumab for treatment-naive patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour.

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

Table 19: Nivolumab + ipilimumab – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Treatment-naive adult patients with advanced (unresectable or metastatic) melanoma with BRAF V600 wt tumour[b]	**Nivolumab** or pembrolizumab	Hint of lesser benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The study underlying the benefit assessment included patients with an ECOG PS of 0 or 1. It is unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); BRAF V600 wt: BRAF V600 wild type; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which overall derived an indication of non-quantifiable added benefit.

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

2.6 List of included studies

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. 17.04.2017 [Accessed: 31.07.2017]. URL: https://ClinicalTrials.gov/show/NCT01844505.

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: 23.08.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005371-13.

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; final clinical study report [unpublished]. 2016.

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]. 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.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-27-nivolumab-melanoma-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.7915.html.