IQWiG Reports – Commission No. A21-39

Nivolumab (melanoma, adjuvant) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (Melanom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 29 June 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
BRAF	rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf)
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IIT	investigator-initiated trial
MEK	mitogen-activated extracellular signal-regulated kinase
NED	no evidence of disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 April 2021.

The company submitted a first dossier for the early benefit assessment of nivolumab, the drug to be assessed, on 27 August 2018. In this procedure, the G-BA limited its decision until 1 April 2021. The limitation was set due to pending analyses from the CA209-238 study, as there were no analyses on the outcome "overall survival" for any of the available data cut-offs and the analyses on recurrence-free survival were based on results of interim analyses. For the reassessment after expiry of the decision, the results on all patient-relevant outcomes, particularly on overall survival and recurrence, were to be presented in the dossier.

Research question

The aim of the present report is the assessment of the added benefit of nivolumab as monotherapy in comparison with the appropriate comparator therapy (ACT) in the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT**[a]
Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection	▪ Pembrolizumab (only for patients in tumour stage III after complete resection) or ▪ dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection) or ▪ **watchful waiting**[b]
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. The G-BA did not further specify the ACT "watchful waiting". ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; G-BA: Federal Joint Committee	

From the ACT options presented, the company chose watchful waiting, thus following the G-BA's specification.

In clinical practice, the disease severity of melanoma is assessed based on the American Joint Committee on Cancer (AJCC) classification. The S3 guideline on diagnosis, treatment and follow-up of melanoma also uses this classification to categorize tumours and structure treatment and follow-up recommendations.

The therapeutic indication presented in Table 2 represents disease stages III to IV according to the current 8th edition of the AJCC classification with melanoma stage III or higher being characterized by lymph node involvement and stage IV or higher by distant metastasis.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool and study characteristics

For the direct comparison of nivolumab with the ACT watchful waiting, the company identified the randomized controlled trial (RCT) IMMUNED. The analyses based on the total population of this study presented by the company are unsuitable for the present benefit assessment, however (see below for reasons). The company itself only used the IMMUNED study as support for an adjusted indirect comparison of nivolumab against the ACT watchful waiting based on RCTs. For this indirect comparison, the company identified the studies CA209-238 and CA184-029 (hereinafter referred to as "study 238" and "study 029").

The analyses presented by the company on the basis of the total population of the IMMUNED study are unsuitable for the present benefit assessment because the total population of the study partly also comprises patients without complete surgical resection of the melanoma with distant metastasis. These patients are not covered by the present research question and might have been under-treated with the strategy of watchful waiting in the placebo arm. How many patients this actually concerns cannot be estimated from the available information. The results on the basis of the total population of the study therefore have a potential risk of bias in favour of nivolumab. For this reason, analyses of the IMMUNED study based on a subpopulation corresponding to the research question (patients after complete resection) would be necessary for the present benefit assessment. However, the company presented no such analyses.

The check of the completeness of the study pool identified no additional relevant RCT for the direct comparison of nivolumab against the ACT.

For the adjusted indirect comparison presented by the company, no additional relevant studies were identified from the check of the completeness of the study pool.

The benefit assessment was therefore conducted on the basis of the adjusted indirect comparison of nivolumab against the ACT presented by the company.

Study 238 (study with nivolumab)

Study 238 is a randomized, active-controlled, double-blind phase 3 study. The study compared nivolumab with ipilimumab. It included patients aged ≥ 15 years with complete surgical resection of AJCC (7th edition) stage IIIB, IIIC or IV melanoma who were considered free of disease and who had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. According to the inclusion criteria, adolescents aged < 18 years were suitable for study inclusion, but only adults were included in the study.

In the study, 453 patients were randomized in a 1:1 ratio into each study arm. Randomization was stratified according to the factors programmed cell death ligand 1 (PD-L1) status and AJCC disease stage.

In the intervention arm, treatment with nivolumab was conducted following a weight-based dosing regimen in compliance with the original approval of nivolumab for the present therapeutic indication. In addition to nivolumab, patients in the intervention arm received placebo that matched the treatment regimen of the comparator intervention ipilimumab. Treatment in the comparator arm was with ipilimumab and a placebo for nivolumab. Ipilimumab is not approved in Germany for the present therapeutic indication.

In compliance with the Summary of Product Characteristics (SPC) of nivolumab, the treatment duration in both study arms was limited to 1 year. Patients were treated until recurrence or unacceptable persistent toxicity.

The primary outcome of the study was recurrence-free survival. Secondary outcomes were overall survival, symptoms, health-related quality of life, and adverse events (AEs).

The results of the final data cut-off (29 January 2020) were used for the benefit assessment.

Study 029 (study with placebo)

Study 029 is a randomized, active-controlled, double-blind phase 3 study. The study compared ipilimumab with placebo. It included adult patients with complete resection of melanoma in AJCC (6th edition) stage IIIA with metastases > 1 mm, IIIB or IIIC without in-transit metastases who were considered free of disease. Patients had to be in good general condition corresponding to ECOG PS 0 or 1.

Randomization in the study was in a 1:1 ratio; 475 patients were randomized to the ipilimumab arm and 476 patients to the placebo arm. Randomization was stratified by the factors of AJCC disease stage and region.

Treatment was until recurrence or unacceptable persistent toxicity. The specified treatment duration in both study arms was 3 years.

The primary outcome of the study was recurrence-free survival. Secondary outcomes were overall survival, distant-metastasis-free survival, symptoms, health-related quality of life, and AEs.

The results of the final data cut-off (13 May 2016) were used for the benefit assessment.

Operationalization and implementation of the appropriate comparator therapy watchful waiting

For the present benefit assessment, the ACT watchful waiting is operationalized as a follow-up strategy that particularly comprises the diagnosis of recurrence in accordance with the S3 guideline on diagnosis, treatment and follow-up of melanoma.

Study 029 used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison.

Although the investigations carried out in the study do not fully encompass the recommendations of the guideline, a close-meshed follow-up strategy targeted at the detection of local, regional and distant recurrences was used. This was assessed to be a sufficient approximation to the operationalization of watchful waiting described above.

Similarity of the studies in the indirect comparison

The inclusion criteria of the studies resulted in differences in the disease stages of the included patients (study 238: disease stage IIIB/C and IV, study 029: disease stage IIIA and IIIB/C). Thus, study 239 provides no data on stage IIIA disease, and study 029 no data on stage IV disease. For both studies, analyses of the subpopulation of patients with stage IIIB and IIIC disease are used for the indirect comparison for the present benefit assessment.

The therapeutic indication of nivolumab for the present research question is not completely represented by the indirect comparison on the basis of the subpopulation, however. There are only data on patients with lymph node involvement (stage III), but not with distant metastasis (stage IV). All results of the present benefit assessment therefore refer to the subpopulation with stage IIIB and IIIC disease.

Apart from the different disease stages of the patients included in each study, the check of the similarity of the studies 238 and 029 did not show any differences that question the assumption of similarity for the indirect comparison across outcomes. Overall, the studies are therefore considered sufficiently similar for an adjusted indirect comparison using the common comparator ipilimumab for the subpopulation of patients with stage IIIB and IIIC disease.

However, the indirect comparison cannot always be conducted for specific outcomes because, for various reasons, no results are available that can be used for the indirect comparison (overall survival: no sufficiently similar results due to differences in health care standards, health status recorded with the European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]: outcome recorded in only one study, symptoms and health-related quality of life

recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]: different recording strategies, immune-related AEs: no analyses on a suitable operationalization available). The requirement for the certainty of results for carrying out an adjusted indirect comparison is not met for the outcomes of the category of side effects.

Risk of bias

The risk of bias across outcomes was rated as low for the two studies 238 and 029.

The risk of bias of the results was not assessed for outcomes for which no results usable for the indirect comparison are available.

The risk of bias of the results for the outcome "recurrence" was rated as low for both studies.

The risk of bias of the results for the outcomes "serious AEs (SAEs)", "severe AEs" and "further specific AEs" was rated as high. The risk of bias of the results for the outcome "discontinuation due to AEs" was rated as low, but the certainty of results is nonetheless restricted. Thus, the requirement for the certainty of results for carrying out an adjusted indirect comparison was not met for these outcomes of the category of side effects; no indirect comparison was performed in each case.

There was one RCT on each side of the available adjusted indirect comparison. Hence, a check of the homogeneity assumption was not required. As there was no study of direct comparison of nivolumab against placebo, the consistency assumption could not be checked. Therefore, the adjusted indirect comparison had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived based on the data available from the adjusted indirect comparison.

Mortality

Overall survival

There were no usable data for an indirect comparison for the outcome "overall survival". This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting for the outcome "overall survival"; an added benefit is therefore not proven.

Morbidity

Health status (EQ-5D VAS)

No usable data for an indirect comparison were available for the outcome "health status" measured with the EQ-5D VAS. This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting for the outcome "health status"; an added benefit is therefore not proven.

Recurrence

For the present benefit assessment, the proportion of patients with recurrence and, additionally, the time to recurrence were used for the outcome "recurrence".

The adjusted indirect comparison showed a statistically significant difference in favour of nivolumab in comparison with placebo for both operationalizations. This resulted in a hint of an added benefit of nivolumab in comparison with watchful waiting for patients with stage IIIB and IIIC disease. The results of both operationalizations differed in their extent, however. In the present data situation, taking into account the differences in the proportions of patients with recurrence and the time courses, the overall extent of the added benefit is rated as "major".

Symptoms (EORTC QLQ-C30)

No usable data for an indirect comparison were available for the outcome "symptoms" measured with the EORTC QLQ-C30. This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is not proven.

Health-related quality of life

No usable data for an indirect comparison were available for the outcome "health-related quality of life" measured with the EORTC QLQ-C30. This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is not proven.

Side effects

Due to an insufficient certainty of results for conducting an adjusted indirect comparison, no indirect comparison was conducted for the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs". There were no usable analyses on a suitable operationalization for the outcome "immune-related AEs".

Hence, there was overall no hint of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Transferability of the added benefit to patients with stage IV disease

The added benefit in the indirect comparison was derived on the basis of the results in the subpopulation of patients with stage IIIB and IIIC disease investigated in the studies 238 and 029. In the present specific data situation, however, the conclusion on the added benefit can be transferred to patients with stage IV disease. A transfer of the added benefit to patients with stage IIIA disease, however, is not sufficiently supported by data and therefore not possible.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

In the overall consideration, there is a positive effect of nivolumab in comparison with watchful waiting for the outcome "recurrence" with the extent "major". For the outcomes in the categories of mortality, health-related quality of life and side effects, there are no usable data for the indirect comparison. Due to outcome-specific aspects that call into question the fulfilment of the similarity assumption for the indirect comparison and the insufficient certainty of results for the implementation of an adjusted indirect comparison, no hint of an added benefit or of greater or lesser harm is derived for the patient-relevant outcomes of these categories. Adequate balancing of benefit and harm is not possible, in particular because the results on the outcomes of the category of side effects are not usable. In the present specific data situation, however, it is not assumed that the potential harm in these outcomes can completely call into question the major added benefit for the outcome "recurrence". The extent of added benefit is non-quantifiable in the present data situation, however.

The added benefit in the indirect comparison was derived on the basis of the results in the subpopulation of patients with stage IIIB and IIIC disease investigated in the studies 238 and 029. Here, however, the conclusion on the added benefit can be transferred to patients with stage IV disease.

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

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection[b]	▪ Pembrolizumab (only for patients in tumour stage III after complete resection) or ▪ dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection) or ▪ **watchful waiting**	*Stage IIIB/C and IV disease:* hint of non-quantifiable added benefit *Stage IIIA disease:* 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 respective choice of the company is printed in **bold**. b. Study 238 included only patients with an ECOG PS of 0 or 1; the ipilimumab arm of study 029 included one patient with ECOG PS = 2. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of nivolumab as monotherapy in comparison with the ACT in the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

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

Table 4: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT**[a]
Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection	▪ Pembrolizumab (only for patients in tumour stage III after complete resection) or ▪ dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection) or ▪ **watchful waiting**[b]
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. The G-BA did not further specify the ACT "watchful waiting". For information on the definition of the ACT in the present benefit assessment, see Section 2.3.2.1. ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; G-BA: Federal Joint Committee	

From the ACT options presented, the company chose watchful waiting, thus following the G-BA's specification.

In clinical practice, the disease severity of melanoma is assessed based on the AJCC classification. The S3 guideline on diagnosis, treatment and follow-up of melanoma also uses this classification to categorize tumours and structure treatment and follow-up recommendations [3].

The therapeutic indication presented in Table 4 represents disease stages III to IV according to the current 8th edition of the AJCC classification with melanoma stage III or higher being characterized by lymph node involvement and stage IV or higher by distant metastasis [4].

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists (status: 10 February 2021)
- bibliographical literature search on nivolumab (last search on 10 February 2021)
- search in trial registries/trial results databases for studies on nivolumab (last search on 1 February 2021)
- search on the G-BA website for nivolumab (last search on 2 February 2021)
- bibliographical literature search on the ACT (last search on 10 February 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 2 February 2021)
- search on the G-BA website for the ACT (last search on 2 February 2021)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 16 April 2021); for search strategies, see Appendix F of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 19 April 2021); for search strategies, see Appendix F of the full dossier assessment

For the direct comparison of nivolumab with the ACT watchful waiting, the company identified the RCT IMMUNED [5]. The analyses presented by the company for this study are unsuitable for the present benefit assessment, however (for reasons, see the following text section on the company's study pool). The company itself only used the IMMUNED study as support for an adjusted indirect comparison of nivolumab against the ACT watchful waiting based on RCTs. The company identified 2 studies for this indirect comparison.

The check of the completeness of the study pool identified no additional relevant RCT for the direct comparison of nivolumab against the ACT.

Analogous to the previous benefit assessment of nivolumab (dossier assessment A18-53 [6] and addendum A19-01 [7]), no additional relevant studies were identified from the check of the completeness of the study pool for the adjusted indirect comparison presented by the company.

Study pool of the company

For its benefit assessment, the company used an adjusted indirect comparison, which comprised the studies CA209-238 and CA184-029 (hereinafter referred to as "study 238" and "study 029") and which was considered relevant already in the previous benefit assessment of nivolumab [6,7]. In addition, the company used the RCT IMMUNED on the direct comparison of nivolumab and placebo (as an approximation to the ACT watchful waiting) as supporting evidence. According to the company, the adjusted indirect comparison was the primary data source of its benefit assessment. It justified this with the argument that the IMMUNED study

was an ongoing study with results on the outcome "overall survival" still pending, as well as with the argument that the patient collective of the study did not completely cover the therapeutic indication of nivolumab.

The analyses on the IMMUNED study presented by the company are unsuitable for the present benefit assessment. This is justified below.

Study design of the IMMUNED study

The IMMUNED study is an RCT, which started in 2015 and is still ongoing. According to information provided by the company in Module 4 I of the dossier, this is an investigator-initiated trial (IIT), in which the company is involved financially only by providing the experimental interventions. The company stated in Module 4 I of the dossier that it is not involved in any other way in the planning, conduct and analysis of the study. According to information in Zimmer et al [5], the company supported the study as a sponsor by providing third-party funding for study coordination and documentation, monitoring, and data management. For its benefit assessment, the company nevertheless relied exclusively on publicly available information in the form of registry entries [8,9] as well as one publication [5].

The IMMUNED study is a multicentre, randomized, double-blind study with 3 study arms on the comparison of nivolumab, or the combination of nivolumab and ipilimumab, against placebo. The study is only conducted in Germany. A total of 167 adult patients with stage IV melanoma (with distant metastases) were included in the study and assigned in a 1:1:1 ratio to treatment with nivolumab (N = 59), nivolumab in combination with ipilimumab (N = 56) or placebo (N = 52). The patients had to have undergone surgery or radiotherapy for the treatment of their melanoma within 8 weeks before enrolment and with subsequently no evidence of disease (NED). In addition, the patients had to have an ECOG PS of 0 or 1 at baseline.

The primary outcome of the study is recurrence-free survival; secondary outcomes include overall survival and side effect outcomes, among others. To date, analyses on recurrence-free survival and outcomes in the category of side effects from a predefined interim analysis (data cut-off from 2 July 2019) are available from the study. This analysis was planned after 90 events in recurrence-free survival and an observation period of at least 6 months for all patients. The final analysis of recurrence-free survival and the secondary outcomes, including overall survival, is planned after a follow-up period of at least 24 months for all patients (according to information provided by the company in Module 4 I of the dossier, probably in October 2021).

Detailed information on the study design, the interventions used, and the patient characteristics for the nivolumab arm and the placebo arm of the IMMUNED study is provided in Table 32, Table 33 and Table 34 in Appendix E of the full dossier assessment. Patients receiving a combination of nivolumab and ipilimumab are not considered further in the following, as the combination of the 2 drugs is not approved in the present therapeutic indication and is not relevant for a direct comparison of nivolumab with the ACT.

Potential under-treatment of the total population in the control arm of the IMMUNED study

According to the SPC, nivolumab is approved as monotherapy for the treatment of patients with melanoma with involvement of lymph nodes or metastatic disease (AJCC stage III or IV disease) who have undergone complete resection [10]. For the definition of complete resection, the SPC refers to the approval study 238, for which, according to the study protocol, complete surgical resection with negative surgical margins was a prerequisite for study inclusion [11].

According to the study design, the IMMUNED study included patients who had undergone surgery or radiotherapy and subsequently showed no evidence of disease (NED). It is not clear from the study protocol which criteria were used to define NED in the IMMUNED study [5]. Thus, it remains unclear to what extent patients had to fulfil the criteria of a complete surgical resection according to the approval study 238 after surgery and thus correspond to the patient population relevant for the research question of the benefit assessment. In fact, 81% of the patients in the nivolumab arm and 71% in the placebo arm received only surgery as pretreatment. Information on whether these patients had a complete resection is not available. 10% of the patients in both study arms received radiotherapy alone, and 8% of the patients in the nivolumab arm and 19% in the placebo arm received a combination of surgery and radiotherapy (see Table 34 in Appendix E of the full dossier assessment). No information is available on why patients in the latter group received radiotherapy in addition to surgery. Should the reason be that an initial operation did not lead to a complete resection, the patients would not be covered by the research question of the present benefit assessment and would possibly be under-treated by a strategy of watchful waiting in the placebo arm. The same applies to those patients in the placebo arm who were treated exclusively with radiotherapy or who did not have a complete resection after surgery alone. How many patients this actually concerns overall cannot be estimated from the available information.

For patients with unresectable metastatic melanoma, targeted therapy options are approved (for example, nivolumab or the combination of nivolumab and ipilimumab [10]), which are recommended according to the guideline [3]. In this stage of the disease, patients without complete resection in the nivolumab arm, in contrast to those in the placebo arm, thus received one of the recommended available therapy options in the IMMUNED study. The results on the basis of the total population of the study therefore have a potential risk of bias in favour of nivolumab. For this reason, analyses of the IMMUNED study based on a subpopulation corresponding to the research question (patients after complete resection) would be necessary for the present benefit assessment. However, the company presented no such analyses.

In addition, the patients' disease history prior to study inclusion appears unclear based on the information on previous systemic therapies (see Table 34 in Appendix E of the full dossier assessment). For example, the available information does not allow any conclusions to be drawn about which adjuvant systemic therapies were given as part of the treatment of a previous disease and which therapies, if any, were given concomitantly with surgery or radiotherapy directly before study inclusion. However, it is clear from the information that the proportion of

patients with systemic pretreatment in the placebo arm (38%) was about twice as high as in the nivolumab arm.

Summary

On the basis of the available information, it remains unclear which proportion of the patients included in the IMMUNED study received a complete resection before the start of the study, and thus corresponds to the patient population relevant to the research question of the benefit assessment. Some patients with unresectable metastatic melanoma, who are not covered by the research question of the present benefit assessment, were also included in the study. The total number of patients actually concerned remains unclear. In contrast to patients in the placebo arm, patients in the nivolumab arm of the study received nivolumab and thus one of the recommended available therapy options at this stage of the disease. Thus, the results on the basis of the total population of the study have a potential risk of bias in favour of nivolumab. The analyses on the total population of the IMMUNED study presented by the company are therefore unsuitable for the present benefit assessment. Instead, analyses on the subpopulation of patients after complete resection would be necessary.

Analogous to the previous benefit assessment [6,7], the present benefit assessment was conducted on the basis of the adjusted indirect comparison of nivolumab against the ACT presented by the company.

2.3.1 Studies included

The company presented an adjusted indirect comparison using the common comparator ipilimumab for the assessment of the added benefit of nivolumab. The indirect comparison comprises one study on each side of the comparison. According to the company, both ipilimumab and the combination of nivolumab and ipilimumab (nivolumab + ipilimumab) are possible common comparators in the present therapeutic indication. For the ACT side of an indirect comparison using the common comparator nivolumab + ipilimumab, the company identified only the ongoing IMMUNED study, which it had already used as directly comparative supporting evidence for its benefit assessment. For this reason, and consistent with the previous benefit assessment procedure, the company chose ipilimumab as common comparator for its indirect comparison.

The company's justification is comprehensible. Concurring with the company, ipilimumab was used as common comparator for an adjusted indirect comparison. The studies of the indirect comparison listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: nivolumab vs. placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Nivolumab vs. ipilimumab						
CA209-238 CheckMate 238 (238[d])	Yes	Yes	No	No[e]	Yes [12,13]	Yes [6,11,14-16]
Placebo vs. ipilimumab						
CA184-029 (029[d])	No	Yes	No	No[e]	Yes [17,18]	Yes [6,16,19-22]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the indirect comparison concurs with that of the company and with that of the previous benefit assessment of nivolumab [6,7]. Figure 1 shows a schematic representation of the indirect comparison.

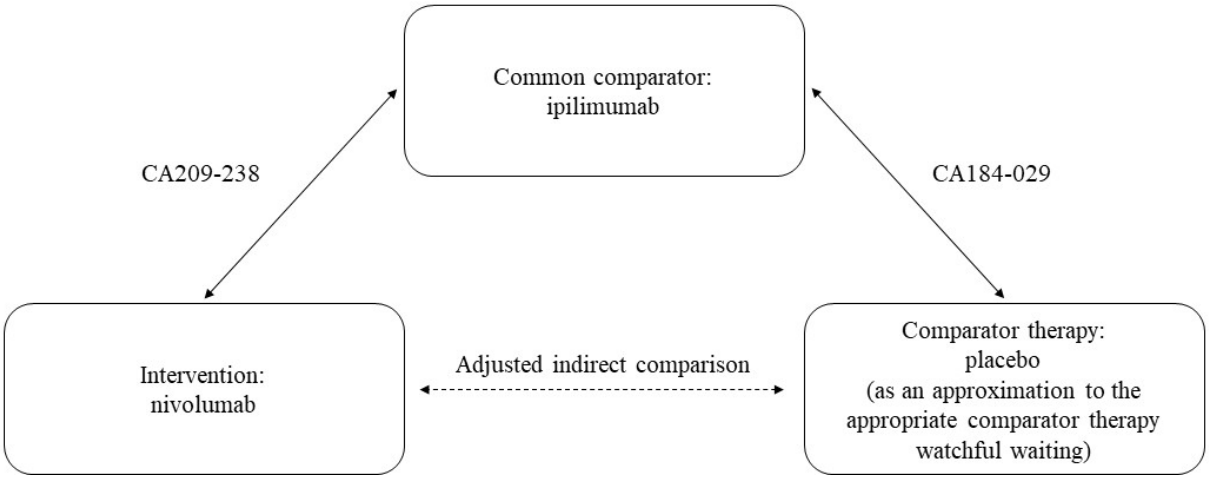

Figure 1: Study pool for the indirect comparison between nivolumab and the ACT watchful waiting

2.3.2 Study characteristics

2.3.2.1 Study design of the studies 238 and 029

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

Table 6: Characteristics of the studies included – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Nivolumab vs. ipilimumab						
238	RCT, double-blind, parallel	Adolescents and adults (≥ 15 years[b]) with completely resected melanoma, stage IIIB/C and IV[c]	Nivolumab (N = 453) Ipilimumab (N = 453) Subpopulation used for the indirect comparison[d]: nivolumab (n = 367) ipilimumab (n = 366)	Screening: 28 days Treatment: 1 year until disease progression, unacceptable toxicity, or treatment discontinuation following the physician's or patient's decision Observation[e]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	130 centres in Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Finland, France, Greece, Hungary, Ireland, Italy, Japan, Netherlands, Norway, Poland, Romania, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, USA 3/2015–1/2020 ▪ First data cut-off[f]: 12 June 2017 ▪ Second data cut-off[g]: 14 December 2017 ▪ Third data cut-off[h] (final analysis): ▪ 29 January 2020	Primary: recurrence-free survival Secondary: overall survival, symptoms, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Placebo vs. ipilimumab						
029	RCT, double-blind, parallel	Adults (≥ 18 years) with completely resected melanoma, stage IIIA/B/C[i]	Ipilimumab (N = 475) placebo (N = 476) Subpopulation used for the indirect comparison[d]: ipilimumab (n = 377) placebo (n = 388)	Screening: up to 6 weeks Treatment: 3 years until disease progression, unacceptable toxicity, or treatment discontinuation following the physician's or patient's decision Observation[e]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	92 centres in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, Switzerland, United Kingdom, USA 6/2008–11/2018 ▪ First data cut-off[j]: 17 December 2013 ▪ Second data cut-off (final analysis)[k]: 13 May 2016	Primary: recurrence-free survival Secondary: overall survival, symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. No adolescents aged < 18 years were included.
c. Classification according to AJCC (7th edition).
d. Because of different inclusion criteria, the total populations of the studies 238 and 029 are not sufficiently similar for conducting an indirect comparison. Study 238 excluded patients with stage IIIA disease, and study 029 excluded patients with stage IV disease. The overlapping subpopulation of patients with stage IIIB/IIIC disease is therefore used for the indirect comparison.
e. Outcome-specific information is provided in Table 8.
f. Predefined interim analysis for recurrence-free survival after ~ 350 events (≥ 18 months observation).
g. Data cut-off for recurrence-free survival/distant-metastasis-free survival (≥ 24 months observation); at the request of the regulatory authority.
h. Final analysis for recurrence-free survival (after ~ 450 events; ≥ 36 months observation) and overall survival (≥ 48 months observation).
i. Classification according to AJCC (6th edition).
j. Predefined primary analysis for recurrence-free survival after 512 events.
k. Final analysis for the outcomes "overall survival" and "distant-metastasis-free survival" follow-up analysis for recurrence-free survival (≥ 53 months observation).

AE: adverse event; AJCC: American Joint Committee on Cancer; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, indirect comparison: nivolumab vs. placebo

Study	Intervention/comparator therapy	Common comparator
Nivolumab vs. ipilimumab		
238	Nivolumab 3 mg/kg BW IV, every 2 weeks + ipilimumab placebo every 3 weeks for 4 doses, from week 24 every 12 weeks	Ipilimumab 10 mg/kg BW IV, every 3 weeks for 4 doses, from week 24 every 12 weeks + nivolumab placebo every 2 weeks
	No dose adjustment[a] allowed for nivolumab and ipilimumab	
	Permitted pretreatment ▪ adjuvant interferon therapy if completed ≥ 6 months prior to randomization ▪ resection of melanoma ≤ 12 weeks prior to randomization ▪ systemic corticosteroids (≥ 10 mg/day) until ≤ 14 days prior to study start ▪ adjuvant radiotherapy after resection of CNS metastases[b] **Non-permitted pretreatment** ▪ systemic or local therapies for the treatment of melanoma ▪ radiotherapy ▪ radiopharmaceuticals **Permitted concomitant treatment** ▪ corticosteroids (administration forms with minimal systemic absorption), only very restricted use of systemic corticosteroids ▪ intravitreal injections of VEGF inhibitors (macular degeneration) **Non-permitted concomitant treatment** ▪ immunosuppressants ▪ immunosuppressant doses of systemic corticosteroids ▪ other systemic antineoplastic treatments	
Placebo vs. ipilimumab		
029	Placebo IV, every 3 weeks for 4 doses, from week 24 every 12 weeks	Ipilimumab 10 mg/kg BW IV, every 3 weeks for 4 doses, from week 24 every 12 weeks
	No dose adjustment[c] allowed for placebo and ipilimumab	
	Permitted pretreatment ▪ resection of involved lymph nodes ≤ 12 weeks prior to randomization ▪ resection of melanoma **Prohibited prior and concomitant treatment** ▪ radiotherapy in the area of lymph node dissection ▪ interferon, oncologic agents, immunosuppressants (except for the treatment of AEs), systemic corticosteroids (except for endocrinopathies that occurred during the study and required a stable dose such as hydrocortisone) ▪ ipilimumab ▪ other investigational products within 4 weeks prior to randomization ▪ vaccines until 4 weeks prior to initiation and after the end of the study medication	

a. Dose discontinuation due to AEs and at the investigator's discretion or dose adjustment if weight difference ≥ 10% from baseline is possible.
b. Does not concern the subpopulation used in the indirect comparison (disease stages IIIB/IIIC).
c. Dose discontinuation due to AEs and at the investigator's discretion is possible.

AE: adverse event; BW: body weight; CNS: central nervous system; IV: intravenous; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Study 238 (nivolumab vs. ipilimumab)

Study 238 is a randomized, active-controlled, double-blind phase 3 study. The study compared nivolumab with ipilimumab. It included patients aged ≥ 15 years with complete surgical resection of AJCC (7th edition) stage IIIB, IIIC or IV melanoma who were considered free of disease and who had an ECOG PS of 0 or 1. According to the inclusion criteria, adolescents aged < 18 years were suitable for study inclusion, but only adults were included in the study.

In the study, 453 patients were randomized in a 1:1 ratio into each study arm. Randomization was stratified according to the factors PD-L1 status and AJCC disease stage.

In the intervention arm, treatment with nivolumab was conducted following a weight-based dosing regimen. Nivolumab was originally approved with the dosing regimen used in this study. This dosing regimen was adjusted after approval and now provides for the administration of nivolumab in a flat dose regimen (240 mg every 2 weeks or 480 mg every 4 weeks) irrespective of body weight [23]. According to the SPC of nivolumab, based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between the dosing regimens [10]. For the comparison examined in the present benefit assessment, it was assumed that the deviation in the dosing regimen of nivolumab had no relevant influence on the observed effects.

In addition to nivolumab, patients in the intervention arm received placebo that matched the treatment regimen of the comparator intervention ipilimumab. Treatment in the comparator arm was with ipilimumab and a placebo for nivolumab (see Table 7). Ipilimumab is not approved in Germany for the present therapeutic indication.

In compliance with the SPC of nivolumab, the treatment duration in both study arms was limited to 1 year. Patients were treated until recurrence or unacceptable persistent toxicity. There were no limitations regarding subsequent therapy after recurrence. Switching to the treatment of the other study arm was not allowed.

The primary outcome of the study was recurrence-free survival. Secondary outcomes were overall survival, symptoms, health-related quality of life, and AEs.

Study 029 (placebo vs. ipilimumab)

Study 029 is a randomized, active-controlled, double-blind phase 3 study. The study compared ipilimumab with placebo. It included adult patients with complete resection of melanoma in AJCC (6th edition) stage IIIA with metastases > 1 mm, IIIB or IIIC without in-transit metastases who were considered free of disease. Patients had to be in good general condition corresponding to ECOG PS 0 or 1.

Randomization in the study was in a 1:1 ratio; 475 patients were randomized to the ipilimumab arm and 476 patients to the placebo arm. Randomization was stratified by the factors of AJCC disease stage and region.

Treatment was until recurrence or unacceptable persistent toxicity. The specified treatment duration in both study arms was 3 years. There were no limitations regarding subsequent therapy after recurrence. Switching to the treatment of the other study arm was not allowed.

The primary outcome of the study was recurrence-free survival. Secondary outcomes were overall survival, distant-metastasis-free survival, symptoms, health-related quality of life, and AEs.

Appropriate comparator therapy

Operationalization of the ACT watchful waiting

Analogous to the previous benefit assessment of nivolumab [6,7], the ACT watchful waiting is operationalized as a follow-up strategy that particularly comprises the diagnosis of recurrence in accordance with the S3 guideline on diagnosis, treatment and follow-up of melanoma [3]. A detailed description of the follow-up strategy recommended according to the guideline version 3.1 [24], which consists of the components physical examination, imaging tests (computed tomography or magnetic resonance imaging), lymph node sonography, and detection of the tumour marker S100B can be found in dossier assessment A18-53 [6]. The current guideline version 3.3, which has been published in the meantime, contains no changes to the recommendations on follow-up care compared with version 3.1.

Implementation of the ACT in study 029

Study 029 used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting. As already discussed in detail in dossier assessment A18-53 [6], the investigations carried out in the study did not fully encompass the recommendations of the guideline, but a close-meshed follow-up strategy targeted at the detection of local, regional and distant recurrences was used. This was still assessed to be a sufficient approximation to the operationalization of watchful waiting described above.

Suitable patient population for the indirect comparison

In Module 4 I of the dossier, the company presented analyses of the total population for each of the studies 238 and 029, which it used for the benefit assessment. Deviating from the company, and analogous to the previous benefit assessment, for both studies, the present benefit assessment uses analyses of the subpopulation of patients with stage IIIB and IIIC disease are used for the indirect comparison (see Section 2.3.3.1 for reasons). All results of the present benefit assessment therefore refer to the subpopulation with stage IIIB and IIIC disease.

2.3.2.2 Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up – RCT, indirect comparison: nivolumab vs. placebo

Study **Outcome category** **Outcome**	**Planned follow-up observation**
Nivolumab vs. ipilimumab	
238	
Mortality	
Overall survival	At most 5 years until death, discontinuation of participation in the study, or end of study
Morbidity	
Recurrence	At most 5 years or until occurrence of local, regional or distant recurrence, new melanoma, death, or end of study
Symptoms (EORTC QLQ-C30)	First follow-up visit: 30 ± 7 days after the last dose of study medication or at study discontinuation[a] Second follow-up visit: 84 ± 7 days after the first follow-up visit
Health-related quality of life	
EORTC QLQ-C30	First follow-up visit: 30 ± 7 days after the last dose of study medication or at study discontinuation[a] Second follow-up visit: 84 ± 7 days after the first follow-up visit
Side effects	
All outcomes in the category of side effects	Follow-up observation period of 100 days after the last dose of study medication
Placebo vs. ipilimumab	
029	
Mortality	
Overall survival	Until death, discontinuation of participation in the study or end of study
Morbidity	
Recurrence	Until occurrence of local, regional or distant recurrence, death, or end of study
Symptoms (EORTC QLQ-C30)	Up to 2 years regardless of course of disease
Health-related quality of life	
EORTC QLQ-C30	Up to 2 years regardless of course of disease
Side effects	
All outcomes in the category of side effects	Follow-up observation period of 70 days[b] after the last dose of study medication

a. ± 7 days if study discontinuation was > 37 days after the last dose.
b. Later toxicities were documented also beyond the follow-up observation period of 70 days. There is information that side effects were recorded > 360 days after the last dose, but not for how long the overall recording of side effects was planned.

EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial

In both studies, the observation periods for the outcomes on symptoms and health-related quality of life, both recorded with the EORTC QLQ-C30, were systematically shortened. To be

able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

For study 238, the observation periods for the outcomes of the category of side effects were also systematically shortened. In study 029, recording of these outcomes was continued after treatment discontinuation or termination also beyond the follow-up period in a post-study observation. However, there is no information available on whether this recording of side effects overall was to be conducted until the end of the study.

2.3.2.3 Data cut-offs

Study 238

Three data cut-offs were performed for study 238:

- The first data cut-off (12 June 2017) was a predefined interim analysis for recurrence-free survival after about 350 events and an observation period of at least 18 months for all patients.
- The second data cut-off (14 December 2017) was conducted post hoc, at the request of the regulatory authority, 6 months after the first data cut-off (≥ 24 months observation period), and comprised only analyses on recurrence-free survival and on distant metastasis-free survival.
- The third data cut-off (29 January 2020) was the final analysis for recurrence-free survival and overall survival after an observation period of at least 48 months for all patients, in accordance with the planned final analysis for overall survival. The final analysis for recurrence-free survival was planned after about 450 events and an observation period of at least 36 months for all patients.

For the previous benefit assessment, the company had presented results for study 238 for the first 2 data cut-offs (on 12 June 2017 and on 14 December 2017), for each of which no analysis of the outcome "overall survival" was planned. In addition, the final analysis on recurrence-free survival with an observation period of at least 36 months was still pending. In accordance with the G-BA's condition of the limitation, the company now presented analyses of all patient-relevant outcomes for the final data cut-off from 29 January 2020 in Module 4 I of the dossier. These analyses were used for the present benefit assessment.

Study 029

Two data cut-offs were performed for study 029:

- The first, a priori planned data cut-off for the primary analysis on recurrence-free survival was performed on 17 December 2013. The median observation period for this data cut-off was 2.7 years.

- The second data cut-off from 13 May 2016 was the final analysis on overall survival and distant metastasis-free survival as well as a follow-up analysis for recurrence-free survival. The planned observation period for this analysis was at least 53 months for all patients.

In the previous benefit assessment, the company had already presented results for study 029 for the 2 data cut-offs conducted. In Module 4 I of the dossier, the company now presented results of the final data cut-off from 13 May 2016. These analyses were used for the present benefit assessment.

Summary

In summary, and in line with the approach of the company, the adjusted indirect comparison between nivolumab and placebo for the present benefit assessment consisted of the results of the final data cut-offs of the 2 studies 238 (data cut-offs from 29 January 2020) and 029 (data cut-off from 13 May 2016) with an observation period of at least 48 or 53 months respectively.

2.3.2.4 Patient characteristics

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

Table 9: Characteristics of the study populations – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Study	238		029	
Characteristic Category	Nivolumab	Ipilimumab	Ipilimumab	Placebo
	N[a] = 367	N[a] = 366	N[a] = 377	N[a] = 388
Age [years], mean (SD)	54.8 (13.4)	53.2 (13.7)	51.5 (13.1)	52.5 (12.6)
< 65, n (%)	265 (72.2)	277 (75.7)	308 (81.7)	309 (79.6)
≥ 65 – < 75, n (%)	87 (23.7)	78 (21.3)	58 (15.4)	71 (18.3)
≥ 75, n (%)	15 (4.1)	11 (3.0)	11 (2.9)	8 (2.1)
Sex [F/M], %	41/59	42/58	37/63	36/64
Family origin, n (%)				
Caucasian	342 (93.2)	350 (95.6)	373 (98.9)	388 (100.0)
Other	25 (6.8)[b]	16 (4.4)	4 (1.1)[b]	0 (0)[b]
Region, n (%)				
Europe	209 (56.9)	199 (54.4)	266 (70.6)	280 (72.2)
USA + Canada	110 (30.0)	116 (31.7)	95 (25.2)	95 (24.5)
Rest of the world	48 (13.1)	51 (13.9)	16 (4.2)	13 (3.4)
Disease stage according to AJCC at baseline, n (%)				
IIIA	0 (0)	0 (0)	0 (0)	0 (0)
IIIB	163 (44.4)	148 (40.4)	213 (56.5)	207 (53.4)
IIIC	204 (55.6)	218 (59.6)	164 (43.5)[b]	181 (46.6)[b]
IV	0 (0)	0 (0)	0 (0)	0 (0)
In-transit metastases, n (%)[c]	ND	ND	ND	ND
Ulceration of primary tumour, n (%)[c]	ND	ND	ND	ND
PD-L1 status, n (%)				
Positive (≥ 1% tumour cell membrane staining)	234 (63.8)	248 (67.8)	ND	ND
Negative (< 1% tumour cell membrane staining)	132 (36.0)	118 (32.2)	ND	ND
Non-quantifiable/unknown	1 (0.3)	0 (0)	ND	ND
Time since tumour resection [weeks], mean (SD)	8.9 (2.6)	9.2 (3.0)	9.3 (2.2)	9.3 (2.3)
ECOG PS				
0	331 (90.2)	329 (89.9)	354 (93.9)	366 (94.3)
1	36 (9.8)	37 (10.1)	22 (5.8)	22 (5.7)
2	0 (0)	0 (0)	1 (0.3)	0
Treatment discontinuation, n (%)[c]	ND	ND	ND	ND
Study discontinuation, n (%)[c]	ND	ND	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. For the previous benefit assessment, the company had presented only information for the total population of the study [6]. The company did not provide any information on the characteristics of the subpopulation with stage IIIB/C disease in Module 4 I of the dossier.

Table 9: Characteristics of the study populations – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Study Characteristic Category	238		029	
	Nivolumab	Ipilimumab	Ipilimumab	Placebo
	N[a] = 367	N[a] = 366	N[a] = 377	N[a] = 388

AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

In Module 4 I of the dossier, the company presented only information on the characteristics of the total population of both studies. Analogous to the previous benefit assessment, however, the present benefit assessment uses the subpopulation of patients with stage IIIB and IIIC disease from both studies for the indirect comparison (see Section 2.3.3.1). Table 9 therefore shows information on the characteristics of this subpopulation, which the company had presented in the commenting procedure of the previous benefit assessment (see addendum A19-01 [7]).

The characteristics of the patients are sufficiently balanced both between the study arms and between the studies 238 and 029. In both studies, most patients were male, had a mean age of about 53 years and were of Caucasian origin. The majority of the patients had an ECOG PS of 0 at baseline, and the time from resection to randomization (about 9 weeks) was comparable in all study arms.

The distribution of patients between AJCC stages IIIB and IIIC shows differences between the studies with a slightly higher proportion with stage IIIC disease in study 238 (about 57%) than in study 029 (about 45%).

Information on the proportion of patients with treatment or study discontinuation for the final data cut-offs of the studies is only available for the total population of the 2 studies, whereby information on study discontinuation is only available for the total population of study 238.

In study 238, 39% of the patients in the total population in the nivolumab arm and 73% of the patients in the ipilimumab arm had discontinued treatment at the time of the final data cut-off. Treatment discontinuations in the nivolumab arm were mainly due to recurrence, and in the ipilimumab arm due to toxicity or AEs. At the final data cut-off, 30% of the patients in the nivolumab arm and 34% in the ipilimumab arm had discontinued the study; the majority of these study discontinuations was due to death.

In study 029, 70% of the patients in the placebo arm and 87% of the total population in the ipilimumab arm had discontinued treatment at the time of the final data cut-off. Treatment discontinuations in the placebo arm were mainly due to recurrence, and in the ipilimumab arm due to AEs.

Overall, the information available for the present benefit assessment, analogous to the previous benefit assessment, does not call into question the suitability of the subpopulations of patients with stage IIIB and IIIC disease from the 2 studies for the indirect comparison (see also Section 2.3.3).

2.3.2.5 Treatment duration and observation period

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

Table 10: Information on the course of the study – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Study **Duration of the study phase** **Outcome category**	**Intervention**	**Common comparator**
Study with nivolumab vs. ipilimumab		
238	**Nivolumab** N = 367	**Ipilimumab** N = 367
Data cut-off 29 January 2020		
Treatment duration [months]		
Median [min; max]	11.50 [0; 11.8]	2.73 [0; 12.2]
Mean (SD)	8.97 (ND)	5.25 (ND)
Observation period[a] [months]		
Overall survival		
Median [Q1; Q3]	51.09 [38.77; 52.70]	50.89 [37.95; 52.27]
Mean (SD)	43.94 (14.44)	43.03 (15.36)
Recurrence-free survival		
Median [Q1; Q3]	49.54 [9.53; 51.98]	24.02 [5.59; 51.32]
Mean (SD)	33.79 (21.77)	27.82 (21.63)
Symptoms (EORTC QLQ-C30)	No usable data available	
Health-related quality of life (EORTC QLQ-C30)	No usable data available	
Side effects		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Study with placebo vs. ipilimumab		
029	**Placebo** N = 377	**Ipilimumab** N = 373
Data cut-off 13 May 2016		
Treatment duration [months]		
Median [min; max]	8.61 [0; 43.8]	2.10 [0; 39.1]
Mean (SD)	15.42 (ND)	9.31 (ND)
Observation period[a] [months]		
Overall survival		
Median [Q1; Q3]	52.63 [19.32; 64.76]	55.52 [24.25; 65.58]
Mean (SD)	43.90 (24.76)	46.65 (23.39)
Recurrence-free survival		
Median [Q1; Q3]	11.96 [3.88; 55.36]	20.83 [5.75; 60.88]
Mean (SD)	26.07 (26.67)	31.66 (27.31)
Symptoms (EORTC QLQ-C30)	No usable data available	
Health-related quality of life (EORTC QLQ-C30)	No usable data available	
Side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Study Duration of the study phase Outcome category	Intervention	Common comparator
a. The company did not provide any information on the methods used to determine observation periods.		
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation		

There were differences in treatment duration in the subpopulation of patients with stage IIIB and IIIC disease both between the treatment arms of the studies 238 and 029 and between the studies. In both studies, treatment of the patients was substantially shorter in the ipilimumab arm than in the nivolumab or placebo arm. Furthermore, there was a clear difference in the mean treatment duration between the ipilimumab arms of the 2 studies. No clear difference was shown in the median treatment duration, however. Premature treatment discontinuations in the ipilimumab arms of both studies were mainly due to toxicity or AEs.

No relevant differences were shown in the observation periods for the outcome "overall survival". There was a marked difference in observation periods for recurrence-free survival. In study 238, the median observation period was twice as long in the nivolumab arm as in the ipilimumab arm. In study 029, the median observation period of the outcome was twice as long in the ipilimumab arm as in the placebo arm. No information on observation periods was available for the outcomes of the category of side effects.

See Sections 2.3.3 and 2.4.2 for the outcome-specific effects on similarity and the risk of bias of the results caused by the differences described above for the present benefit assessment.

2.3.3 Similarity of the studies for the indirect comparison

From the study characteristics described in the previous Section 2.3.2, several aspects concerning the similarity of studies arise. These aspects across outcomes and these outcome-specific aspects are discussed below. Some of the aspects had already been discussed in detail in the previous benefit assessment of nivolumab (dossier assessment A18-53 [6] and addendum A19-01 [7]); to which reference is made at the respective points in each case.

2.3.3.1 Similarity of the study populations

Suitable patient population for the indirect comparison

In Module 4 I of the dossier, the company presented analyses of the total population for each of the studies 238 and 029, which it used for the benefit assessment. The inclusion criteria of the studies resulted in differences in the disease stages of the included patients (study 238: disease stage IIIB/C and IV, study 029: disease stage IIIA and IIIB/C), however. Thus, study 239 provides no data on stage IIIA disease, and study 029 no data on stage IV disease. In

Module 4 I of the dossier, the company presented additional analyses for both studies, which included only patients with stage IIIB and IIIC disease (i.e. overlapping disease stages).

Deviating from the company, and analogous to the previous benefit assessment, for both studies, the present benefit assessment uses analyses of the subpopulation of patients with stage IIIB and IIIC disease for the indirect comparison (see Section 2.3.2.2 of dossier assessment A18-53 [6] for detailed reasons).

The therapeutic indication of nivolumab for the present research question is not completely represented by the indirect comparison on the basis of the subpopulation, however. There are only data on patients with lymph node involvement (stage III), but not with distant metastasis (stage IV). All results of the present benefit assessment therefore refer to the subpopulation with stage IIIB and IIIC disease.

Similarity of the subpopulations with stage IIIB and IIIC disease

As described in dossier assessment A18-53, there are differences also for the subpopulations of patients with stage IIIB and IIIC disease in the studies of the indirect comparison.

In accordance with the exclusion criteria, study 029 included no patients with stage IIIC disease with in-transit metastases before resection. Study 238, in contrast, did not have such a restriction, and about 36% of the patients in the total population had in-transit metastases before resection. The proportion of patients with stage IIIC disease was also slightly higher in study 238 than in study 029. Therefore, it cannot be excluded that also the subpopulation in study 238 included patients with slightly poorer prognosis than study 029. The results for the common comparator ipilimumab in the course of the study do not confirm this, however (see Table 11). Both studies showed comparable results on recurrence-free survival in the course of the studies. For overall survival, on the other hand, the 2 studies showed different rates over the course of the studies, and it is unclear to what extent these were due to different health care standards (see Section 2.3.3.2. for explanation).

Overall, the differences between the patient populations are not considered serious enough to question the fulfilment of the similarity assumption. The subpopulations are therefore considered to be sufficiently similar to conduct an adjusted indirect comparison.

Table 11: Survival rates in the common comparator ipilimumab – RCT, indirect comparison: nivolumab vs. placebo

Outcome Documentation time	Ipilimumab			
	238[a]		029[b]	
	N	Survival rates in % [95% CI][c]	N	Survival rates in % [95% CI][c]
Overall survival				
12 months	367	94.7 [91.8; 96.6]	377	92.1 [88.8; 94.4]
24 months	367	87.6 [83.7; 90.6]	377	79.9 [75.4; 83.7]
36 months	367	82.1 [77.6; 85.7]	377	70.1 [65.1; 74.6]
48 months	367	77.0 [72.2; 81.1]	377	63.4 [58.2; 68.2]
Recurrence-free survival				
12 months	367	61.1 [55.8; 65.9]	377	62.0 [56.8; 66.8]
24 months	367	51.9 [46.5; 56.9]	377	46.7 [41.4; 51.8]
36 months	367	45.6 [40.3; 50.7]	377	40.2 [35.0; 45.4]
48 months	367	42.4 [37.2; 47.6]	377	38.3 [33.2; 43.4]

a. Data cut-off from 29 January 2020.
b. Data cut-off from 13 May 2016.
c. Survival rates based on Kaplan-Meier estimators.

CI: confidence interval; N: number of analysed patients; RCT: randomized controlled trial

2.3.3.2 Periods of study conduct

Studies 238 and 029 were conducted in markedly different time periods (see Table 6). As already discussed in detail in dossier assessment A18-53, this resulted in differences in the available subsequent therapies after recurrence for both studies (see Section 2.3.2.2 in dossier assessment A18-53 for details). For example, at the time most recurrences occurred in study 029, in contrast to study 238, the majority of currently available drugs for the treatment of advanced, unresectable melanoma from the drug classes of mitogen-activated extracellular signal-regulated kinase (MEK), serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B [BRAF]) and immune checkpoint inhibitors, as well as corresponding drug combinations were not approved and were not available to a relevant extent to the patients as subsequent therapy after recurrence.

The available data (see Table 31 in Appendix D of the full dossier assessment on documented subsequent therapies in the total population of both studies) on the subsequent therapies administered show that particularly immunotherapies were administered substantially more frequently in the common comparator arm of study 238 (i.e. to 34% of the patients in the total population). In study 029, in contrast, only about 5% of the patients in the common comparator received ipilimumab or an anti-programmed cell death 1 (PD-1) drug as immunotherapy. It remains unclear to what extent the data from the 2 studies are directly comparable. However, the available data suggest that current treatment options were not available to a relevant extent to patients in the placebo arm of study 029, in contrast to those in the nivolumab arm of study

238. As described in dossier assessment A18-53, these differences particularly concern the comparability of the results on overall survival.

In Module 4 I of the dossier, the company mentioned the differences in the availability of subsequent therapies in the studies of the indirect comparison. It argued that the calculated indirect comparison according to Bucher et al. was based on the comparison of relative effect measures within the individual studies, so that study effects such as the differences in the possible subsequent therapies did not lead to a relevant bias. Furthermore, it stated that in order to check the robustness of the results on overall survival, it had carried out an analysis that adjusted survival after recurrence for patients with subsequent therapies in study 029 to that of study 238, simulating the effect of the availability of modern subsequent therapies. From the company's point of view, these analyses showed consistent significant results in favour of nivolumab.

The company's reasoning is not appropriate. As described in dossier assessment A18-53, the subsequent therapies used in the advanced, unresectable stage can have an important influence on the results on overall survival, which questions the fulfilment of the similarity assumption for conducting the adjusted indirect comparison.

The results on overall survival for the common comparator ipilimumab in the course of the study show clearly higher survival rates for study 238 than for study 029 (see Table 11). After a documentation time of 48 months, the survival rate in study 238, for example, which was conducted at the later time period, was 77%, which is substantially higher than that in study 029 with a rate of about 63%. This notable difference suggests that the health care context described above in the studies 238 and 029 was not sufficiently comparable, which has an effect on the results for the outcome "overall survival".

The analyses conducted by the company to check the robustness of the results on overall survival are unsuitable for the present benefit assessment. In Module 4 I of the dossier, the company provided neither information on the methods nor the results of these analyses, but cited only a poster contribution [25]. This poster contribution contained only insufficient information on the methods used by the company in the adjustment of the survival rates. Furthermore, the analyses referred to the total populations of both studies. However, the subpopulation of patients with stage IIIB and IIIC disease is used for the indirect comparison for the present benefit assessment.

In contrast to the company, the results for overall survival from the studies for the present benefit assessment are not considered to be sufficiently similar for an indirect comparison due to the differences in health care standard between studies 238 and 029. The results on overall survival from the 2 studies are therefore not comparable in terms of content and cannot be used for an indirect comparison.

2.3.3.3 Similarity of the common comparator

As already described in dossier assessment A18-53, there are differences between the designs of studies 238 and 029 with regard to the planned treatment duration for the common comparator ipilimumab (maximum of 1 year compared with a maximum of 3 years, see Table 6. Although there was no relevant difference in the median treatment duration between the study arms of the common comparator ipilimumab of studies 238 and 029, there was a clear difference in the mean treatment duration. The mean treatment duration of the patients with ipilimumab was about twice as long in study 029 as in study 238 (see Table 10).

However, it is not evident that the different treatment durations had an important effect on the results in the ipilimumab arm and calls into question the comparability of the common comparator. For example, the rates of recurrence-free survival in the common comparator arm were consistently comparable at several time points during the course of the study (see Table 11).

2.3.3.4 Similarity for the outcome "recurrence"

Operationalization of the outcome "recurrence"

As already described in detail in dossier assessment A18-53, the operationalizations of the outcome "recurrence" are comparable between the studies 238 and 029 except for the following aspects: In both studies, the outcome included local, regional and distant recurrence or metastasis and death from any cause. In study 238, however, new primary melanoma was rated as recurrence in addition to the components mentioned above. In addition, recurrence events were censored in study 238 if subsequent cancer therapy was administered before a recurrence was documented. Study 029 did not have such a censoring rule.

In Module 4 I of the dossier, the company now presented analyses based on the operationalization and the censoring rules of study 029. This approach is appropriate. The analyses presented by the company are considered sufficiently similar for carrying out an adjusted indirect comparison.

Examination intervals for the detection of recurrence

The examinations for the detection of recurrences (physical examinations and cross-sectional imaging) were performed in both studies according to defined schemes and are considered sufficiently similar for the present benefit assessment to conduct an adjusted indirect comparison. Although the time intervals at which the examinations were performed differed to some extent between the 2 studies, the differences only existed for individual study parts and not over the entire period of study conduct. The imaging diagnostics (computed tomography, magnetic resonance imaging) were initially performed every 12 weeks in both studies. In study 238, biannual examinations were carried out already after 2 years, in study 029 only after 3 years. The physical examination was performed every 1 to 2 weeks over a period of 1 year in study 238. In study 029, patients were examined for a total of 5 years: initially every 3 weeks, after 12 weeks and up to 3 years every 12 weeks, and then every 24 weeks. In the present data

situation, it is not assumed that these differences led to systematic earlier detection of recurrences in one of the 2 studies, for example. The courses of the Kaplan-Meier curves for recurrence-free survival from the 2 individual studies (see Figure 5 and Figure 6 in Appendix A.2 of the full dossier assessment) do not suggest that the examination intervals had an important influence on the results for recurrence-free survival in the studies. The influence of this temporal component on the event time analyses for recurrence-free survival is therefore not considered to be so large as to call into question the fulfilment of the similarity assumption for conducting an adjusted indirect comparison for recurrence-free survival.

Observation period

The final data cut-offs of the 2 studies essentially refer to a sufficiently comparable minimum observation period of about 48 months in study 238 and about 53 months in study 029. However, the median observation periods for recurrence-free survival differ substantially between the 2 study arms within each of the studies 238 and 029 (see Table 10). In study 238, the median observation period was substantially shorter in the ipilimumab arm than in the nivolumab arm, while in study 029, the median observation time was substantially shorter in the placebo arm than in the ipilimumab arm.

Treatment discontinuations in the ipilimumab arms of both studies were mainly due to toxicity or AEs. However, recurrences were also observed in both studies beyond treatment discontinuation due to toxicity or AEs. Treatment discontinuations in the placebo arm of study 029 were mainly due to recurrences. Similar differences as for the median observation periods were also seen in the median time to event for recurrence-free survival (see Table 16). In the present data situation, it is therefore assumed that the differences in the observation periods are primarily due to the occurrence of recurrences. Furthermore, the median observation period in the common comparator ipilimumab is of a comparable magnitude in both studies.

Overall, the differences in the observation periods for recurrence-free survival do not call into question the fulfilment of the similarity assumption for conducting an adjusted indirect comparison.

2.3.3.5 Recording strategies for outcomes on symptoms and health-related quality of life

As already described in detail in dossier assessment A18-53, there were clear differences between the studies 238 and 029 in the recording strategies for patient-reported outcomes recorded with the EORTC QLQ-C30 instrument (see also Table 8). Consequently, the results for the corresponding outcomes on symptoms and health-related quality of life are not comparable in terms of content and cannot be used for an indirect comparison. The company presented the results of the individual studies in Module 4 I of the dossier, but, with reference to the previous benefit assessment, also did not calculate an indirect comparison.

2.3.3.6 Operationalization of immune-related AEs

Immune-related AEs were recorded in both studies 238 and 029, but, as described in the previous benefit assessment, this was done based on different operationalizations: In study 238, immune-related AEs were recorded based on the administration of immunomodulatory drugs, whereas in study 029, the recording of immune-related AEs was not linked to the administration of such drugs. It is therefore assumed that a retrospective adjustment of the operationalizations of immune-related AEs from the 2 studies is not possible for the indirect comparison.

In the appendix to Module 4 I in the dossier, the company presented analyses of immune-related AEs, which, analogous to its approach in the previous benefit assessment procedure, it classified into different categories (including endocrine AEs, gastrointestinal AEs, hepatic AEs, skin AEs) in accordance with study 238. It still did not provide any information on the operationalization of immune-related AEs in general or on the categories it presented.

As already discussed in detail in dossier assessment A18-53 and addendum A19-01, it remains unclear which events were included in these categories and whether the operationalizations are sufficiently similar for the indirect comparison. The analyses presented by the company are therefore not usable for the present benefit assessment.

2.3.3.7 Summary on the comparability of the studies

In the overall picture, there are a number of differences between the studies 238 and 029. These have outcome-specific effects (see Section 2.4.1), but do not lead to a fundamental questioning of the similarity of the studies for an adjusted indirect comparison.

2.3.4 Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, indirect comparison: nivolumab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Nivolumab vs. ipilimumab							
238	Yes	Yes	Yes	Yes	Yes	Yes	Low
Placebo vs. ipilimumab							
029	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

Transferability of the study results to the German health care context

From the point of view of the company, the results of the individual studies 238 and 029 and the resulting indirect comparison are transferable to the German health care context. It justified this assessment with the fact that 10 centres in Germany were involved in study 029, and that study 238 was sufficiently designed for transferability of the study results to Germany due to the participation of centres in France, the Netherlands, Austria or Switzerland, for example. In addition, it stated that 50% and 60% of the study participants could be assigned to the Western European region.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - health status (EQ-5D VAS)
  - recurrence
  - symptoms, recorded with the EORTC QLQ-C30
- Health-related quality of life
  - EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in Module 4 I of the dossier.

Table 13 shows for which outcomes in the included studies data are available (yes/no) and whether an indirect comparison is possible based on the available data (yes/no).

Table 13: Matrix of outcomes – RCT, indirect comparison: nivolumab vs. placebo

Study	Outcomes									
	Overall survival	Health status (EQ-5D VAS)	Recurrence[a]	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Immune-related AEs[b]	Further specific AEs[b]
Nivolumab vs. ipilimumab										
238	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes
Placebo vs. ipilimumab										
029	Yes	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes
Indirect comparison possible	No[f]	No	Yes	No[f]	No[f]	No[g]	No[g]	No[g]	No	No[g]

a. Presented based on the recurrence rate and recurrence-free survival, includes the events of local recurrence, regional recurrence, distant metastasis and death from any cause. Study 029 additionally lists separate data for the event of in-transit metastases.
b. For outcomes in the category of side effects, the company presented analyses for both studies without recording progression of the underlying disease, which relate in each case to a period from the start of treatment to 100 days after the end of treatment.
c. Operationalized as CTCAE grade ≥ 3.
d. Outcome not recorded.
e. There are no analyses on a suitable operationalization (see Section 2.3.3.6).
f. There are no results suitable for the indirect comparison; see running text for reasons.
g. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section 2.4.2).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No data usable for the indirect comparison are available for the following outcomes:

- Overall survival: Due to differences in health care standard between the studies 238 and 029, the results for overall survival are not considered sufficiently similar for an indirect comparison (see Section 2.3.3.2). The results on overall survival from the 2 studies are therefore not comparable in terms of content and cannot be used for an indirect comparison.

- Health status (EQ-5D VAS): An indirect comparison is not possible because the outcome was not recorded in study 029.
- Symptoms and health-related quality of life (each recorded with the EORTC QLQ-C30): Due to different recording strategies for patient-reported outcomes measured with the EORTC QLQ-C30 in studies 238 and 029, the results for the outcomes of symptoms and health-related quality of life are not comparable in terms of content and cannot be used for an indirect comparison (see Section 2.3.3.5).
- SAEs, severe AEs, discontinuation due to AEs: The results for the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs" are not usable for an indirect comparison, as the requirement for the certainty of results for conducting an adjusted indirect comparison is not met in each case (see Section 2.4.2).
- Immune-related AEs: For the outcome "immune-related AEs", it remains unclear on the basis of the information provided by the company which events were included in the outcome and whether there is sufficient similarity of the operationalizations for the indirect comparison (see Section 2.3.3.6). The analyses presented by the company are therefore not usable for the present benefit assessment. Regardless of the adequate operationalization, the results for the outcome "immune-related AEs" would not be usable for an indirect comparison, as the requirement for the certainty of results for conducting an adjusted indirect comparison is not met (see Section 2.4.2).
- Further specific AEs: Since the requirement for the certainty of results for conducting an adjusted indirect comparison is not met (see Section 2.4.2), no choice of further specific AEs was made.

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: nivolumab vs. placebo

Study	Outcomes										
	Study level	Overall survival	Health status (EQ-5D VAS)	Recurrence[a]	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related AEs	Further specific AEs
Nivolumab vs. ipilimumab											
238	L	–[c]	–[c]	L	–[c]	–[c]	H[d]	H[d]	L[e]	–[f]	H[d]
Placebo vs. ipilimumab											
029	L	–[c]	–[c]	L	–[c]	–[c]	H[d]	H[d]	L[e]	–[f]	H[d]

a. Presented based on the recurrence rate and recurrence-free survival, includes the events of local recurrence, regional recurrence, distant metastasis and death from any cause. Study 029 additionally lists separate data for the event of in-transit metastases.
b. Operationalized as CTCAE grade ≥ 3.
c. There are no results usable for the indirect comparison (see Section 2.4.1).
d. Large proportion of incomplete observations for potentially informative reasons.
e. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be limited (see running text for reasons).
f. There are no analyses on a suitable operationalization (see Section 2.3.3.6).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No indirect comparison can be calculated for outcomes that are not assessed to be sufficiently similar for an indirect comparison or for which no usable data are available (see Section 2.4.1). Hence, the risk of bias was not assessed for the results of these outcomes.

The risk of bias of the results for the outcome "recurrence" was rated as low for both studies. This concurs with the assessment of the company in that the company assumed a low risk of bias for recurrence-free survival.

The results of all further patient-relevant outcomes had a high risk of bias or a low certainty of results despite low risk of bias.

Due to incomplete observation for potentially informative reasons in the presence of clearly different median treatment durations between the study arms in both studies, the risk of bias was rated as high for the results of the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3) as well as of other specific AEs. Regardless of the question of adequate operationalization, this assessment would equally apply to the outcome "immune-related AEs". This concurs with the

assessment of the company in that the company assumed a high risk of bias also for SAEs and severe AEs. The company presented no assessment of the risk of bias of the results for further specific AEs and immune-related AEs.

The risk of bias of the results on the outcome "discontinuation due to AEs" was rated as low. The certainty of results was limited despite low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome "discontinuation due to AEs" to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns. This assessment deviates from that of the company, which assumed a high risk of bias for the outcome "discontinuation due to AEs".

Impact of the risk of bias on the indirect comparison

The risk of bias of the results for the outcomes "SAEs", "severe AEs" and "specific AEs" was high in both studies. The certainty of results for the outcome "discontinuation due to AEs" was limited despite a low risk of bias. Thus, the requirement for the certainty of results for carrying out an adjusted indirect comparison was not met for these outcomes; no indirect comparison was performed in each case.

2.4.3 Results

Table 15 and Table 16 summarize the results on the comparison of nivolumab with placebo in patients with melanoma with stage IIIB and IIIC disease who have undergone complete resection. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves on the presented event time analyses can be found in Appendix A of the full dossier assessment. The results on common AEs, SAEs, severe AEs as well as discontinuations due to AEs for the 2 individual studies 238 and 029 can be found in Appendix B of the full dossier assessment.

Table 15: Results (overall survival, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Outcome category Outcome Comparison Study	Nivolumab or placebo N	Nivolumab or placebo Median time to event in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
Nivolumab vs. ipilimumab					
238 (data cut-off 29 January 2020)	368	NA 85 (23.1)	367	NA 89 (24.3)	0.93 [0.69; 1.25]; 0.634
Placebo vs. ipilimumab					
029 (data cut-off 13 May 2016)	378[b]	59.14 [48.39; NA] 189 (50.0)	377	NA [79.41; NA] 144 (38.2)	1.39 [1.12; 1.72]; 0.003
Indirect comparison using common comparators[c]:					
Nivolumab vs. placebo					-[d]
Morbidity					
Health status (EQ-5D VAS)	No usable data[d]				
Symptoms (EORTC QLQ-C30)	No usable data[d]				
Health-related quality of life					
EORTC QLQ-C30	No usable data[d]				
Side effects					
AEs[e] (supplementary information)					
Nivolumab vs. ipilimumab					
238 (data cut-off 29 January 2020)	367	0.49 [0.43; 0.56] 360 (98.1)	367	0.33 [0.26; 0.39] 362 (98.6)	-
Placebo vs. ipilimumab					
029 (data cut-off 13 May 2016)	377[b]	0.82 [0.72; 1.05] 334 (88.6)	373	0.26 [0.26; 0.36] 366 (98.1)	-
SAEs[e]					
Nivolumab vs. ipilimumab					
238 (data cut-off 29 January 2020)	367	NA 75 (20.4)	367	NA [6.44; NA] 172 (46.9)	0.31 [0.23; 0.40]; < 0.001
Placebo vs. ipilimumab					
029 (data cut-off 13 May 2016)	377[b]	NA 80 (21.2)	373	9.69 [4.21; 21.22] 200 (53.6)	0.28 [0.22; 0.36][f]; < 0.001
Indirect comparison using common comparators[c]:					
Nivolumab vs. placebo					-[g]

Table 15: Results (overall survival, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Outcome category Outcome Comparison Study	Nivolumab or placebo N	Nivolumab or placebo Median time to event in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value[a]
Severe AEs[e, h]					
Nivolumab vs. ipilimumab					
238 (data cut-off 29 January 2020)	367	NA 111 (30.2)	367	3.25 [2.76; 4.80] 228 (62.1)	0.30 [0.24; 0.38]; < 0.001
Placebo vs. ipilimumab					
029 (data cut-off 13 May 2016)	377[b]	NA [38.60; NA] 96 (25.5)	373	8.08 [3.29; 14.52] 204 (54.7)	0.33 [0.26; 0.42][f]; < 0.001
Indirect comparison using common comparators[c]:					
Nivolumab vs. placebo					-[g]
Discontinuation due to AEs[e]					
Nivolumab vs. ipilimumab					
238 (data cut-off 29 January 2020)	367	NA 43 (11.7)	367	NA [7.85; NA] 173 (47.1)	0.18 [0.13; 0.25]; < 0.001
Placebo vs. ipilimumab					
029 (data cut-off 13 May 2016)	377[b]	NA 22 (5.8)	373	17.97 [8.31; 28.78] 184 (49.3)	0.09 [0.05; 0.13][f]; < 0.001
Indirect comparison using common comparators[c]:					
Nivolumab vs. placebo					-[g]
Immune-related AEs[e]	No usable data[i]				

a. Unstratified Cox model; unstratified log-rank test.
b. It remains unclear why a small proportion of the randomized patients (n = 11, see Table 6) are not included in the analyses, in contrast to the analyses of study 029 for the same data cut-off presented by the company for the previous benefit assessment [7].
c. Indirect comparison according to Bucher [26].
d. There are no results usable for the indirect comparison (see Section 2.4.1).
e. For outcomes in the category of side effects, the company presented analyses for both studies without recording progression of the underlying disease, which relate in each case to a period from the start of treatment to 100 days after the end of treatment.
f. Institute's calculation; inverse direction of effect (company presented comparison of ipilimumab vs. placebo).
g. No indirect comparison is performed due to the insufficient certainty of results (see Section 2.4.2).
h. Operationalized as CTCAE grade ≥ 3.
i. There are no analyses on a suitable operationalization (see Section 2.3.3.6).

AE: adverse event; 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 Questionnaire-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Table 16: Results (morbidity) – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Outcome category Outcome Comparison Study	Nivolumab or placebo N	Nivolumab or placebo Patients with event n (%)	Ipilimumab N	Ipilimumab Patients with event n (%)	Group difference RR [95% CI]; p-value
Morbidity					
Recurrence					
Nivolumab vs. ipilimumab					
238 (data cut-off 29 January 2020)					
Recurrence rate[a]	368	166 (45.1)	367	205 (55.9)	0.81 [0.70; 0.93]; ND
Local recurrence	368	32 (8.7)	367	42 (11.4)	-
Regional recurrence	368	33 (9.0)	367	39 (10.6)	-
Distant metastasis	368	97 (26.4)	367	111 (30.2)	-
Death	368	3 (0.8)	367	11 (3.0)	-
Placebo vs. ipilimumab					
029 (data cut-off 13 May 2016)					
Recurrence rate[a]	378[b]	274 (72.5)	377	227 (60.2)	1.20 [1.09; 1.33][c]; ND
Local recurrence	378[b]	10 (2.6)	377	13 (3.4)	-
In-transit metastases	378[b]	28 (7.4)	377	23 (6.1)	-
Regional recurrence	378[b]	57 (15.1)	377	39 (10.3)	-
Distant metastasis	378[b]	170 (45.0)	377	136 (36.1)	-
Death	378[b]	9 (2.4)	377	16 (4.2)	-
Indirect comparison using common comparators[d]:					
Nivolumab vs. placebo					0.67 [0.56; 0.80]; < 0.001

Table 16: Results (morbidity) – RCT, indirect comparison: nivolumab vs. placebo (multipage table)

Outcome category Outcome Comparison Study	Nivolumab or placebo N	Patients with event n (%)	Ipilimumab N	Patients with event n (%)	Group difference RR [95% CI]; p-value
Morbidity					
Recurrence					
Nivolumab vs. ipilimumab 238 (data cut-off 29 January 2020)					
Recurrence-free survival[e]	368	Median time to event: 52.37 [43.96; NA]	367	Median time to event: 26.87 [17.08; 38.01]	HR: 0.71 [0.58; 0.87]; < 0.001[f]
Placebo vs. ipilimumab 029 (data cut-off 13 May 2016)					
Recurrence-free survival[e]	378[b]	Median time to event: 11.63 [10.32; 16.20]	377	Median time to event: 21.19 [16.46; 28.12]	HR: 1.33 [1.12; 1.59][c]; 0.001[f]
Indirect comparison using common comparators[g]: **Nivolumab vs. placebo**					HR: 0.53 [0.41; 0.70]; < 0.001

a. Proportion of patients, individual components are presented in the lines below.
b. It remains unclear why a small proportion of the randomized patients (n = 11, see Table 6) are not included in the analyses, in contrast to the analyses of study 029 for the same data cut-off presented by the company for the previous benefit assessment [7].
c. Institute's calculation; inverse direction of effect (company presented comparison of ipilimumab vs. placebo).
d. Institute's calculations: adjusted indirect comparison according to Bucher [26]
e. Operationalized as time from the day of randomization to the first occurrence of an event, for individual components see recurrence rate; the primary operationalization of the censoring rule and the definition of recurrence in accordance with study 029 was used for both studies.
f. Unstratified Cox model, unstratified log-rank test.
g. Adjusted indirect comparison according to Bucher [26].

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; RR: relative risk

There was one RCT on each side of the available adjusted indirect comparison. Hence, a check of the homogeneity assumption was not required. As there was no study of direct comparison of nivolumab against placebo, the consistency assumption could not be checked. Therefore, the adjusted indirect comparison had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived based on the data available from the adjusted indirect comparison.

With the exception of the outcome "recurrence", no indirect comparison was conducted for all other patient-relevant outcomes for various reasons and, as a rule, no hint of an added benefit was derived (not assessed as sufficiently similar for an indirect comparison, no data usable for the indirect comparison available, or requirement for the certainty of results for conducting an adjusted indirect comparison not met, see Sections 2.4.1 and 2.4.2).

This assessment does not concur with that of the company, which performed an indirect comparison for all further outcomes except for the outcomes recorded with the EORTC QLQ-C30, and, with the exception of the outcomes of the category of side effects, derived an indication of an added benefit in each case. In addition, the company used the results for the total population of the studies 238 and 029 for the indirect comparison for its benefit assessment and derived the added benefit at outcome level on this basis. However, the subpopulation of patients with stage IIIB and IIIC disease is used for the indirect comparison for the present benefit assessment (see Section 2.3.3.1).

Mortality

Overall survival

There were no usable data for an indirect comparison for the outcome "overall survival". This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting for the outcome "overall survival"; an added benefit is therefore not proven.

This deviates from the assessment of the company, which performed an indirect comparison on the basis of the results of the total populations of the studies and derived an indication of an added benefit from this.

Morbidity

Health status (EQ-5D VAS)

No usable data for an indirect comparison were available for the outcome "health status" measured with the EQ-5D VAS. This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting for the outcome "health status"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Recurrence

Operationalization

For the present benefit assessment, the proportion of patients with recurrence and, additionally, the time to recurrence were used for the outcome "recurrence".

Results

For the outcome "recurrence" (operationalized as recurrence rate and recurrence-free survival), the adjusted indirect comparison showed a statistically significant difference in favour of

nivolumab in comparison with placebo for both operationalizations. This resulted in a hint of an added benefit of nivolumab in comparison with watchful waiting for patients with stage IIIB and IIIC disease. The results of both operationalizations differed in their extent, however. In the present data situation, taking into account the differences in the proportions of patients with recurrence and the time courses (see Appendix A.2 of the full dossier assessment), the overall extent of the added benefit is rated as "major" (see Section 2.5.1).

This deviates from the assessment of the company in that the company performed an indirect comparison on the basis of the results of the total populations of the studies exclusively for recurrence-free survival for its assessment and derived an indication of an added benefit.

Symptoms (EORTC QLQ-C30)

No usable data for an indirect comparison were available for the outcome "symptoms" measured with the EORTC QLQ-C30. This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is not proven.

This concurs with the company's assessment.

Health-related quality of life

No usable data for an indirect comparison were available for the outcome "health-related quality of life" measured with the EORTC QLQ-C30. This resulted in no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is not proven.

This concurs with the company's assessment.

Side effects

Due to an insufficient certainty of results for conducting an adjusted indirect comparison, no indirect comparison was conducted for the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs". There were no usable analyses on a suitable operationalization for the outcome "immune-related AEs".

Hence, there was overall no hint of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

The result of this assessment concurs with that of the company. However, the company conducted an indirect comparison on the basis of the results of the total populations of the studies for the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs", and arrived at the same conclusion on the basis of the results of the indirect comparison. The company did not use the outcome "immune-related AEs" for its derivation of the added benefit.

Transferability of the added benefit to patients with stage IV disease

The added benefit in the indirect comparison was derived on the basis of the results in the subpopulation of patients with stage IIIB and IIIC disease investigated in the studies 238 and

029. In the present specific data situation, however, the conclusion on the added benefit can be transferred to patients with stage IV disease. This is justified below:

The indirect comparison between nivolumab and placebo showed a clear effect in favour of nivolumab for the outcome "recurrence" based on patients with stage IIIB and IIIC disease (see description of results in this section above). Additional data on the use of nivolumab and ipilimumab in patients with stage IV disease are available from study 238. The subgroup analyses on disease stage presented in the previous benefit assessment (see Table 9 in Appendix D of addendum A19-01 [7]) showed that there was no significant effect modification by the characteristic of disease stage (IIIB/C versus IV) for the outcomes on recurrence and AEs, and that the effect estimations were comparable in each case. Although the company did not present subgroup analyses for the characteristic of disease stage in Module 4 I of the dossier for the present benefit assessment, the assessment of transferability is supported by event time analyses for recurrence-free survival for the patient groups IIIB/C and IV at the final data cut-off of study 238, which also showed comparable effect estimations (see Figure 13 in Appendix C of the full dossier assessment, [11]).

For the comparator therapy (watchful waiting, operationalized as placebo), no data are available for patients with stage IV disease in study 029. However, taking into account the results of the above-mentioned subgroup analyses and Kaplan-Meier curves as well as the results from the indirect comparison for patients with stage IIIB/IIIC disease, a plausible conclusion can be drawn about the comparison between nivolumab and placebo for patients with stage IV disease. In the present data situation, it is not to be expected that the comparison of ipilimumab against placebo would produce such deviating effects for patients with stage IV disease that the effect of nivolumab in comparison with watchful waiting from the indirect comparison would change to a relevant extent regarding recurrence. A transfer of the results of the indirect comparison to patients with stage IV disease therefore appears justified in the present specific data situation.

The situation is different for patients with stage IIIA disease. These patients were investigated only in study 029 on the comparison of ipilimumab with placebo, but not in study 238 on the comparison of nivolumab with ipilimumab. Hence, there are no data on adjuvant treatment with nivolumab in these patients. A transfer of the added benefit to these patients would therefore be not sufficiently supported by data and is therefore not appropriate.

2.4.4 Subgroups and other effect modifiers

No subgroup analyses for the indirect comparison are available for the present benefit assessment of nivolumab. Thus, no conclusions on potential effect modifications are possible for the comparison of nivolumab against watchful waiting.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit for the subpopulation of patients with stage IIIB and IIIC disease is presented below at outcome level, taking into account the

different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for the outcome "recurrence"

It cannot be inferred from the dossier for the outcome "recurrence" whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

The outcome "recurrence" is considered to be severe/serious. On the one hand, recurrence of the cancer can be life-threatening, or rather a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach was not successful. On the other hand, the event "death from any cause" is a component of the outcome "recurrence".

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

Outcome category **Outcome**	**Nivolumab vs. placebo** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	No usable data[c]	Lesser benefit/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)	No usable data[c]	Lesser benefit/added benefit not proven
Recurrence Recurrence rate	RR: 0.67 [0.56; 0.80]; < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: "major"
Recurrence-free survival	HR: 0.53 [0.41; 0.70]; < 0.001 Probability: "hint"	
Symptoms (EORTC QLQ-C30)	No usable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No usable data[c]	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable data[d]	Greater/lesser harm not proven
Severe AEs	No usable data[d]	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data[d]	Greater/lesser harm not proven
Immune-related AEs	No usable data[d, e]	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. There are no results usable for the indirect comparison (see Section 2.4.1).
d. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section 2.4.2).
e. There are no analyses on a suitable operationalization (see Section 2.3.3.6).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; QLQ-C30: Quality of Life Questionnaire-Core 30; RR; relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

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

Table 18: Positive and negative effects from the assessment of nivolumab in comparison with watchful waiting

Positive effects	Negative effects
Morbidity Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: "major"	-
For the outcomes of the categories of mortality, health-related quality of life and side effects, there are no usable data for the indirect comparison.	

In the overall consideration, there is a positive effect of nivolumab in comparison with watchful waiting for the outcome "recurrence" with the extent "major".

For the outcomes in the categories of mortality, health-related quality of life and side effects, there are no usable data for the indirect comparison. Due to outcome-specific aspects that call into question the fulfilment of the similarity assumption for the indirect comparison and the insufficient certainty of results for the implementation of an adjusted indirect comparison, no hint of an added benefit or of greater or lesser harm is derived for the patient-relevant outcomes of these categories.

Adequate balancing of benefit and harm is not possible, in particular because the results on the outcomes of the category of side effects are not usable. In the present specific data situation, however, it is not assumed that the potential harm in these outcomes can completely call into question the major added benefit for the outcome "recurrence". The extent of added benefit is non-quantifiable in the present data situation, however.

The added benefit in the indirect comparison was derived on the basis of the results in the subpopulation of patients with stage IIIB and IIIC disease investigated in the studies 238 and 029. Here, however, the conclusion on the added benefit can be transferred to patients with stage IV disease (see Section 2.4.3 for reasons).

In summary, there is a hint of an added benefit of nivolumab in comparison with watchful waiting, which is non-quantifiable in the present data situation, in the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease (stage IIIB to IV disease) who have undergone complete resection.

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

Table 19: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection[b]	▪ Pembrolizumab (only for patients in tumour stage III after complete resection) or ▪ dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection) or ▪ **watchful waiting**	*Stage IIIB/C and IV disease:* hint of non-quantifiable added benefit *Stage IIIA disease:* 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 respective choice of the company is printed in **bold**. b. Study 238 included only patients with an ECOG PS of 0 or 1; the ipilimumab arm of study 029 included one patient with ECOG PS = 2. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of a considerable added benefit for all patients in the present therapeutic indication regardless of disease stage (i.e. stages IIIA to IV).

The approach for the derivation of an overall conclusion on the 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.

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

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