IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Nivolumab – 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 – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 October 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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 mut	BRAF V600 mutated
BRAF V600 wt	BRAF V600 wildtype
BSA	body surface area
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	cytotoxic T-lymphocyte-associated antigen
DMC	Data Monitoring Committee
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)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	intravenous
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
PD-L1	programmed cell death ligand 1
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire Core-30
RCT	randomized controlled trial
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 15 July 2015.

Research questions

The aim of this report was to assess the added benefit of nivolumab compared with the appropriate comparator therapy (ACT) in adult patients with advanced (unresectable or metastatic) melanoma.

For the benefit assessment, the following 3 research questions resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Treatment-naive patients with BRAF V600 mutation-positive tumour	Vemurafenib
2	Treatment-naive patients with BRAF V600 mutation-negative tumour	**Dacarbazine** or ipilimumab[b]
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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold.
b: The company additionally investigated the research question on the comparison of nivolumab versus ipilimumab and presented it in Module 4 A as supplementary information (see Appendix B of the full benefit assessment).
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; G-BA: Federal Joint Committee; vs.: versus

The 3 research questions were investigated under consideration of the ACT specified by the G-BA. Hereinafter, patients with serine/threonine-protein kinase B-Raf (BRAF) V600 mutation-positive tumour are referred to as „patients with BRAF V600 mutated (mut) tumour". Patients with BRAF V600 mutation-negative tumour are referred to as "patients with BRAF V600 wildtype (wt) tumour".

Hereinafter, the expression "individual treatment specified by the physician under consideration of the approval status and the respective prior therapy" is replaced with "treatment of physician's choice" for better readability.

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

Results

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

Research question 1 concerns the comparison of nivolumab with the ACT (vemurafenib) in treatment-naive patients with BRAF V600 mut tumour.

Direct comparison

There were no direct comparative studies of nivolumab versus the ACT vemurafenib.

Indirect comparison

The company conducted an adjusted indirect comparison of nivolumab with vemurafenib using dacarbazine as common comparator. It included study CA209-066 with nivolumab and study BRIM 3 with vemurafenib in this comparison.

The indirect comparison presented by the company was unsuitable to draw conclusions on the added benefit of nivolumab versus vemurafenib.

On the one hand, the CA209-066 study included only patients with BRAF V600 wt tumour, which, accordingly, did not concur with patients of the research question. The company, however, considered the BRAF V600 mutation status to have no effect on the treatment success under nivolumab and dacarbazine. The sources presented by the company cannot dispel the doubts concerning the independence of the effects of nivolumab and dacarbazine from the BRAF V600 mutation status of the melanoma, however.

Irrespective of this question, there was no similarity of the studies CA209-066 and BRIM 3. This became apparent in the notable differences of the results in the outcomes on adverse events (AEs) between the dacarbazine arms of both studies. In the CA209-066 study (BRAF V600 wt), 78 (38%) of the 205 patients reported at least one serious AE (SAE), whereas in the BRIM 3 study (BRAF V600 mut), only 45 (16%) of the 282 patients reported such an event. In the CA209-066 study, 24 (12%) of the patients in the dacarbazine arm discontinued treatment due to an AE, whereas only 12 (4%) patients discontinued treatment due to an AE in the BRIM 3 study. Hence at least for these 2 outcomes, there was no comparability of the results on the common comparator in both studies, which is a prerequisite for indirect comparisons. There were therefore no evaluable data for the derivation of the added benefit of nivolumab in comparison with the ACT vemurafenib for treatment-naive patients with BRAF V600 mut melanoma.

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

Research question 2 concerns the comparison of nivolumab with the ACT (dacarbazine or ipilimumab) in treatment-naive patients with BRAF V600 wt tumour. Following the company, the comparison of nivolumab versus dacarbazine was used to derive the added benefit.

Study CA209-066 was used for research question 2.

Study characteristics

Study CA209-066 was a randomized, double-blind, active-controlled, 2-arm parallel group study with treatment-naive adult patients with BRAF V600 wt melanoma (unresectable stage III or stage IV according to the American Joint Committee on Cancer [AJCC]). 418 patients were randomized in a ratio of 1:1, 210 patients to the nivolumab arm and 208 patients to the dacarbazine arm. The randomized study treatment corresponded to the requirements specified in the Summaries of Product Characteristics (SPCs) of nivolumab and dacarbazine.

Primary outcome was overall survival, and secondary outcomes were symptoms, health-related quality of life, health status and AEs.

Two data cut-offs were planned for study CA209-066. Due to an unplanned data cut-off however, the study was ended prematurely because of a statistically significant difference in overall survival in favour of nivolumab and was unblinded on 1 July 2014; patients in the dacarbazine arm were allowed to continue treatment with nivolumab (treatment switching). The present benefit assessment was based on the data cut-off on 24 June 2014 and therefore comprised data that were not yet affected by the unblinding and treatment switching.

Risk of bias

The risk of bias at study level was rated as low for the CA209-066 study. The risk of bias for the outcome “overall survival” was rated as high. This rating resulted from the fact that the study was ended prematurely due to the results on overall survival from an unplanned analysis. Due to the low proportion (about 62% of the randomized patients) of the patients analysed, no evaluable results were available for the remaining benefit outcomes (symptoms, health status and health-related quality of life). Only a qualitative assessment is possible of the results on AEs due to the high proportion of events recorded that represent progression of the underlying disease. No regular rating of the risk of bias was therefore conducted for these results.

Results

Mortality

Nivolumab treatment resulted in a statistically significant prolongation of overall survival in comparison with dacarbazine.

In addition, there was an indication of an effect modification by the characteristic "sex" for the outcome "overall survival" (interaction test p = 0.187). It was therefore meaningful to additionally consider the results separately for men and women. The subgroup analyses showed an indication of an added benefit of nivolumab in comparison with dacarbazine for men, and a hint of an added benefit for women.

Morbidity

The dossier contained no evaluable data for 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) and for health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS). There was thus no hint of an added benefit of nivolumab in comparison with dacarbazine for these outcomes. An added benefit for these outcomes is therefore not proven.

Health-related quality of life

The dossier contained no evaluable data for health-related quality of life measured with the functional scales of the EORTC QLQ-C30 questionnaire. There was thus no hint of an added benefit of nivolumab in comparison with dacarbazine for this outcome. An added benefit for this outcome is therefore not proven.

Adverse events

The survival time analyses on AEs (SAEs, severe AEs [Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3] and treatment discontinuation due to AEs) presented in Module 4 A were not evaluable because of the high proportion of recorded events due to progression of the underlying disease. For example, the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) "neoplasms benign, malignant and unspecified (including cysts and polyps)" with the Preferred Terms (PTs) "progression of malignant melanoma" and "malignant melanoma" was by far the most common category of SAEs. These events also occurred frequently in the analyses on treatment discontinuations due to AEs and severe AEs (CTCAE grade ≥ 3). Analyses of AEs without the progression of the underlying disease would have been required for a meaningful estimation of the harm from nivolumab in comparison with dacarbazine. Suitable analyses would then also allow the balancing of benefit and harm of nivolumab versus dacarbazine.

Since the survival time analyses presented by the company were not evaluable for the reasons stated above, only qualitative conclusions based on the naive proportions of common AEs were drawn for AEs in the present benefit assessment. AEs with potentially important differences between the treatment arms were extracted from the common AEs and interpreted.

Inspection of the naive proportions produced no signs that the analyses on AEs could raise fundamental doubts about the observed advantage in overall survival. Overall, the respective overall rates cannot be interpreted because of the bias caused by the recording of the progression of the underlying diseases. Hence a possible advantage of nivolumab, which the

company had derived on the basis of its hazard ratio (HR) analyses, was not confirmed. Nonetheless, the naive proportions overall, and for most events with potentially important differences between the treatment arms, rather indicate an advantage in favour of nivolumab. Overall, neither greater nor lesser harm of nivolumab in comparison with dacarbazine can be excluded on the basis of the qualitative assessment of SAEs, severe AEs (CTCAE grade ≥ 3) and treatment discontinuation due to AEs.

Overall, there was no hint of greater or lesser harm from nivolumab in comparison with dacarbazine for these outcomes on the basis of the present analyses. Hence greater or lesser harm is not proven for these outcomes.

Research question 3: pretreated patients

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

The company presented one randomized controlled trial (RCT); this was study CA209-037. The CA209-037 study was an open-label RCT with nivolumab in comparison with a treatment of physician's choice. Patients with advanced (unresectable or metastatic) melanoma who were already treated for advanced melanoma were included in the study.

Only 2 chemotherapeutic options (dacarbazine as monotherapy or carboplatin + paclitaxel as combination therapy) were available for the treatment of physician's choice in the comparator arm of the CA209-037 study. The combination of carboplatin and paclitaxel is not approved in Germany for the treatment of melanoma, and is therefore not an option as an operationalization of the ACT. Monotherapy with dacarbazine remains as an operationalization of the ACT. Due to the pretreatment of the patients in the study, it can be assumed that chemotherapy was the only treatment option for these patients at the time point of the study. Hence dacarbazine can be regarded as sufficient operationalization of the ACT for the patients in the study.

The relevant subpopulation of the CA209-037 study therefore consisted of patients in the comparator arm who were treated with dacarbazine, and of patients in the nivolumab arm for whom dacarbazine was the intended treatment if they had been allocated to the comparator arm. These were 111 (40.8%) of the 272 patients in the nivolumab arm, and 56 (42.1%) of the 133 patients in the comparator arm.

The analyses presented by the company for this study were not evaluable, however. The reason for this was that the company had rendered randomization ineffective with the selection of the subpopulation who were treated in accordance with the German approval status (all 272 patients in the nivolumab arm, and 56 patients receiving dacarbazine in the comparator arm). Hence the analyses of the CA209-037 study presented by the company were unsuitable to derive an added benefit of nivolumab in comparison with the ACT. Deviating from this, the company considered the study to be unsuitable because it regarded the study to

be highly biased. It named differences in discontinuation rates in the treatment arms, differences in the distribution of prognostic factors in the study arms despite randomization, and the possibility to switch to anti-programmed cell death ligand 1 (PD-L1) antibody treatment in the dacarbazine arm as further biasing factors. Since the dossier contained only data of the total patient population for the nivolumab arm, no final assessment can be made whether the causes of bias in the study were actually so profound as to make an interpretation of the data impossible.

Since the company considered the risk of bias of the CA209-037 study to be too high, it used data from the studies of research questions 1 and 2 to derive an added benefit of nivolumab for pretreated patients. This approach was not followed because the results of treatment-naive patients cannot simply be transferred to pretreated patients.

Hence there were no evaluable data for the assessment of the added benefit of nivolumab for pretreated patients.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug nivolumab versus the ACT is assessed as follows.

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

For treatment-naive patients with BRAF V600 mut tumour, there was no hint of an added benefit of nivolumab in comparison with the ACT vemurafenib; an added benefit is therefore not proven.

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

For treatment-naive patients with BRAF V600 wt tumour, positive effects remain in the overall consideration. Due to the data availability, it is unclear whether there were positive or negative effects for AEs. However, there were no signs that fundamental doubts could be raised about the positive effect in overall survival. Since there was an indication of an effect modification by the subgroup characteristic “sex” for the outcome “overall survival”, the overall assessment of added benefit was conducted separately for men and women.

[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].

Added benefit for men

For men, there was an indication of major added benefit on the side of positive effects. AEs were not finally assessed because of the data availability. Beyond that, there were no evaluable data for morbidity and health-related quality of life. However, it cannot be assumed that further analyses would show that the extent of added benefit for overall survival is completely outweighed. Due to the uncertainty in the interpretation of AEs, no balancing of benefit and harm was possible. Furthermore, there were no other results that could contribute to such balancing because the data on morbidity and health-related quality of life were not evaluable. The extent of added benefit was therefore downgraded to “considerable”.

Hence there is an indication of considerable added benefit of nivolumab in comparison with the ACT dacarbazine for treatment-naive men whose tumour is BRAF V600 mutation-negative.

Added benefit for women

For women, there was a hint of a minor added benefit on the side of positive effects. AEs were not finally assessed because of the data availability. Beyond that, there were no evaluable data for morbidity and health-related quality of life. However, it cannot be assumed that further analyses would show that the extent of added benefit for overall survival is completely outweighed, particularly because the upper limit of the confidence interval (0.95) was directly on the border between the extents “considerable” and “minor”. The extent of added benefit was therefore not downgraded despite the uncertainty in the interpretation of AEs and the missing data for morbidity and health-related quality of life.

Hence there is a hint of minor added benefit of nivolumab in comparison with the ACT dacarbazine for treatment-naive women whose tumour is BRAF V600 mutation-negative.

Research question 3: pretreated patients

There was no hint of an added benefit of nivolumab in comparison with the ACT (treatment of physician’s choice) in pretreated patients; an added benefit is therefore not proven.

Extent and probability of added benefit – summary

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

Table 3: Nivolumab – extent and probability of added benefit

Research question	Therapeutic indication	Appropriate comparator therapy[a]	Subgroup	Extent and probability of added benefit
1	Treatment-naive patients with BRAF V600 mutation-positive tumour	Vemurafenib	Added benefit not proven	
2	Treatment-naive patients with BRAF V600 mutation-negative tumour	**Dacarbazine** or ipilimumab[b]	Men	Indication of considerable added benefit
			Women	Hint of minor added benefit
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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold.
b: The company additionally investigated the research question on the comparison of nivolumab versus ipilimumab and presented it in Module 4 A as supplementary information (see Appendix B of the full benefit assessment).
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; G-BA: Federal Joint Committee; vs.: versus

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 questions

The aim of this report was to assess the added benefit of nivolumab compared with the ACT in adult patients with advanced (unresectable or metastatic) melanoma.

For the benefit assessment, the following 3 research questions resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Treatment-naive patients with BRAF V600 mutation-positive tumour	Vemurafenib
2	Treatment-naive patients with BRAF V600 mutation-negative tumour	**Dacarbazine** or ipilimumab[b]
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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold.
b: The company additionally investigated the research question on the comparison of nivolumab versus ipilimumab and presented it in Module 4 A as supplementary information.
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; G-BA: Federal Joint Committee; vs.: versus

The 3 research questions were investigated under consideration of the ACT specified by the G-BA and are presented in the following sections:

- Section 2.3: research question 1 (research question A1 according to Module 4 A)
  - treatment-naive patients with serine/threonine-protein kinase B-Raf (BRAF) V600 mutation-positive tumour, hereinafter referred to as „patients with BRAF V600 mutated (mut) tumour"
- Section 2.4: research question 2 (research question A2-1 according to Module 4 A)
  - treatment-naive patients with BRAF V600 mutation-negative tumour, hereinafter referred to as "patients with BRAF V600 wildtype (wt) tumour"
- Section 2.5: research question 3 (research question A3 according to Module 4 A)
  - pretreated patients

The comparator therapy chosen by the company (dacarbazine) was used for investigating research question 2. For research question 3, however, deviating from the company, the drugs lomustine and dabrafenib were considered in addition to the drugs dacarbazine, ipilimumab and vemurafenib considered by the company as part of the individual treatment specified by the treating physician under consideration of the approval status and the respective prior

therapy. Hereinafter, the expression “individual treatment specified by the physician under consideration of the approval status and the respective prior therapy” is replaced with “treatment of physician’s choice” for better readability.

The company presented a comparison of nivolumab with ipilimumab as additional information for treatment-naive patients with BRAF V600 wt tumour. This research question (referred to by the company as “comparison A2-2”) was also presented as additional information (see Appendix B of the full dossier assessment).

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

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

Research question 1 concerns the comparison of nivolumab with the ACT (vemurafenib) in treatment-naive patients with BRAF V600 mut tumour.

2.3.1 Information retrieval and study pool (research question 1)

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

Sources of the company in the dossier:

- study list on nivolumab (status: 9 June 2015)
- bibliographical literature search on nivolumab (last search on 6 May 2015)
- search in trial registries for studies on nivolumab (last search on 12 May 2015)
- bibliographical literature search on the ACT (last search on 11 May 2015)
- search in trial registries for studies on the ACT (last search on 21 May 2015)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 30 July 2015)

Direct comparison

No studies of direct comparisons of nivolumab versus vemurafenib were identified from the check of the completeness of the study pool. This concurs with the company's findings.

Indirect comparison

Due to a lack of studies of direct comparisons, the company conducted an adjusted indirect comparison according to Bucher [3]. Nivolumab was compared with vemurafenib using dacarbazine as common comparator in this comparison. The company identified study CA209-066 with nivolumab [4] and the study BRIM 3 with vemurafenib [5] from the steps of information retrieval mentioned.

The indirect comparison presented by the company was unsuitable to draw conclusions on the added benefit of nivolumab versus vemurafenib.

Hereinafter it is justified whether the indirect comparison is unsuitable for conclusions on the added benefit of nivolumab versus vemurafenib. For this purpose, the studies used by the company are first presented. In a next step, it is shown that both studies do not fulfil the assumption of similarity required for an indirect comparison.

The study pool of the company is shown in Table 5.

Table 5: Study pool of the company – RCT, indirect comparison: treatment-naive patients with BRAF V600 mut tumour, nivolumab vs. vemurafenib

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CA209-066	Yes	Yes	No
BRIM 3 (NO25026)	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 mut: BRAF V600 mutated; RCT: randomized controlled trial; vs.: versus

The studies included by the company in its indirect comparison are described in Table 29 and Table 30 in Appendix A of the full dossier assessment.

Characteristics of the study and of the interventions of study CA209-066

The CA209-066 study was a randomized, double-blind, active-controlled, 2-arm parallel group study. It was conducted in Australia, Europe, Israel as well as in Latin and North America. Treatment-naive adult patients with BRAF V600 wt melanoma (unresectable stage III or stage IV according to the AJCC) were included in the study.

418 patients were randomized in a ratio of 1:1, 210 patients to the nivolumab arm and 208 patients to the dacarbazine arm. Overall, the criteria of the therapeutic indication were regarded as being fulfilled for the patients enrolled in the study. This concurs with the company's assessment.

The randomized study treatment corresponded to the requirements specified in the SPCs of nivolumab [6] and dacarbazine [7].

The patients in both treatment arms could receive additional concomitant treatments. Restrictions in concomitant treatment only concerned treatment of the melanoma and administration of immunosuppressants.

The randomized study treatment was continued until at least one of the following criteria for discontinuation 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

Occurrence of a criterion for discontinuation did not automatically lead to unblinding of the randomized study treatment. The randomized study treatment was unblinded for 54 patients in the course of the study. Each unblinding was conducted for safety management or further planning of treatment.

Primary outcome was overall survival, and secondary outcomes were symptoms, health-related quality of life, health status and AEs.

Further details of the CA209-066 study are described in Section 2.4.1.2.

Characteristics of the study and of the interventions of study BRIM 3

The BRIM 3 study was a randomized, open-label, active-controlled, 2-arm parallel group study. It was conducted in Australia/New Zealand, Europe and North America. Adult patients with histologically confirmed, metastatic melanoma (unresectable Stage IIIc or Stage IV according to AJCC) and proven BRAF V600 mutation were enrolled in the study. According to the inclusion criteria of the study, patients were not pretreated with systemic anti-cancer drugs for the treatment of advanced melanoma.

Patients were randomized in a ratio of 1:1 and allocated to treatment with vemurafenib (337 patients) or dacarbazine (338 patients). The study treatments were administered according to a treatment regimen concurring with the specifications in both SPCs [7,8].

The patients in both treatment arms could receive additional concomitant medication. Concomitant medication was only restricted regarding treatment of the melanoma.

The randomized study treatment was continued until at least one of the following criteria for discontinuation occurred:

- withdrawal of the patient’s consent
- safety concerns (e.g. toxicity of CTCAE grade 3 or 4 despite adequate dose reduction)
- occurrence of progression

Overall survival was recorded as the primary outcome of the study. Relevant secondary outcomes were pain, health-related quality of life and adverse events.

Planned duration of follow-up

Of the outcomes included, only overall survival was recorded in both studies until the end of study participation. In the CA209-066 study, however, health status measured with the EQ-5D VAS was also recorded for this length of time. All other outcomes were only recorded for a certain length of time after the end of the randomized study treatment.

Analysis and data cut-offs

Two data cut-offs were planned for study CA209-066. The first data cut-off should have been conducted after about 218 deaths, and the second data cut-off after at least 312 deaths. After the death of 110 patients it was decided to end the study prematurely and unblind it because of a statistically significant difference in overall survival in favour of nivolumab. The study was ended prematurely due to the data cut-off from 23 May 2014. A further analysis was conducted with the data cut-off from 24 June 2014, on which this benefit assessment was based. Further details are described in Section 2.4.1.2.

The BRIM 3 study was ended prematurely on the basis of the results on median overall survival in a first interim analysis after running for one year (first data cut-off on 30 December 2010). Prior to this point, patients with progression could change to a subsequent melanoma treatment, but not from dacarbazine to vemurafenib. After the first data cut-off, patients in the dacarbazine arm also had the opportunity to switch to the vemurafenib arm (treatment switching). For the patient-relevant outcome "overall survival", patients were continued to be observed after the first data cut-off, and the results were analysed after 2 further data cut-offs (second data cut-off on 31 March 2011, third data cut-off on 3 October 2011). In addition, there were analyses on the 4th and 5th data cut-off. No new findings on the added benefit of vemurafenib in comparison with dacarbazine can be derived from the results of the 4th and 5th data cut-off [9].

Relevance of the CA209-066 study for research question 1

The relevant population for research question 1 comprises patients whose tumour has a mutation of the BRAF V600 gene. However, only patients without BRAF V600 mutation were included in the CA209-066 study. Hence patients in the CA209-066 study do not concur with research question 1. The company, however, considered the BRAF V600 mutation status to have no effect on the treatment success under nivolumab and dacarbazine. For nivolumab, it justified this using the results of the CA209-067 study [10], in which patients both with and without BRAF V600 mutation were included, and using a published pooled analysis of 4 further studies by the company [11]. The company presented 2 further publications for the common comparator dacarbazine [12,13]. These sources cannot dispel the doubts concerning the independence of the effects of nivolumab and dacarbazine from the BRAF V600 mutation status of the melanoma, however. The pooled retrospective analysis [11] of 4 nivolumab studies with pretreated patients, which was cited by the company, showed that the proportions of patients with AEs might differ according to their tumour status: Under nivolumab treatment, more severe AEs of CTCAE grades 3 and 4 occurred in patients with BRAF V600 wt melanoma (39 [11.7%] of 334 patients) than in patients with BRAF V600 mut melanoma (3 [2.8%] of 106 patients)[5].

[5] Only AEs in which a causal relation with the treatment was assumed (so-called "treatment-related AEs") were considered in the analysis.

Similarity of the studies included

Irrespective of the question whether the mutation status plays a role, the prerequisite for an adequate indirect comparison – the similarity of the studies included – was not fulfilled for the studies CA209-066 and BRIM 3 also because of other factors.

Apart from the BRAF mutation status, no notable differences between the studies were initially shown in the patient characteristics (see also Table 31 and Table 32 in Appendix A of the full dossier assessment). This concurs with the company's assessment. The studies differed in the patients' age: In the CA209-066 study, the mean age was 62 and 64 years and thus about 10 years higher than in the BRIM 3 study with a mean age of 53 and 55 years. This difference alone would not necessarily lead to rating these studies as being incomparable, however.

The fact that there is no similarity of the studies became apparent in the notable differences of the results in the outcomes on AEs between the dacarbazine arms of both studies. In the CA209-066 study (BRAF V600 wt), 78 (38%) of the 205 patients reported at least one serious AE (SAE), whereas in the BRIM 3 study (BRAF V600 mut), only 45 (16%) of the 282 patients reported such an event. In the CA209-066 study, 24 (12%) of the patients in the dacarbazine arm discontinued treatment due to an AE, whereas only 12 (4%) patients discontinued treatment due to an AE in the BRIM 3 study. Hence at least for these 2 outcomes, there was no comparability of the results on the common comparator in both studies, which is a prerequisite for indirect comparisons. The studies were therefore not similar enough to include them in a joint indirect comparison, and the indirect comparison is not evaluable. It is not important whether these differences can be explained by differences in the BRAF V600 mutation status or by the patients' age (see Table 31 of the full dossier assessment) or whether they were caused by other factors. A sign for the explanation by the BRAF V600 mutation status might be the differences in AEs in the analysis by Larkin [11] presented in the previous section.

Due to the lack of comparability of the studies, the indirect comparison presented by the company was not used for the present benefit assessment. Hence no evaluable data were available for the derivation of the added benefit of nivolumab in comparison with the ACT vemurafenib.

2.3.2 Results on added benefit (research question 1)

There were no evaluable data for the assessment of the added benefit of nivolumab for treatment-naive patients with BRAF V600 mut melanoma. There was therefore no hint of an added benefit of nivolumab in comparison with the ACT vemurafenib for these patients; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit (research question 1)

There were no evaluable data for the assessment of the added benefit of nivolumab for treatment-naive patients with BRAF V600 mut melanoma. There was therefore no hint of an added benefit of nivolumab in comparison with the ACT vemurafenib for these patients; an added benefit is therefore not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

In contrast, the company derived a hint of considerable added benefit for treatment-naive patients with BRAF V600 mut melanoma.

2.3.4 List of included studies (research question 1)

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

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

Research question 2 concerns the comparison of nivolumab with the ACT (dacarbazine or ipilimumab) in treatment-naive patients with BRAF V600 wt tumour. Following the company, the comparison of nivolumab versus dacarbazine was used for the derivation of the added benefit, and the comparison of nivolumab versus ipilimumab was presented as additional information.

2.4.1 Information retrieval and study pool (research question 2)

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

Sources of the company in the dossier:

- study list on nivolumab (status: 9 June 2015)
- bibliographical literature search on nivolumab (last search on 6 May 2015)
- search in trial registries for studies on nivolumab (last search on 12 May 2015)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 30 July 2015)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The study listed in Table 6 was included in the benefit assessment.

Table 6: Study pool – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CA209-066	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of nivolumab in comparison with dacarbazine for treatment-naive patients with BRAF V600 wt tumour consisted of the CA209-066 study and concurred with that of the company.

The company additionally included the CA209-067 study on the comparison of nivolumab versus ipilimumab for treatment-naive patients with BRAF V600 wt tumour as additional

information. This study is also presented as additional information (see Appendix B of the full dossier assessment).

Section 2.4.4 contains a reference list for the study included for research question 1.

2.4.1.2 Study characteristics

Table 7 and Table 8 describe the studies used for the benefit assessment.

Table 7: Characteristics of the studies included – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-066	RCT, double-blind, parallel	Treatment-naive adults with BRAF V600 wt melanoma: unresectable stage III or stage IV according to the AJCC	Nivolumab (N = 210) dacarbazine (N = 208)	Screening within 28 days before randomization Treatment phase: until progression or after progression for as long as the investigator considers the treatment to be beneficial to the patient or until intolerance Observation period: until death or discontinuation of study participation	76 centres in Argentina, Australia, Canada, Chile, Denmark, Germany, Finland, France, Greece, Israel, Italy, Mexico, Norway, Poland, Spain, Sweden 1/2013–6/2014 Data cut-off of the analysis presented on 24 June 2014 Since this date opportunity for treatment switching and ongoing open-label extension phase	Primary: overall survival Secondary: symptoms, health-related quality of life, health status, 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.

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 wildtype; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 8: Characteristics of the interventions – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Study	Intervention	Comparison	Prior and concomitant medication
CA209-066	Nivolumab 3 mg/kg body weight IV, every 2 weeks + placebo IV every 3 weeks (6-week cycle) no change in dosing allowed for nivolumab for placebo, reductions following the same criteria as for dacarbazine	Dacarbazine 1000 mg/m^2 BSA IV, every 3 weeks + placebo IV every 2 weeks (6-week cycle) no dose increase allowed for dacarbazine dose reduction for dacarbazine in certain AEs following a fixed regimen	**Pretreatment** ▪ no pretreatment with systemic treatment in advanced stage (III or IV) ▪ adjuvant or neoadjuvant treatment had to be completed at least 6 weeks before randomization **Concomitant treatment** ▪ antiemetics before treatment with dacarbazine or with dacarbazine placebo ▪ palliative radiotherapy or surgery in non-target lesions ▪ bisphosphonates and RANKL inhibitors for bone metastases and hormone replacement therapy if treatment started before randomization **Non-permitted concomitant treatment** ▪ immunosuppressants, systemic corticosteroids > 10 mg/day prednisone equivalent ▪ other antineoplastic treatment

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; BSA: body surface area; IV: intravenous; RANKL: receptor activator of nuclear factor-κB ligand; RCT: randomized controlled trial; vs.: versus

The CA209-066 study was a randomized, double-blind, active-controlled, 2-arm parallel group study. It was conducted in Australia, Europe, Israel as well as in Latin and North America. Treatment-naive adult patients with BRAF V600 wt melanoma (unresectable stage III or stage IV according to the AJCC) were included in the study.

418 patients were randomized in a ratio of 1:1, 210 patients to the nivolumab arm and 208 patients to the dacarbazine arm. Overall, the criteria of the therapeutic indication were regarded as being fulfilled for the patients enrolled in the study. This concurs with the company's assessment.

The patients in the nivolumab arm received 3 mg nivolumab per kg body weight intravenously (IV) every 2 weeks; changes in dosing were not permitted. This concurs with the requirements of the SPC [6]. The patients in the dacarbazine arm received 1000 mg dacarbazine per m^2 body surface area (BSA) IV, every 3 weeks. Dose increases were not allowed, whereas dose reductions in certain AEs were allowed following a fixed regimen. The use of dacarbazine concurred with the requirements of the SPC [7]. The dose was higher than

specified in the SPC (850 mg dacarbazine per m^2 BSA IV, every 3 weeks), but this deviation is in accordance with the SPC referring to dose recommendations in the current scientific literature. The S3-guideline "diagnosis, therapy and follow-up of melanoma" [14], for instance, recommends a dacarbazine dosage of 800 to 1200 mg/m^2 BSA IV on day 1 every 3 to 4 weeks.

The patients in both treatment arms could receive additional concomitant treatments. Restrictions in concomitant treatment only concerned treatment of the melanoma and administration of immunosuppressants.

The randomized study treatment was continued until at least one of the following criteria for discontinuation 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

Occurrence of a criterion for discontinuation did not automatically lead to unblinding of the randomized study treatment. The randomized study treatment was unblinded for 54 patients in the course of the study. Each unblinding was conducted for safety management or further planning of treatment. No restrictions for the choice of subsequent therapy after the end of the randomized study treatment were described in the study protocol.

Primary outcome was overall survival, and secondary outcomes were symptoms, health-related quality of life, health status and AEs.

Table 9 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 9: Planned duration of follow up – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Study Outcome category	Planned follow-up
CA209-066	
Overall survival	Until death, discontinuation of participation in the study or end of study
Morbidity	
EORTC QLQ-C30 (symptoms)	First follow-up visit: 30 ± 7 days after treatment discontinuation 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 (functions)	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 70 to 84 days after the first follow-up visit
Adverse events	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 70 to 84 days after the first follow-up visit

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; 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

Of the outcomes included, overall survival and health status measured with the EQ-5D VAS were recorded until the end of participation in the study. All other outcomes were only recorded for a certain length of time after the end of the randomized study treatment.

Analysis and data cut-offs

Two data cut-offs were planned for the study. The first data cut-off should have been conducted after about 218 deaths, and the second data cut-off after at least 312 deaths. After the death of 110 patients it was decided to end the study prematurely and unblind it because of the following reasons.

There was a Data Monitoring Committee (DMC) in the study, which had access to unblinded interim reports on efficacy and safety at regular intervals. On 5 November 2013, the DMC determined a possible difference in overall survival and therefore requested monthly reports on deaths starting from December 2013, and additionally the corresponding Kaplan-Meier curves starting from January 2014 (see Table 18). Since a statistically significant difference in favour of nivolumab was shown in the data cut-off on 23 May 2014, the DMC decided to end the study prematurely due to good efficacy. The study was unblinded on 1 July 2014, and the patients in the dacarbazine arm were allowed to continue treatment with nivolumab after the end of their randomized study treatment (treatment switching). A further analysis was conducted with the data cut-off on 24 June 2014. The European Medicines Agency (EMA) approval and the present benefit assessment were based on the results of this data cut-off, i.e. on data that were not yet affected by the unblinding and the treatment switching.

The study is continued as extension phase.

Patient characteristics

Table 10 shows the characteristics of the patients in the studies included.

Table 10: Characteristics of the study populations – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine

Study **Characteristics** **Category**	**Nivolumab** **N = 210**	**Dacarbazine** **N = 208**
CA209-066		
Age [years], mean (SD)	62 (13)	64 (13)
Sex [F/M], %	42/58	40/60
Skin colour, n (%)		
White	209 (99.5)	207 (99.5)
Other	1 (0.5)[a]	1 (0.5)[a]
Metastases at baseline, n (%)		
M0	17 (8.1)	13 (6.3)
M1a	21 (10.0)	20 (9.6)
M1b	44 (21.0)	48 (23.1)
M1c	128 (61.0)	127 (61.1)
Extent of metastases (number of locations), n (%)		
< 3	127 (60.5)[a,b]	113 (54.3)[a]
≥ 3	82 (39.0)[a,b]	95 (45.7)[a]
PD-L1 status, n (%)		
Positive (≥ 5% tumour cell membrane staining)	74 (35.2)	74 (35.6)
Negative/non-quantifiable	136 (64.8)	134 (64.4)
Time since first diagnosis [years], median [min; max]	1.9 [0.1; 32.6]	1.7 [0.1; 22.2]
Baseline LDH serum level, n (%)		
≤ ULN	120 (57.1)	125 (60.1)
> ULN	79 (37.6)	74 (35.6)
No data	11 (5.2)	9 (4.3)
History of brain metastases, n (%)		
Yes	7 (3.3)	8 (3.8)
No	203 (96.7)	200 (96.2)
ECOG PS, n (%)		
0	148 (70.5)	121 (58.2)
1	60 (28.6)	84 (40.4)
2	1 (0.5)	3 (1.4)
No data	1 (0.5)	0 (0)
Disease stage according to the AJCC at baseline, n (%)		
III	27 (12.9)	22 (10.6)
IV	183 (87.1)	186 (89.4)
Study discontinuations, n (%)	54 (26.2)[c,d]	107 (52.2)[c,d]
Treatment discontinuations, n (%)	111 (53.9)[c]	192 (93.7)[c]

(continued)

Table 10: Characteristics of the study populations – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine (continued)

a: Institute's calculation.
b: Information available on only 209 patients, but the percentages are based on 210 patients.
c: Percentages calculated on the basis of all patients treated: nivolumab = 206, dacarbazine = 205.
d: Including deaths.
AJCC: American Joint Committee on Cancer; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; ECOG: Eastern Cooperative Oncology Group; F: female; LDH: lactate dehydrogenase; M: male; max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; ULN: upper limit of normal; vs.: versus

Patient characteristics were largely comparable in the 2 treatment arms. Mean age was 62 years in the nivolumab arm, and 64 years in the dacarbazine arm; whereas the median of disease duration was 1.9 versus 1.7 months. None of the patients had BRAF V600 mutation, and 99.5% of the patients were white. About 12% of the patients were in AJCC stage III, and about 88% of the patients were in AJCC stage IV. More than 90% of the patients had distant metastases with 61% of the patients having M1c metastases. Almost all patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at baseline, with 70.5% of the patients in the nivolumab arm, and 58.2% of the patients in the dacarbazine arm having an ECOG PS of 0.

Table 11 shows the mean and median treatment duration of the patients and the follow-up period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Study **Duration of the study phase** **Outcome category**	**Nivolumab** **N = 210**	**Dacarbazine** **N = 208**
CA209-066		
Treatment duration [months]	n = 206	n = 205
Median [min; max]	5.1 [< 0.1; 16.6]	2.1 [< 0.1; 12.9]
Mean (SD)	6.4 (4.6)	3.3 (2.8)
Observation period (treatment + follow up observation) [months]		
Overall survival	n = 210	n = 208
Median [min; max]	8.9 [0.6; 16.7]	6.8 [0.0; 15.7]
Mean (SD)	8.7 (4.1)	7.2 (3.9)
Morbidity, health-related quality of life, adverse events		
Median [min; max]	ND	ND

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

The observation period in some of the patients was very short because of the unplanned data cut-off on 24 June 2014 and the late start of the treatment of the last patient (24 February 2014).

The median treatment duration on the basis of all treated patients differed considerably in the 2 treatment arms (5.1 versus 2.1 months), whereas the difference in the median observation period for overall survival based on the randomized patients was not as pronounced (8.9 versus 6.8 months). There was no information on the observation period of morbidity, health-related quality of life and AEs.

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

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			
CA209-066	Yes	Yes	Yes	Yes	Yes	Yes	Low
BRAF V600 wt: BRAF V600 wildtype; RCT: randomized controlled trial; vs.: versus							

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

Restrictions that may result from the unblinding of the 54 patients and the premature ending of the study due to the unplanned interim analysis are described in the outcome-specific risk of bias in Section 2.4.2.2.

2.4.2 Results on added benefit (research question 2)

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 VAS of the EQ-5D

- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Adverse events
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - treatment discontinuations due to AEs

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

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine

Study	Outcomes						
	Overall survival	Symptoms (EORTC QLQ-C30)[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	SAEs	Treatment discontinuations due to AEs	Severe AEs (CTCAE grade ≥ 3)
CA209-066	Yes	No[c]	No[c]	No[c]	No[c]	No[c]	No[c]

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: No evaluable data available; for reasons, see Sections 2.4.2.2 and 2.4.2.3 as well as 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 wildtype; 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

2.4.2.2 Risk of bias

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Study	Study level	Outcomes						
		Overall survival	Symptoms (EORTC QLQ-C30)[a]	Health status (EQ-5D VAS)	Health-related quality of life EORTC QLQ-C30)[b]	SAEs	Treatment discontinuations due to AEs	Severe AEs (CTCAE grade ≥ 3)
CA209-066	L	H[c]	–[d]	–[d]	–[d]	–[d]	–[d]	–[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: Discontinuation due to the results of an unplanned interim analysis.
d: No evaluable data available.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; 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 study level was rated as low. This assessment concurs with that of the company.

The risk of bias for the outcome "overall survival" was rated as high. This rating resulted from the fact that the study was ended prematurely due to the results on overall survival from an unplanned analysis. The fact that 54 patients were unblinded in the course of the study did not contribute to an increase of the risk of bias. The assessment of the risk of bias for overall survival deviates from the company's assessment, which considered the risk of bias as low.

Due to the low proportion (about 62% of the randomized patients) of the patients analysed, no evaluable results were available for the remaining benefit outcomes (symptoms, health status and health-related quality of life).

Only a qualitative assessment is possible of the results on AEs due to the high proportion of events recorded that represent progression of the underlying disease (see Appendix D of the full dossier assessment). No regular rating of the risk of bias was therefore conducted for these results. The fact that 54 patients were unblinded in the course of the study had no consequences because the analyses were not evaluable or because the data of AEs can only be interpreted in qualitative terms. This deviates from the company's assessment, which attributed a high risk of bias to the benefit outcomes, and a low risk of bias to the AEs.

2.4.2.3 Results

The results on the comparison of nivolumab versus dacarbazine in treatment-naive patients with advanced (unresectable or metastatic) BRAF V600 wt melanoma are summarized in Table 15. The Kaplan-Meier curve on overall survival is presented in Appendix C of the full dossier assessment. Common AEs with potentially important differences between the treatment arms are shown in Table 16.

Table 15: Results – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine

Study Outcome category Outcome	Nivolumab		Dacarbazine		Nivolumab vs. dacarbazine	
	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 [95% CI]	p-value
CA209-066						
Mortality						
Overall survival	210	NA [NA; NA] 50 (23.8)	208	10.84 [9.33; 12.09] 96 (46.2)	0.42 [0.30; 0.60]	< 0.001
Morbidity						
Symptoms (EORTC QLQ-C30)[b]				No evaluable data[c]		
Health status (EQ-5D VAS)				No evaluable data[c]		
Health-related quality of life						
EORTC QLQ-C30[d]				No evaluable data[c]		
Adverse events						
AEs				No evaluable data[e]		
SAEs				No evaluable data[e]		
Treatment discontinuation due to AEs				No evaluable data[e]		
Severe AEs (CTCAE grade ≥ 3)[f]				No evaluable data[e]		

a: The 2-sided 95% CI was calculated with a log-log transformation (according to Brookmeyer and Crowley [15]).
b: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.0.
c: Too few subjects included in the analysis.
d: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.0.
e: The analyses presented by the company in Module 4 A include a large number of events caused by progression of the underlying disease. The analyses on the basis of the overall rates are therefore not interpretable.
f: The HR in Module 4 A deviate and are based on AEs of CTCAE grade 3 and 4.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Table 16: Results (common AEs with potentially important differences between the treatment arms) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine

Study	Nivolumab		Dacarbazine	
Outcome category Outcome	N	Patients with event n (%)	N	Patients with event n (%)
CA209-066				
Specific AEs				
Rash	206	46 (22.3)	205	16 (7.8)
Erythema	206	21 (10.2)	205	6 (2.9)
Pruritus	206	46 (22.3)	205	24 (11.7)
Vitiligo	206	22 (10.7)	205	1 (0.5)
Vomiting	206	23 (11.2)	205	51 (24.9)
Nausea	206	48 (23.3)	205	96 (46.8)
Pulmonary embolism (severe AEs with CTCAE grade ≥ 3)[a]	206	2 (1.0)	205	7 (3.4)
Pleural effusion (severe AEs with CTCAE grade ≥ 3)[b]	206	0 (0)	205	7 (3.4)
Neutropenia (severe AEs with CTCAE grade ≥ 3)	206	0 (0)	205	9 (4.4)
Thrombocytopenia (severe AEs with CTCAE grade ≥ 3)	206	0 (0)	205	11 (5.4)

a: The SAE "pulmonary embolism" occurred in 0 (0%) patients in the nivolumab arm, and in 5 (2.4%) patients in the dacarbazine arm. These patients are probably included in the patients with severe AE (CTCAE grade ≥ 3).
b: Identical numbers resulted for the SAE "pleural effusion".

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

The particular requirements for derivation of proof from a single study are not met by the CA209-066 study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, at most "indications", e.g. of an added benefit, could be derived from the data. This deviates from the company's assessment, which considered the CA209-066 study suitable for deriving proof.

Mortality

Nivolumab treatment resulted in a statistically significant prolongation of overall survival in comparison with dacarbazine.

In addition, an indication of effect modification by the characteristics "sex" (interaction test: p = 0.187) and ECOG PS (interaction test: p = 0.087) was shown in each case for the outcome "overall survival" (see Section 2.4.2.4). As can be inferred from the information in Section 2.4.2.4, additional separate consideration of the results in men and women was therefore meaningful. The subgroup analyses showed an indication of an added benefit of

nivolumab in comparison with dacarbazine for men, and a hint of an added benefit for women.

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

Morbidity

The dossier contained no evaluable data for symptoms measured with the symptom scales of the EORTC QLQ-C30 questionnaire and for health status measured with the EQ-5D VAS (see Section 2.7.2.4.3 of the full dossier assessment). There was thus no hint of an added benefit of nivolumab in comparison with dacarbazine for these outcomes. An added benefit for these outcomes is therefore not proven.

This assessment concurs with that of the company, which considered the analyses, but derived no added benefit because of lacking statistically significant or clinically relevant differences between the treatment arms.

Health-related quality of life

The dossier contained no evaluable data for health-related quality of life measured with the functional scales of the EORTC QLQ-C30 questionnaire (see Section 2.7.2.4.3 of the full dossier assessment). There was thus no hint of an added benefit of nivolumab in comparison with dacarbazine for this outcome. An added benefit for this outcome is therefore not proven.

This assessment concurs with that of the company, which considered the analyses, but derived no added benefit because of lacking statistically significant differences between the treatment arms.

Adverse events

Due to the large proportion of recorded events that were caused by progression of the underlying disease (see Section 2.7.2.4.3 and the tables on common AEs in Appendix D of the full dossier assessment), the survival time analyses on AEs (SAEs, severe AEs [CTCAE grade ≥ 3] and discontinuation due to AEs) presented in Module 4 A were not evaluable. For example, the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) “neoplasms benign, malignant and unspecified (including cysts and polyps)” with the Preferred Terms (PTs) “progression of malignant melanoma” and “malignant melanoma” was by far the most common category of SAEs (patients with event, see Table 42 in Appendix D of the full dossier assessment). These events also occurred frequently in the analyses on treatment discontinuations due to AEs and severe AEs (CTCAE grade ≥ 3) (see Table 43 and Table 44 in Appendix D of the full dossier assessment). Hence only qualitative conclusions on the basis of the naive proportions of the common events presented in Appendix D of the full dossier assessment were drawn for AEs in the present benefit assessment. The common AEs with potentially important differences between the treatment arms presented in Table 16

were extracted and interpreted from the tables presented in Appendix D of the full dossier assessment.

Inspection of the naive proportions in Appendix D of the full dossier assessment and in Table 16 produced no signs that the analyses on AEs could raise fundamental doubts about the observed advantage in overall survival. Overall, the respective overall rates cannot be interpreted because of the bias caused by the recording of the progression of the underlying diseases. Hence a possible advantage of nivolumab, which the company had derived on the basis of its hazard ratio (HR) analyses, was not confirmed. Nonetheless, the naive proportions overall, and for most events with potentially important differences between the treatment arms in Table 16, rather indicate an advantage in favour of nivolumab. Overall, neither greater nor lesser harm of nivolumab in comparison with dacarbazine can be excluded on the basis of the qualitative assessment of SAEs, severe AEs (CTCAE grade ≥ 3) and treatment discontinuation due to AEs.

An interpretation of the results on AEs would be possible if the company conducted its survival time analyses and calculations of HR in a way that does not consider the events caused by progression of the underlying disease (such as recording of the PTs “malignant neoplasm progression” or “malignant melanoma”) (see Section 2.7.2.4.3 of the full dossier assessment). Suitable analyses would then also allow the balancing of benefit and harm of nivolumab versus dacarbazine.

Overall, there was no hint of greater or lesser harm from nivolumab in comparison with dacarbazine for these outcomes on the basis of the present analyses. Hence greater or lesser harm is not proven for these outcomes.

This assessment deviates from that of the company, which derived proof of added benefit for severe AEs (CTCAE grade 3 or 4), and an indication of added benefit for the outcome “treatment discontinuation due to AEs”. The company derived no added benefit on the basis of specific AEs.

2.4.2.4 Subgroups and other effect modifiers

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

In order to uncover possible effect differences between patient groups, the following subgroup characteristics were included:

- age (< 65 years versus ≥ 65 to < 75 years versus ≥ 75 years)
- sex (male versus female)
- metastases at baseline according to the case report form (CRF) (M0/M1a/M1b versus M1c)

- ECOG PS (0 versus 1)
- lactate dehydrogenase (LDH) serum level (≤ upper limit of normal [ULN] versus > ULN)
- PD-L1 status according to the CRF (positive versus negative or non-quantifiable)

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). An indication of differing effects results from a p-value between 0.05 and 0.2. The dossier contained the interaction tests for all subgroup characteristics.

There was no proof ($p < 0.05$) of an effect modification from any of the subgroup analyses. There was an indication ($p = 0.109$) of an effect modification for the subgroup characteristic "age". Since the pairwise comparisons calculated by the Institute showed no important heterogeneity (< 65 years versus ≥ 65 to < 75 years [$p = 0.675$] and ≥ 65 to < 75 years versus ≥ 75 years [$p = 0.309$]), however, the results of the individual age subgroups were not presented.

Table 17 shows the results of the subgroup analyses for subgroup characteristics for which an indication of an effect modification was provided.

Table 17: Subgroups (dichotomous outcomes) – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median survival time in months [95% CI] Patients with event n (%)	Dacarbazine N	Dacarbazine Median survival time in months [95% CI] Patients with event n (%)	Nivolumab vs. dacarbazine HR [95% CI][a]	Nivolumab vs. dacarbazine p-value[b]
Study CA209-066						
Overall survival						
Sex						
Men	121	N.A. (NA; NA) 27 (22.3)	125	9.92 (8.38; 11.70) 62 (49.6)	0.34 [0.22; 0.54]	< 0.001
Women	89	N.A. (NA; NA) 23 (25.8)	83	12.39 (7.59; NA) 34 (41.0)	0.56 [0.33; 0.95]	0.028
					Interaction:	0.187[c]
ECOG PS						
0	148	N.A. (NA; NA) 23 (15.5)	121	11.83 (9.59; 15.18) 48 (39.7)	0.32 [0.20; 0.53]	< 0.001
1	60	12.68 (7.48; NA) 26 (43.3)	84	7.43 (5.16; 11.70) 46 (54.8)	0.64 [0.40; 1.04]	0.072
					Interaction:	0.087[c]

a: Unstratified Cox model.
b: Unstratified log-rank test; exceptions are provided.
c: From Cox model with interaction term treatment group*subgroup characteristic.
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

There was an indication of effect modification by the subgroup characteristics “sex” and “ECOG PS” for overall survival. The effect modification by ECOG PS was not considered in the derivation of the added benefit because the effect modification was not shown on the other subgroup characteristics on the severity of the disease (metastases and LDH serum level). Moreover, there was only an indication of effect modification, and the effect estimations in both subgroups had the same direction.

Treatment with nivolumab in comparison with dacarbazine resulted in a statistically significant prolongation of overall survival for men and women, but with different certainty of results and different extent (see Table 19).

As shown, the risk of bias for the outcome "overall survival" was rated as high because the study was ended prematurely due to the results on overall survival from an unplanned analysis. Hence only the certainty of results "hint" could be derived for overall survival on the basis of a single study. However, a notable statistically significant effect was shown for the total population in the present situation, which, in addition, had been present since the analysis in March 2014 according to the information in Table 18. On this basis, an indication can be derived for the total population. Due to the effect size for the subpopulation of men, this assumption can also be transferred to men so that an indication was derived here as well. However, this assumption cannot be transferred to the subpopulation of women, for whom a notably lesser advantage was shown than for men and for the total population. The certainty of results for the outcome "overall survival" in women therefore remains a "hint".

Table 18: Course of effect on overall survival: RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Date of data transfer	Nivolumab n/N (%)	Dacarbazine n/N (%)	Nivolumab vs. dacarbazine HR [95% CI]	Data presented to the DMC
20 Sep 2013	8/136 (5.9)	12/139 (8.6)	0.5 (0.2; 1.3)	Deaths
4 Nov 2013	12/159 (7.5)	21/161 (13.0)	0.4 (0.2; 0.9)	Deaths
11 Dec 2013	21/178 (11.8)	27/177 (15.3)	0.6 (0.3; 1.0)	Deaths
7 Jan 2014	24/187 (12.8)	30/187 (16.0)	0.7 (0.4; 1.1)	Deaths
24 Jan 2014	25/193 (13.0)	32/193 (16.6)	0.6 (0.4; 1.1)	Deaths, KM
3 Mar 2014	28/210 (13.3)	44/208 (21.2)	0.5 (0.3; 0.8)	Deaths, KM
1 Apr 2014	29/210 (13.8)	44/208 (21.2)	0.5 (0.3; 0.9)	Deaths, KM
5 May 2014	35/210 (16.7)	65/208 (31.3)	0.5 (0.3; 0.7)	Deaths, KM, HR
27 May 2014	39/210 (18.6)	71/208 (34.1)	0.5 (0.3; 0.7)	Deaths, KM, HR, p-value

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B);
BRAF V600 wt: BRAF V600 wildtype; CI: confidence interval; DMC: Data Monitoring Committee;
HR: hazard ratio; KM: Kaplan-Meier curves; n: number of patients with event; N: number of randomized patients; vs.: versus

This assessment deviates from that of the company, which derived proof of added benefit for this outcome on the basis of the total population and did not consider the indication of effect modification.

2.4.3 Extent and probability of added benefit (research question 2)

The following text presents the derivation of the extent and probability of added benefit at outcome level, under consideration of 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.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 resulted in indications or hints of an added benefit of nivolumab in comparison with dacarbazine for the outcome “overall survival”. There was an indication of an effect modification by the subgroup characteristic “sex” for the outcome “overall survival”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 19). In the overall assessment, it was investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 19: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. dacarbazine** **Time to event** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Sex		
Men	Median: NA vs. 9.92 months HR 0.34 [0.22; 0.54] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Women	Median: NA vs. 12.39 months HR 0.56 [0.33; 0.95[c]] p = 0.028 probability: "hint"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"[c]
Morbidity		
Symptoms (EORTC QLQ-C30)	No evaluable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No evaluable data	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No evaluable data	Lesser benefit/added benefit not proven
Adverse events		
SAEs	No evaluable data	Greater/lesser harm not proven
Treatment discontinuation due to AEs	No evaluable data	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	No evaluable data	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Due to the rough rounding in the CI_u (0.95), considerable added benefit cannot be excluded either.
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; NA: not applicable or not achieved; QLQ-C30: Quality of Life Questionnaire Core-30; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 20 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of nivolumab in comparison with dacarbazine for treatment-naive patients with BRAF V600 wt tumour

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Sex (men) indication of an added benefit – extent: “major” ▫ Sex (women) hint of an added benefit – extent: “minor”	
Adverse events The presence of positive effects due to AEs cannot be excluded.	Adverse events The presence of negative effects due to AEs cannot be excluded.
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype	

Overall, positive effects remain. Due to the data availability, it is unclear whether there were positive or negative effects for AEs. However, there were no signs that fundamental doubts could be raised about the positive effect in overall survival. Since there was an indication of an effect modification by the subgroup characteristic “sex” for the outcome “overall survival”, the overall assessment of added benefit was conducted separately for men and women.

Added benefit for men

For men, there was an indication of major added benefit on the side of positive effects. AEs were not finally assessed because of the data availability. Beyond that, there were no evaluable data for morbidity and health-related quality of life. However, it cannot be assumed that further analyses would show that the extent of added benefit for overall survival is completely outweighed. Due to the uncertainty in the interpretation of AEs, no balancing of benefit and harm was possible. Furthermore, there were no other results that could contribute to such balancing because the data on morbidity and health-related quality of life were not evaluable. The extent of added benefit was therefore downgraded to “considerable”, and the certainty of results “indication” was taken from the certainty of results of the outcome “overall survival”.

Hence there is an indication of considerable added benefit of nivolumab in comparison with the ACT dacarbazine for treatment-naive men whose tumour is BRAF V600 mutation-negative.

Added benefit for women

For women, there was a hint of a minor added benefit on the side of positive effects. AEs were not finally assessed because of the data availability. Beyond that, there were no evaluable data for morbidity and health-related quality of life. However, it cannot be assumed that further analyses would show that the extent of added benefit for overall survival is completely outweighed, particularly because the upper limit of the confidence interval (0.95)

was directly on the border between the extents “considerable” and “minor”. The extent of added benefit was therefore not downgraded despite the uncertainty in the interpretation of AEs and the missing data for morbidity and health-related quality of life.

Hence there is a hint of minor added benefit of nivolumab in comparison with the ACT dacarbazine for treatment-naive women whose tumour is BRAF V600 mutation-negative.

Summary

In summary, there is an indication of considerable added benefit of nivolumab in comparison with the ACT dacarbazine for treatment-naive men whose tumour is BRAF V600 mutation-negative, and a hint of a minor added benefit for treatment-naive women whose tumour is BRAF V600 mutation-negative.

This deviates from the company’s approach, which claimed proof of a major added benefit irrespective of sex.

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

2.4.4 List of included studies (research question 2)

Bristol-Myers Squibb. A phase 3, randomized, double-blind study of BMS-936558 vs dacarbazine in subjects with previously untreated unresectable or metastatic melanoma: revised protocol 03; including protocol amdt 07 [online]. In: EU Clinical Trials Register. [Accessed: 20 August 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003718-16.

Bristol-Myers Squibb. Study of BMS-936558 vs. dacarbazine in untreated, unresectable or metastatic melanoma (CheckMate 066): full text view [online]. In: ClinicalTrials.gov. 3 July 2015 [accessed: 30 July 2015]. URL: https://ClinicalTrials.gov/show/NCT01721772.

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

Bristol-Myers Squibb. A phase 3, randomized, double-blind study of BMS-936558 (nivolumab) versus dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma: study CA209066; final clinical study report [unpublished]. 2014.

Bristol-Myers Squibb. A phase III, randomized, double-blind study of nivolumab vs. dacarbazine in subjects with previously untreated unresectable or metastatic melanoma: study CA209066; safety and efficacy report; closed report [unpublished]. 2014.

F. Hoffmann-La Roche. BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving vemurafenib (RO5185426) or dacarbazine [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 24 June 2015]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L et al. Supplementary appendix for "Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2014; 372(4): 320-330" [online]. 15 December 2014. URL: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1412082/suppl_file/nejmoa1412082_appendix.pdf.

Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2014; 372(4): 320-330.

Statistics Collaborative. Memorandum: supplemental closed presentations for the June 10, 2014 CA209-066 report [unpublished]. 2014.

2.5 Research question 3: pretreated patients

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

2.5.1 Information retrieval and study pool (research question 3)

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

Sources of the company in the dossier:

- study list on nivolumab (status: 9 June 2015)
- bibliographical literature search on nivolumab (last search on 6 May 2015)
- search in trial registries for studies on nivolumab (last search on 12 May 2015)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 30 July 2015)

No additional relevant study was identified from the check.

2.5.1.1 Studies included

From the steps of information retrieval mentioned, the company identified one RCT; this was study CA209-037, in which nivolumab was compared with a treatment of physician's choice in pretreated patients. The analyses presented by the company for this study were not evaluable. The reason was that the company had rendered randomization ineffective with the selection of the subpopulation who were treated in accordance with the German approval status. Hence the analyses of the CA209-037 study presented by the company were unsuitable to derive an added benefit of nivolumab in comparison with the ACT. Since no conclusive assessment can be made whether conclusions on the added benefit of nivolumab versus a treatment of physician's choice can be drawn on the basis of different analyses of this study, the CA209-037 study is described, and their relevance for the research question is presented.

Table 21: Study pool of the company – RCT, direct comparison: pretreated patients, nivolumab vs. treatment of physician's choice

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CA209-037	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The company additionally considered the two studies of direct comparisons with treatment-naive patients on the comparison of nivolumab versus dacarbazine (study C209-066) and nivolumab versus ipilimumab (study CA209-067) as well as the indirect comparison of nivolumab with vemurafenib of research question 1, also with treatment-naive patients, for the derivation of the added benefit. This approach was not followed because the results of treatment-naive patients cannot simply be transferred to pretreated patients (see Sections 2.7.2.3.2.3 and 2.7.2.9.3 of the full dossier assessment).

Section 2.5.4 contains a reference list for the study included.

2.5.1.2 Study characteristics

Table 22 and Table 23 describe the studies used for the benefit assessment.

Table 22: Characteristics of the study included – RCT, direct comparison: pretreated patients, nivolumab vs. treatment of physician's choice

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-037	RCT, open-label, parallel	Pretreated adults with advanced (unresectable or metastatic) melanoma (stage III or IV) evidence of progression during or following treatment with anti-CTLA-4 containing therapy (ipilimumab) in BRAF V600 wt or during or following anti-CTLA-4 containing therapy (ipilimumab) and BRAF inhibitor therapy in BRAF V600 mutation	Nivolumab (N = 272) treatment of physician's choice (N = 133) Relevant subpopulation thereof[b]: nivolumab (n = 111) treatment of physician's choice dacarbazine (n = 56)	Screening: within 28 days before randomization Treatment phase: nivolumab until progression or after progression for as long as the investigator considers the treatment to be beneficial to the patient or until intolerance treatment of physician's choice until progression Observation period: until death or discontinuation of study participation	90 centres in Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, USA, United Kingdom 12/2012–ongoing Data cut-off of prespecified analysis of ORR on 30 April 2014 Data cut-off of prespecified analysis of overall survival on 12 November 2014	Primary: overall survival, ORR (non-comparative in the nivolumab arm) Secondary: symptoms, health-related quality of life, health status, 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: Patients for whom treatment with dacarbazine was intended before randomization in case of allocation to the arm with treatment of physician's choice.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; N: number of randomized patients; n: relevant subpopulation; ORR: objective response rate; RCT: randomized controlled trial; vs.: versus

Table 23: Characteristics of the interventions – RCT, direct comparison: pretreated patients, nivolumab vs. treatment of physician's choice

Study	Intervention	Comparison	Prior and concomitant medication
CA209-037	Nivolumab 3 mg/kg body weight IV, every 2 weeks no change in dosing allowed for nivolumab	Dacarbazine[a] 1000 mg/m^2 BSA IV, every 3 weeks no dose increase allowed for dacarbazine dose reduction for dacarbazine in certain AEs following a fixed regimen	**Pretreatment** ▪ previous treatments for advanced disease ▫ at least one treatment for patients with BRAF BV600 wt tumour ▫ at least 2 treatments for patients with BRAF BV600 mut tumour ▪ chemotherapy or immunotherapy had to be completed at least 4 weeks before randomization, anti-CTLA-4 therapy had to be completed at least 6 weeks before randomization, radiotherapy had to be completed at least 2 weeks before randomization **Concomitant treatment** ▪ non-systemic corticosteroids ▪ palliative radiotherapy **Non-permitted concomitant treatment** ▪ immunosuppressants, immunosuppressive dosages of systemic corticosteroids ▪ non-palliative radiotherapy or other antineoplastic treatments ▪ surgical resection of lesions

a: Under consideration of the approval status and the respective prior therapy, monotherapy with dacarbazine was the only possibly operationalization of the ACT (treatment of physician's choice) for the patients included in the study at the time point the study was conducted.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 mut: BRAF V600 mutated; BRAF V600 wt: BRAF V600 wildtype; BSA: body surface area; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; RCT: randomized controlled trial; vs.: versus

The CA209-037 study was an open-label RCT with nivolumab in comparison with a treatment of physician's choice. It was conducted in Europe and Israel as well as in North and South America.

Patients with advanced (unresectable or metastatic) melanoma were enrolled in the study. Both patients with BRAF V600 mutation of the tumour and patients without such mutation (BRAF V600 wt) were included. The patients included had already received treatment for their advanced melanoma. There was to be objective evidence of disease progression during or after treatment for advanced melanoma. Patients without BRAF V600 mutation had received at least one treatment with an antibody against the cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4 antibody). Ipilimumab was the only option of an anti-CTLA-4 antibody at the time point of the study. Patients with BRAF V600 mutation must have had another pretreatment with a BRAF inhibitor in addition to the anti-CTLA-4 antibody (ipilimumab).

405 patients were randomized in a ratio of 2:1, 272 patients to the nivolumab arm and 133 patients to the arm with treatment of physician's choice. Overall, the criteria of the therapeutic indication were regarded as being fulfilled for the patients enrolled in the study. This concurs with the company's assessment.

The study had 2 treatment arms: nivolumab and treatment of physician's choice. Treatment options for the treatment of physician's choice were either dacarbazine as monotherapy or carboplatin + paclitaxel as combination therapy. Using the interactive voice response system (IVRS) the investigator specified before randomization which treatment (dacarbazine or carboplatin + paclitaxel) a patient was to receive in case of randomization to the comparator arm. Then the patients were allocated in a ratio of 2:1 to the 2 study arms with randomization being stratified by BRAF V600 mutation status, PD-L1 status and prior anti-CTLA-4 best response.

Relevant primary outcome was overall survival, and patient-relevant further outcomes were symptoms, health-related quality of life, health status and AEs.

Table 24 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 24: Planned duration of follow-up – RCT, direct comparison: pretreated patients, nivolumab vs. treatment of physician's choice

Study **Outcome category**	**Planned follow-up**
CA209-037	
Overall survival	Every 3 months, until death or end of study
Morbidity	
EORTC QLQ-C30 (symptoms)	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 one year, and then every 6 months until death
Health-related quality of life	
EORTC QLQ-C30 (functions)	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 84 ± 7 days after the first follow-up visit
Adverse events	First follow-up visit: 30 ± 7 days after treatment discontinuation Second follow-up visit: 84 ± 7 days after the first follow-up visit
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	

Two predefined data cut-offs were performed in the study. The first data cut-off on 30 April 2014 was conducted for the interim analysis of the primary outcome "objective response rate". The second data cut-off on 12 November 2014 was conducted for the interim analysis of the coprimary outcome "overall survival". In December 2014, based on the results on

overall survival, the DMC recommended the unchanged continuation of the study. The final analysis of overall survival is expected by the end of 2015.

Relevance of the CA209-037 study

Appropriate comparator therapy

In pretreated patients, the G-BA specified individual treatment chosen by the treating physician under consideration of the approval status and the respective prior therapy (treatment of physician's choice) as ACT. However, the investigator in the CA209-037 study could only choose between 2 chemotherapeutic options (dacarbazine as monotherapy or carboplatin + paclitaxel as combination therapy). The combination of carboplatin and paclitaxel is not approved in Germany for the treatment of melanoma, and is therefore not an option as an operationalization of the ACT. Monotherapy with dacarbazine remains as an operationalization of the ACT. Due to the pretreatment of the patients in the study, it can be assumed that chemotherapy was the only treatment option for these patients at the time point of the study. Hence dacarbazine can be regarded as sufficient operationalization of the ACT for the patients in the study.

The relevant subpopulation of the CA209-037 study therefore consisted of patients in the comparator arm who were treated with dacarbazine, and of patients in the nivolumab arm for whom dacarbazine was the intended treatment if they had been allocated to the comparator arm.

Relevant subpopulation

The relevant subpopulation of the CA209-037 study consisted of patients for whom the investigator, before randomization, had intended dacarbazine as treatment of physician's choice. These were 111 (40.8%) of the 272 patients in the nivolumab arm, and 56 (42.1%) of the 133 patients in the comparator arm. The company presented data of the relevant subpopulation for the comparator arm in Module 4 A of the dossier. However, it presented data for the total population for the nivolumab arm, and not for the 111 patients in the nivolumab arm for whom the investigator had intended dacarbazine as treatment of physician's choice before randomization. Hence the balance of patient characteristics aimed at with the randomization was not ensured in the study arms. The company recognized this itself and mentioned this as a reason for potential bias of the study. However, it would be possible for the company to select the corresponding subpopulations from the study arms. There would then be a valid randomization for these subpopulations.

The analyses of the CA209-037 study presented by the company were not evaluable for the present benefit assessment because the randomization was rendered ineffective.

Exclusion of the CA209-037 study by the company

Besides the fact presented that randomization was rendered ineffective by the company's selection of the subpopulation, the company named the following factors that it considered to increase the risk of bias of the study:

- differences in discontinuation rates in the treatment arms
- differences in the distribution of prognostic factors in the study arms despite randomization
- possibility to switch to anti-PD-L1 antibody treatment in the dacarbazine arm

The company was followed insofar as the aspects mentioned by the company may influence the risk of bias of a study and of individual outcomes. A high risk of bias does not mean that the data of a study cannot be interpreted at all, however. Since the dossier contained only data of the total patient population for the nivolumab arm, no final assessment can be made whether the causes of bias in the study were actually so profound as to make an interpretation of the data impossible. A detailed presentation of the company's rationale can be found in Section 2.7.2.3.2.3 of the full dossier assessment.

The company presented the CA209-037 study and its results in Module 4 A of the dossier, but did not use them to derive an added benefit. It justified this with the risk of bias of the study being too high. This justification is not finally comprehensible.

Summary

The analyses of the CA209-037 study presented by the company were not evaluable for the present benefit assessment because the balance of patient characteristics in the study arms aimed at by the randomization was no longer ensured because of the selection of the subpopulation treated in compliance with the German approval status. The data from the studies of research questions 1 and 2 alternatively used by the company were not relevant for the present research question 3 on pretreated patients.

Hence there were no relevant data for the derivation of the added benefit of nivolumab versus treatment of physician's choice in pretreated patients.

2.5.2 Results on added benefit (research question 3)

There were no evaluable data for the assessment of the added benefit of nivolumab for pretreated patients. There was therefore no hint of an added benefit of nivolumab in comparison with the ACT (treatment of physician's choice) in pretreated patients; an added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit (research question 3)

There were no evaluable data for the assessment of the added benefit of nivolumab for pretreated patients. There was therefore no hint of an added benefit of nivolumab in

comparison with the ACT (treatment of physician's choice) in pretreated patients; an added benefit is therefore not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The company, in contrast, derived a hint of a non-quantifiable added benefit for pretreated patients on the basis of the data of research questions 1 and 2 (treatment-naive patients with and without BRAF V600 mutation).

2.5.4 List of included studies (research question 3)

Bristol-Myers Squibb. A study to compare BMS-936558 to the physician's choice of either dacarbazine or carboplatin and paclitaxel in advanced melanoma patients that have progressed following anti-CTLA-4 therapy (CheckMate 037): full text view [online]. In: ClinicalTrials.gov. 6 May 2015 [accessed: 12 May 2015]. URL: http://ClinicalTrials.gov/show/NCT01721746.

Bristol-Myers Squibb. A randomized open-label phase III trial of BMS-936558 versus investigators choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy [online]. In: EU Clinical Trials Register. [Accessed: 12 May 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-001828-35.

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

Bristol-Myers Squibb. A randomized open-label phase III trial of BMS-936558 versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 12 May 2015]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Bristol-Myers Squibb. A randomized, open-label, phase 3 trial of BMS-936558 (nivolumab) versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy: study CA209037; interim clinical study report [unpublished]. 2014.

Bristol-Myers Squibb. Nivolumab (BMS-936558): study CA209037; adhoc report for additional efficacy analyses [unpublished]. 2014.

Bristol-Myers Squibb. A randomized, open-label phase 3 trial of BMS-936558 (nivolumab) versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy: study CA209037; clinical protocol; revised protocol number 05; incorporates amendment 12 [unpublished]. 2014.

Bristol-Myers Squibb. Nivolumab (BMS-936558): study CA209037; interim adhoc report [unpublished]. 2015.

Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16(4): 375-384.

Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial; supplementary appendix. Lancet Oncol 2015; 16(4): 375-384.

2.6 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 25.

Table 25: Nivolumab – extent and probability of added benefit

Research question	Therapeutic indication	Appropriate comparator therapy[a]	Subgroup	Extent and probability of added benefit
1	Treatment-naive patients with BRAF V600 mutation-positive tumour	Vemurafenib	Added benefit not proven	
2	Treatment-naive patients with BRAF V600 mutation-negative tumour	**Dacarbazine** or ipilimumab[b]	Men	Indication of considerable added benefit
			Women	Hint of minor added benefit
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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold.
b: The company additionally investigated the research question on the comparison of nivolumab versus ipilimumab and presented it in Module 4 A as supplementary information.
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; G-BA: Federal Joint Committee; vs.: versus

This deviates from the company's approach, which derived an added benefit for all patients as follows:

- Treatment-naive patients with BRAF V600 mutation-positive tumour:

  hint of considerable added benefit
- Treatment-naive patients with BRAF V600 mutation-negative tumour:

  proof of major added benefit
- Pretreated patients:

  hint of a non-quantifiable added benefit

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

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Please see full dossier assessment for full reference list.

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