Nivolumab
(Melanoma, adjuvant, stage IIB or IIC)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Anne Wispler.

IQWiG thanks the respondent and Hautkrebs-Netzwerk Deutschland e. V. for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent and Hautkrebs-Netzwerk Deutschland e. V. were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse events of special interest
AJCC	American Joint Committee on Cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
imAEs	Immune-mediated adverse events
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model repeated measures
MRI	magnetic resonance imaging
PT	Preferred Term
RCT	randomized controlled trial
RFS	relapse-free survival
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 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 29 September 2023.

Research question

The aim of this report is to assess the added benefit of nivolumab in comparison with watchful waiting as appropriate comparator therapy (ACT) for the adjuvant treatment of stage IIB or IIC melanoma after complete resection in adults and adolescents 12 years of age and older.

The research question presented in Table 2 is derived 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 stage IIB or IIC melanoma after complete resection in adults and adolescents 12 years of age or older	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

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

Study pool and study design

Study CA209-76K was included for the benefit assessment of nivolumab. The CA209-76K study is an ongoing double-blind, multicentre RCT comparing nivolumab with placebo for the adjuvant treatment of melanoma. The study was to enrol patients aged 12 years and older who had undergone complete resection of a stage IIB or IIC cutaneous melanoma (American Joint Committee on Cancer [AJCC] classification, version 8) and who had received no further treatment of the melanoma. At baseline, patients had to show no indications of residual disease and they had to show a negative sentinel lymph node biopsy. Only patients with a good general condition, corresponding to an Eastern Cooperative Oncology Group-Performance Status (ECOG PS) of 0 or 1, were included. Patients with a pre-existing

autoimmune disease and patients with a history of metastatic melanoma were not included in the study.

The study included a total of 790 patients who were randomly assigned in a 2:1 ratio to treatment with nivolumab or placebo.

The CA209-76K study is divided into 2 parts. Part 1 comprises the initial adjuvant treatment and the subsequent observation period. If a relapse occurs, patients in both study arms have the option to switch to the unblinded Part 2 of the study and be treated with nivolumab under certain conditions regarding the treatment duration and the time point of the relapse. The analyses on relevant outcomes presented by the company in Module 4 X of the dossier refer to Part 1 of the study.

In Part 1 of the study, treatment with nivolumab in the intervention arm was largely carried out in compliance with the Summary of Product Characteristics (SPC), with minor deviations in the recommendations for a restart of treatment after AEs had subsided. The duration of adjuvant treatment of the melanoma was limited to a maximum of 1 year in compliance with the specifications of the SPC.

The primary outcome of the study was relapse-free survival (RFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and side effects.

The present benefit assessment uses the results from the second data cut-off of 20 April 2023.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. The CA209-76K study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison. Despite minor deviations (e.g. no lymph node sonography, no detection of the tumour marker S100B and differences in the frequency of physical examinations and imaging using computed tomography [CT]/magnetic resonance imaging [MRI]) from the recommendations of the S3 guideline, the patients in the study were examined closely and specifically for the detection of recurrences, so that the examination regimen used is considered to be a sufficient approximation to an appropriate operationalization of watchful waiting.

No data available on adolescents aged 12 years and older

Although the study design of the CA209-76K study envisaged the inclusion of patients aged 12 years and older, the study actually only included patients aged > 18 years. Based on the study, it is therefore not possible to draw any conclusions on the added benefit for the population

of adolescents aged 12 years and older with stage IIB or IIC melanoma after complete resection.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the CA209-76K study. The risk of bias of the result on the outcome of all-cause mortality was also rated as low. Although there is a low risk of bias for the outcome of recurrence, the certainty of results for this outcome is limited, as the effect cannot yet be assessed with sufficient certainty due to the relatively short observation period. No suitable data are available for the outcomes of health status (recorded using the EQ-5D visual analogue scale [VAS]), symptoms and health-related quality of life (each recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]). The risk of bias of the results on the outcomes of serious adverse events (SAEs), severe adverse events (AEs) as well as immune-mediated SAEs/severe AEs, and further specific AEs was rated as high. The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. On the basis of the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of all-cause mortality, and at most hints can be derived for all other outcomes due to the high risk of bias and a limited certainty of results.

Results

Mortality

All-cause mortality

An analysis of the outcome “overall survival” is not yet available at the current data cut-off. There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality", based on data on deaths that had occurred up to the data cut-off. There is no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

Regarding the outcome of recurrence, there was a statistically significant difference in favour of nivolumab in comparison with placebo for both “recurrence rate” and “’RFS”. There is a hint of an added benefit of nivolumab in comparison with watchful waiting. However, the results of the operationalizations of recurrence rate and RFS differ in their extent. In the present data situation, taking into account the differences in the proportions of patients with event and the time courses, the overall extent of the added benefit is rated as “considerable”.

Health status (EQ-5D VAS) and symptoms (EORTC QLQ-C30)

No suitable data are available for the outcomes of health status (recorded with the EQ-5D VAS) and symptoms (recorded with the EORTC QLQ-C30). In each case, there is no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data are available for the outcome of health-related quality of life (recorded with the EORTC QLQ-C30). There is no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab in comparison with placebo was shown for each of the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". There was a hint of greater harm from nivolumab in comparison with watchful waiting.

immune-mediated SAEs

No statistically significant difference between the treatment groups was shown for the outcome "immune-mediated SAEs". There was no hint of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

immune-mediated severe AEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of immune-mediated severe AEs. There was a hint of greater harm from nivolumab in comparison with watchful waiting.

Specific AEs

For each of the outcomes of skin and subcutaneous tissue disorders (SOC, AEs), infections and infestations (SOC, SAEs), examinations (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs) and vascular diseases (SOC, severe AEs), there was a statistically significant difference in favour of nivolumab compared to placebo. In each case, there was a hint of greater harm from nivolumab in comparison with watchful waiting.

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

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

Overall, both one positive and several negative effects of nivolumab were found in comparison with the ACT.

A hint of major considerable benefit was shown for the outcome "recurrence". This was offset by several negative effects: With regard to serious/severe side effects, there were several hints of greater harm with extents up to “major”. For non-serious/non-severe side effects, there are also several hints of greater harm; in each case, the extent is “considerable”. However, the effects observed for outcomes of the side effects category are based exclusively on the shortened observation period until treatment end plus up to 100 days. Therefore, the data available for these outcomes allow no conclusions about late-onset or longer-lasting events. There are no suitable analyses on “health-related quality of life”, “symptoms” and “health status”. In the overall weighing, however, the negative effects and the lack of data on health-related quality of life, symptoms and health status do not completely call into question the advantage in recurrences.

In summary, there is a hint of minor added benefit of nivolumab versus the ACT watchful waiting for the adjuvant treatment of adults with stage IIB or IIC melanoma after complete resection.

The CA209-76K study provides no data for the assessment of the added benefit of nivolumab compared with the ACT for the adjuvant treatment of stage IIB or IIC melanoma after complete resection in adolescents aged 12 years and older. An added benefit of nivolumab versus the ACT is therefore not proven for adolescents aged 12 years and older.

Table 3 shows a summary of the probability and extent of 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 stage IIB or IIC melanoma after complete resection in adults and adolescents 12 years of age or older	Watchful waiting	▪ Adults: hint of minor added benefitb ▪ adolescents 12 years of age and older: added benefit not proven
a. Presented is the ACT specified by the G-BA. b. Only patients with an ECOG-PS of 0 or 1 were included in the CA209-76K study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

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

I 2 Research question

The aim of this report is to assess the added benefit of nivolumab in comparison with watchful waiting as ACT for the adjuvant treatment of stage IIB or IIC melanoma after complete resection in adults and adolescents 12 years of age and older.

The research question presented in Table 4 is derived 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 stage IIB or IIC melanoma after complete resection in adults and adolescents 12 years of age or older	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on nivolumab (status: 26 July 2023)
- bibliographical literature search on nivolumab (last search on 26 July 2023)
- search in trial registries / trial results databases for studies on nivolumab (last search on 26 July 2023)
- search on the G-BA website for nivolumab (last search on 26 July 2023)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 05 October 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

Ongoing study in the therapeutic indication

The NivoMela study [3], which was ongoing at the time of the present benefit assessment and for which results are expected from 2027, was identified in agreement with the company. This study is an investigator-initiated multicentre RCT investigating adjuvant treatment with nivolumab versus placebo in stage II melanoma under biomarker-based risk stratification. The results on this study expected from 2027 onwards are potentially relevant to the research question of this benefit assessment.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: nivolumab versus watchful waiting

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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
CA209-76K	Yes	Yes	No	Yes [4-6]	Yes [7,8]	Yes [9,10]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct 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]
CA209-76K	RCT, double-blind[b], parallel	Patients aged ≥ 12 years[c] with histologically confirmed stage IIB or IIC cutaneous melanoma[d] after complete resection[e] ▪ negative sentinel lymph node diagnostics[e] ▪ ECOG PS ≤ 1	Part 1: nivolumab (N = 526[f]) placebo (N = 264) part 2[g]: renewed nivolumab therapy for patients from the nivolumab arm (N = 3), nivolumab therapy for patients from the placebo arm (N = 30)	Screening: no maximum duration treatment: ▪ blinded phase of the study: at most 12 months or until the occurrence of unacceptable toxicity, recurrence or withdrawal of consent ▪ unblinded phase[b]: at most 1 year for resectable recurrence or at most 2 years for non-resectable recurrence observation[h]: outcome-specific, at most up to the final analysis for overall survival[i]	129 centres in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Romania, Spain, Sweden, Switzerland, United Kingdom, USA 10/2019–ongoing data cut-offs[j]: ▪ first data cut-off[k]: DBL: 17 August 2022 ▪ second data cut-off[l]: DBL: 20 April 2023	Primary: RFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct 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]

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. According to the study protocol, patients in the nivolumab or the placebo arm can, under certain circumstances, receive nivolumab (again) in an unblinded second part of the study after the occurrence of a recurrence.
c. The inclusion of adolescents aged 12 years or older was possible according to the inclusion criteria, but only patients > 18 years were included in the study. Based on the study, it is therefore not possible to draw any conclusions on the added benefit for the population of adolescents aged 12 years and older with stage IIB or IIC melanoma after complete resection (see Section I 5.2).
d. According to AJCC classification version 8 [11].
e. Resection and sentinel lymph node biopsy must have taken place within 12 weeks prior to randomization; exceptions are possible with the consent of the study monitor.
f. 2 patients in the intervention arm were randomized but not subsequently treated as they did not meet the inclusion criteria.
g. This part of the study is not relevant for the assessment and is not shown in the next tables. Information on the number of patients with (renewed) nivolumab therapy refers to the data cut-off of 20 April 2023.
h. Outcome-specific information is described in Table 8.
i. The final analysis for overall survival is planned after 277 events or optionally 9 years after randomization of the last patient, if the 277 events have not yet been reached at this time.
j. The company uses the time points of the DBL to label the data cut-offs in the dossier. The time points of the DBL are therefore used analogously in the present benefit assessment. The DCO for the first data cut-off took place on 28 June 2022 and for the second data cut-off on 21 February 2023.
k. Planned interim analysis on RFS.
l. Data cut-off requested by EMA.

AE: adverse event; AJCC: American Joint Committee on Cancer; DBL: database lock; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group-Performance Status; EMA: European Medicines Agency; N: number of randomized patients; RCT: randomized controlled trial; RFS: relapse-free survival

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

Study	Intervention	Comparison
CA209-76K[a]	Placebo IV, every 4 weeks ▪ adults and adolescents with a body weight ≥ 40 kg: 480 mg[b] ▪ adolescents with a body weight < 40 kg: 6 mg/kg (at most 240 mg)	Placebo IV, every 4 weeks
	Treatment adjustments ▪ no dose modifications allowed ▪ treatment interruptions/-delays ≤ 8 weeksc are possible due to AEs or newly occurred concomitant diseases (e.g. COVID-19).	
	Required pretreatment ▪ complete resection of the malignant melanoma including negative sentinel lymph node biopsy[d] **disallowed pretreatment** ▪ immune checkpoint inhibitors (such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibodies) or other drugs with the aim of influencing the IL2 pathway or T-cell co-stimulation ▪ any other treatment of the melanomae,f ▪ immunosuppressants including systemic corticosteroids (prednisone equivalent of > 10 mg/day) within 14 days prior to first dose of study medication ▪ vaccination with a live vaccine within 30 days before the first dose of study medication **disallowed concomitant treatment** ▪ immunosuppressantsg ▪ any antitumour therapy other than the study medication[h] **allowed concomitant treatment** ▪ corticosteroids in topical or inhaled application ▪ systemic corticosteroids > 10 mg/day prednisone equivalent as adrenal replacement therapy or as prophylaxis (e.g. of a contrast medium allergy) and as temporary treatment (< 3 weeks) of non-autoimmune diseases ▪ diphenhydramine or equivalent and/or paracetamol and corticosteroids for the treatment and prophylaxis of infusion-related reactions	

a. All data refer to Part 1 of the study relevant to the assessment.
b. A weight-adapted dosage of 6 mg/kg (at most 480 mg) is also permitted as an option for adolescents with a body weight ≥ 40 kg.
c. Interruption > 8 weeks permitted in the case of delayed tapering of steroid therapy for AEs associated with the investigational medication. Other exceptions for interruptions > 8 weeks for reasons not associated with the investigational medication must be authorized by the clinical monitor.
d. Resection and biopsy had to be performed within 12 weeks prior to randomization.
e. Complementary therapies are not permitted from 2 weeks before randomization/start of treatment and during the study for the treatment of melanoma, but only as supportive measures.
f. Excluded from this is an adjuvant interferon treatment of a melanoma that occurred earlier, provided that the end of treatment is ≥ 6 months before randomization.
g. Immunosuppressants for the treatment of AEs are permitted.
h. Hormone therapy, surgery and radiotherapy for the treatment of completely resectable non-melanoma malignancies that newly occur during the study are excluded.

AE: adverse event; CD137: Cluster of Differentiation 137; Covid-19: Coronavirus Disease 2019; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; PD-1: programmed cell death protein-1; PD-L1/L2: programmed cell death ligand 1/2; RCT: randomized controlled trial

Study design

The CA209-76K study is an ongoing double-blind, multicentre RCT comparing nivolumab with placebo for the adjuvant treatment of melanoma. The study was to enrol patients aged 12 years and older who had undergone complete resection of a stage IIB or IIC cutaneous melanoma (AJCC classification, version 8 [11]) and who had received no further treatment of the melanoma. At baseline, patients had to show no indications of residual disease and they had to show a negative sentinel lymph node biopsy. Only patients with a good general condition, corresponding to an ECOG PS of 0 or 1, were included. Patients with a pre-existing autoimmune disease and patients with a history of metastatic melanoma were not included in the study.

The study included a total of 790 patients, randomized in a 2:1 ratio either to treatment with nivolumab (N = 526) or to placebo (N = 264). Randomization was stratified by the T classification of tumour stage according to AJCC version 8 (T3b [tumour thickness > 2.0 mm to 4.0 mm with ulceration], T4a [> 4.0 mm without ulceration], T4b [> 4.0 mm with ulceration]).

The CA209-76K study is divided into 2 parts. Part 1 comprises the initial adjuvant treatment and the subsequent observation period. If a relapse occurs, patients in both study arms have the option to switch to the unblinded Part 2 of the study and be treated with nivolumab under certain conditions regarding the treatment duration and the time point of the relapse. The analyses on relevant outcomes presented by the company in Module 4 X of the dossier refer to Part 1 of the study.

In Part 1 of the study, treatment with nivolumab in the intervention arm was largely carried out in compliance with the specifications of the SPC [12], with minor deviations in the recommendations for a restart of treatment after AEs had subsided. The duration of adjuvant treatment of the melanoma was limited to a maximum of 1 year in compliance with the specifications of the SPC.

During and after treatment, the patients were closely examined for recurrences (see Section on the implementation of the ACT watchful waiting). After the occurrence of a recurrence, the patient and the attending physician can be unblinded at their request. Under certain conditions, these patients can participate in Part 2 of the study after unblinding. Patients from the intervention arm will be treated with nivolumab again, while patients from the comparator arm will receive nivolumab for the first time. Patients from the intervention arm can only receive nivolumab as subsequent therapy if they previously received complete adjuvant therapy for 12 months and the recurrence occurs within a period of > 6 months and < 3 years after the end of adjuvant treatment. These restrictions do not apply to patients in the placebo arm. Administration of nivolumab is limited to a maximum of 12 months in the case of resectable recurrence and to a maximum of 24 months in the case of non-resectable

recurrence or until unacceptable toxicity occurs, until recurrence/progression or until consent is withdrawn.

The study's primary outcome is RFS. Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and side effects.

Data cut-offs

The CA209-76K study is an ongoing study. So far, 2 data cut-offs are available:

- first data cut-off (17 August 2022): planned interim analysis after completed recruitment and more than 123 events for the RFS, performed after 135 events
- second data cut-off (20 April 2023): interim analysis requested by the European Medicines Agency (EMA), performed after 184 events for the RFS

The company used the analysis at the second data cut-off (20 April 2023) for the benefit assessment. The final analysis on the outcome of RFS is planned when 154 events are reached. As part of the approval procedure, the company initially presented results on the planned interim analysis for the RFS at the first data cut-off. Due to the short observation period for this analysis with a minimum follow-up of 8 months, the EMA requested the interim analysis for the second data cut-off with a minimum follow-up of 15.6 months. This analysis was carried out after 184 events for the RFS. Based on the information provided by the company in the dossier, it remains unclear why no data cut-off was analysed at the time of the originally planned final analysis for the RFS after 154 events. Since the data cut-off of 20 April 2023 requested in the approval procedure is a more recent data cut-off, this has no consequences for the present benefit assessment. The approval, which is based, among other things, on this data cut-off, was granted on the condition that an interim analysis on overall survival is presented in the first quarter of 2029. In addition, EMA recommends the submission of a further updated analysis for the RFS in the fourth quarter of 2024 [9]. One of the reasons given by the EMA for this is that data on overall survival in the present adjuvant therapy situation with curative intent are necessary for the assessment of the benefit-risk ratio in order to assess whether overall survival is prolonged or progression of the disease is only delayed.

No analysis of overall survival was planned for the previous data cut-offs. The first interim analysis for overall survival is planned when 166 events are reached for the outcome, the final analysis is planned when 277 events are reached or in case of a minimum follow-up of 9 years. The study documents show that a total of 37 deaths had occurred in both study arms up to the available second data cut-off.

In concurrence with the company, the present benefit assessment uses the results of the second data cut-off of 20 April 2023. Information available in the study report on the total

number of deaths per study arm up to the current data cut-off is used for all-cause mortality (see Section I 4.1).

Implementation of the ACT watchful waiting

The comparator arm of the CA209-76K study was a sufficient approximation to the ACT watchful waiting. This is explained below:

In this therapeutic indication, watchful waiting should include risk-adapted follow-up in accordance with the current S3 guideline [13].

The following examinations for the assessment of the health status or the detection of recurrences were performed in the CA209-76K study:

- Physical examination
- CT of the chest region and CT/or MRI of the abdomen and the pelvic region; if necessary, further CT and/or MRI according to clinical indication

In Part 1 of the study, the physical examination will be performed during treatment at each treatment cycle, at follow-up visits 1 and 2 (30 and 100 days after the last dose of study medication) and then every 12 weeks for a further 12 months until a recurrence occurs. A CT/MRI of the chest, abdominal and pelvic region is performed every 26 weeks in the first 3 years and every 52 weeks in years 4 and 5 until a recurrence occurs. After the occurrence of a local recurrence, further observation is carried out according to local standards. In the event of a locoregional recurrence, follow-up imaging should be performed until the appearance of distant metastases, with no frequency specified. If a recurrence is suspected outside the follow-up examinations, diagnostic measures according to clinical indication should also be initiated.

The examinations performed in the CA209-76K study do not fully comply with the recommendations of the S3 guideline. The guideline also recommends sonographic examinations of the lymph nodes and the determination of the tumour marker S100B. This was not implemented in the study. There are also differences in the frequency of physical examinations and CT/MRI imaging. Overall, however, patients in the CA209-76K study were closely and specifically examined for the detection of recurrences; the applied examination regimen was thus considered to be a sufficient approximation to an adequate operationalization of watchful waiting.

Planned duration of follow-up observation

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

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

Study **outcome category** **outcome**	**Planned follow-up observation**
CA209-76K[a]	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up or until the final analysis for overall survival[b]
Morbidity	
Recurrences, RFS	Until the occurrence of a recurrence (up to 5 years after the start of treatment) or withdrawal of consent, lost to follow-up or until death
Symptoms (EORTC QLQ-C30)	100 days after the last administration of the blinded study medication[c]
Health status (EQ-5D VAS)	Up to 5 years after start of treatment
Health-related quality of life	
EORTC QLQ-C30	100 days after the last administration of the blinded study medication[c]
Side effects	
All outcomes in the side effects category	100 days after the last administration of the blinded study medication[c]

a. All data refer to Part 1 of the study relevant to the assessment.
b. No analysis on the outcome "overall survival" was planned at the current data cut-off. All-cause mortality was used in the present assessment (see Section I 4.1).
c. After the follow-up visit on Day 100, only newly occurred AEs and SAEs that the investigator considers to be related to the study medication will be recorded. The survey is conducted until at least 15 months after the last administration of the study medication or, in the case of AEs, until the start of a new antineoplastic therapy.

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; RFS: relapse-free survival; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes on symptoms, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 100 days). For the outcomes of recurrence and health status, the observation periods are also systematically shortened with a planned follow-up of 5 years after the start of treatment, but cover a significantly longer period.

In order to draw a reliable conclusion on the total study period or the time to patient death, however, it would be necessary to survey all outcomes over the total period, as was done for survival.

Patient characteristics

Table 9 shows the characteristics of the patients in the CA209-76K study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab versus placebo (multipage table)

Study characteristic category	**Nivolumab N[a] = 526**	**Placebo N[a] = 264**
CA209-76K		
Age [years], mean (SD)	60 (14)	59 (14)
Age group, n (%)		
< 18 years	0 (0)	0 (0)
≥ 18 years to < 65 years	305 (58)	155 (59)
≥ 65 years to < 75 years	140 (27)	77 (29)
≥ 75 years to < 85 years	77 (15)	30 (11)
≥ 85 years	4 (< 1)	2 (< 1)
Sex [F/M], %	39/61	39/61
Family origin, n (%)		
White	515 (98)	262 (99)
Black or African American	2 (< 1)	1 (< 1)
Asian	1 (< 1)	0 (0)
Other	7 (1)	1 (< 1)
Not reported	1 (< 1)	0 (0)
Region, n (%)		
North America	97 (18)	46 (17)
United States	86 (16)	39 (15)
Canada	11 (2)	7 (3)
Western Europe	303 (58)	160 (61)
Eastern Europe	58 (11)	28 (11)
Australia	68 (13)	30 (11)
ECOG PS, n (%)		
0	495 (94)	245 (93)
1	31 (6)	19 (7)
Disease stage according to AJCC, n (%)		
IIB	316 (60)	162 (61)
IIC	210 (40)	102 (39)
AJCC tumour stage according to eCRF, n (%)		
T3b	204 (39)	104 (39)
T4a	112 (21)	58 (22)
T4b	210 (40)	102 (39)
BRAF V600 status, n (%)		
Mutated	148 (28[b])	81 (31[b])
Wild type	293 (56[b])	136 (52[b])
Not available	85 (16[b])	47 (18[b])

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab versus placebo (multipage table)

Study characteristic category	Nivolumab N[a] = 526	Placebo N[a] = 264
Treatment discontinuation, n (%)[c, d]	207 (39)	70 (27)
Study discontinuation, n (%)[e, f]	49 (9)	28 (11)

a. Number of randomized patients.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention versus the control arm were: intolerance to the study medication (18.7% vs. 2.7%), recurrence (5.0% vs. 15.9%), discontinuation at the patient's request (5.7% vs. 0 %). Treatment discontinuations due to Covid-19 in the intervention vs. the control arm: 1.3% vs. 0.8 %.
d. Data refer to the blinded part of the study.
e. Common reasons for study discontinuation in the intervention arm vs. the control arm were death (3.6% vs. 4.5%) and withdrawal of consent (3.4% vs. 4.5%). Study discontinuations due to Covid-19 in the intervention vs. the control arm: 0.4% vs. 0.8 %.
f. Data refer to the entire study including the unblinded Part 2.

AJCC: American Joint Committee on Cancer; COVID-19: coronavirus disease 2019; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both treatment arms were largely comparable. At the time of study inclusion, the mean age of the patients was around 60 years, no patient was younger than 19 years and 14% of patients were older than 75 years. The patient population is almost exclusively of white family origin and predominantly male. The number of patients in the individual disease stages according to AJCC version 8 [11] is comparable in the two treatment arms. Accordingly, 61% of patients were in stage IIB and 39% in stage IIC at the time before resection. At the time point of randomization, the majority of the patients (94%) had an ECOG-PS of 0. Around 89% of patients were treated in centres in North America, Western Europe and Australia.

The proportion of patients who discontinued treatment was significantly higher in the intervention arm than in the comparator arm (39% vs. 27%), while the number of dropouts differed only slightly (9% vs. 11%). The main reason for discontinuation of treatment in the intervention arm was intolerance to the study medication (19%), whereas in the comparator arm it was the occurrence of a recurrence (16%).

No data available on adolescents aged 12 years and older

Although the study design of the CA209-76K study envisaged the inclusion of patients aged 12 years and older, the study actually only included patients aged > 18 years. Based on the study, it is therefore not possible to draw any conclusions on the added benefit for the population

of adolescents aged 12 years and older with stage IIB or IIC melanoma after complete resection (see Section I 5.2).

Information on the course of the study

Table 10 shows the mean and median treatment durations of the patients and the mean and median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab vs. placebo

Study **duration of the study phase** **outcome category**	**Nivolumab** **N[a] = 524**	**Placebo** **N = 264**
CA209-76K		
Treatment duration [months][b]		
Median [min; max]	11.07 [0.0; 12.1]	11.20 [0.0; 12.7]
Mean (SD)	9.01 (ND)	10.17 (ND)
Observation period [months][c]		
Overall survival[d]		
Median [Q1; Q3]	23.49 [19.09; 28.12]	23.05 [19.19; 28.11]
Mean (SD)	23.70 (6.97)	23.66 (6.61)
Morbidity		
RFS		
Median [min; max]	18.14 [0.0; 37.4]	17.84 [0.0; 36.2]
Mean (SD)	18.71 (8.38)	16.54 (8.36)
Symptoms (EORTC QLQ-C30)/health status (EQ-5D VAS)	ND	ND
Health-related quality of life (EORTC QLQ-C30)	ND	ND
Side effects	ND	ND

a. Here, the analysis population is the safety population with N = 524 patients in the intervention arm.
b. Data on the treatment duration refer to the blinded part of the study.
c. The observation period of overall survival is calculated on the basis of the observed time to event or censoring of all patients. The observation period of the outcome "RFS" is presumably calculated analogously.
d. The available data on the observation period for overall survival refer to all randomized patients (N = 526 patients in the intervention arm).

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; RFS: recurrence-free survival; SD: standard deviation; VAS: visual analogue scale

In the analysis of the CA209-76K study presented by the company, both the median treatment durations and the median observation periods were roughly comparable in both treatment arms for all outcomes for which corresponding data are available. Data on the observation

periods for the outcomes of symptoms, health status, health-related quality of life and side effects are not available. While the outcomes of recurrences and health status are to be observed for up to 5 years after the start of treatment, the observation period for the outcomes on symptoms, health-related quality of life and for outcomes of the side effects category was linked to the end of treatment (plus about 100 days) (see Table 8). For these outcomes, conclusions can therefore be drawn only for the period up to 100 days after the end of treatment. Based on the information provided on treatment duration plus 100 days, the estimated maximum median observation duration is about 14 months for both study arms. Hence, the observation durations for these outcomes are shortened in comparison with the median observation period for overall survival. Data for the entire observation period are missing for these outcomes. Based on the comparable treatment durations, it is assumed that the observation duration for these outcomes is also roughly comparable between the study arms.

The data presented shows that at the time of the data cut-off, all patients who had started treatment had either completed or discontinued it. The minimum follow-up time measured as the time from randomization of the last patient to the current data cut-off was 15.6 months. At the time of the second data cut-off, 3 patients (0.6%) from the intervention arm and 30 patients (11.4%) from the comparator arm had moved on to Part 2 of the study .

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication during recurrence.

Table 11: Information on the course of the studya – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study subsequent therapy[a] category drug[b]	Patients with subsequent therapy n (%) intervention N = 526	 comparison N = 264
CA209-76K		
Total	82 (15.6)	78 (29.5)
Radiotherapy	16 (3.0)	7 (2.7)
Curative	8 (1.5)	3 (1.1)
Palliative	9 (1.7)	4 (1.5)
Surgical intervention	55 (10.5)	48 (18.2)
Curative	47 (8.9)	38 (14.4)
Palliative	1 (0.2)	6 (2.3)
Not classified	9 (1.7)	4 (1.5)
Systemic therapy	45 (8.6)	62 (23.5)
Nivolumab in the unblinded part	3 (0.6)	30 (11.4)
Anti-CTLA-4	2 (0.4)	2 (0.8)
Ipilimumab	2 (0.4)	2 (0.8)
Anti-PD-1/anti-PD-L1	10 (1.9)	43 (16.3)
Nivolumab	8 (1.5)[c]	39 (14.8)[c]
Pembrolizumab	3 (0.6)	2 (0.8)
Combination of anti-CTLA-4 + anti-PD-1/anti-PD-L1	21 (4.0)	20 (7.6)
Ipilimumab + nivolumab	21 (4.0)	20 (7.6)
Combination of BRAF, MEK and NRAS inhibitor	9 (1.7)	6 (2.3)
Binimetinib + encorafenib	5 (1.0)	5 (1.9)
Dabrafenib + trametinib	5 (1.0)	3 (1.1)
Combination of PD-1 and LAG-3	1 (0.2)	3 (1.1)
Experimental antineoplastic agent	1 (0.2)	0 (0)
Experimental antineoplastic agents	1 (0.2)	2 (0.8)
MEK-NRAS inhibitor	1 (0.2)	0 (0)
other systemic anticancer drugs	1 (0.2)	0 (0)
Other systemic anticancer therapies	1 (0.2)	3 (1.1)
Platinum-based chemotherapy	2 (0.4)	0 (0)
Not allocated	7 (1.3)	2 (0.8)

a. Includes any subsequent therapies administered in the blinded or unblinded part of the study; patients may have received more than 1 type of subsequent therapy.
b. Results for individual drugs are only listed if they were administered as subsequent therapy in at least 0.3% of patients per study arm.
c. Also includes the patients who received nivolumab in the unblinded part of the study.

Table 11: Information on the course of the studya – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study subsequent therapy[a] category drug[b]	Patients with subsequent therapy n (%) intervention N = 526	 comparison N = 264
CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; LAG-3: lymphocyte-activation gene 3; MEK: mitogen-activated extracellular signal-regulated kinase; n: number of patients with subsequent therapy; N: number of analysed patients; NRAS: neuroblastoma rat sarcoma viral oncogene homologue; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial		

In the CA209-76K study, subsequent therapies in relapse were permitted without restrictions in both study arms. Overall, 16% of the patients in the intervention arm and 30% of patients in the comparator arm received at least one subsequent therapy. In relation to the patients in whom an RFS event other than death occurred (88 patients in the intervention arm versus 81 patients in the comparator arm, see Table 15), this means that 93% of these patients in the intervention arm and 96% in the control arm received at least one subsequent therapy. Of these patients, 67% in the intervention arm and 62% in the comparator arm received surgical treatment. Surgical intervention with curative intent was performed in 57% of patients with at least 1 subsequent therapy in the intervention arm and 49% in the comparator arm. 55% of patients with at least 1 subsequent therapy in the intervention arm and 79% in the comparator arm received subsequent systemic therapy . The most frequently used subsequent systemic therapy in the comparator arm was nivolumab, while the combination of ipilimumab and nivolumab was most frequently used in the intervention arm.

Among the patients with nivolumab as subsequent therapy, 3 patients in the intervention arm and 30 patients in the comparator arm received the drug in the unblinded part of the study. It remains unclear how many patients received the drug as subsequent therapy in the disease stages of the therapeutic indication of the present assessment (IIB/C), in stages I-IIA or in a more advanced disease stage (III/IV). However, the study documents show that, based on the first data cut-off in the unblinded part of the study, of a total of 30 patients treated with nivolumab across both study arms of the blinded part, 14 had non-resectable melanoma and 16 had resectable melanoma. The data on the individual events, which apart from death were recorded in RFS, also show that 68% of patients with recurrence in the intervention arm and 77% of patients with recurrence in the comparator arm had metastases or regional lymph node recurrences. Against the background of the available data, it is therefore altogether assumed that the majority of patients were treated with nivolumab as a subsequent therapy in advanced stages III or IV of the disease in compliance with the approval.

Overall, the subsequent therapies used in the CA209-76K study are in line with the treatment options presented in the guidelines [13,14].

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, direct 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			
CA209-76K	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the CA209-76K study.

Transferability of the study results to the German health care context

The company considers the results of the CA209-76K study to be transferable to the German health care context. The company pointed out that the study was conducted in Germany and in Western industrialized countries (Western Europe, USA and Canada) with similar population groups (around 77% of the randomized patients in the two treatment arms) and that around 98% were of white family origin.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - recurrence
  - health status, recorded using the EQ-5D VAS
  - symptoms, recorded with the EORTC QLQ-C30
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs
  - further specific AEs, if any

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

Table 13 shows the outcomes for which data are available in the included study.

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

Study	Outcomes										
	All-cause mortality	Recurrences[a]	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Immune-mediated SAEs[d]	Immune-mediated severe AEs[c, d]	Further specific AEs[c, e]
CA209-76K	Yes[f]	Yes	No[g]	No[g]	No[g]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented via recurrence rate and RFS, includes the events of local recurrence, in-transit metastases, regional lymph node recurrence, distant metastases, new primary invasive melanoma, melanoma in situ, death from any cause and disease at baseline.
b. Excludes progression events of the underlying disease (several PTs of the SOC "neoplasms benign, malignant and unspecified" [including cysts and polyps]" according to the company's list).
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. The operationalization of a specific MedDRA PT collection ("select AE") presented by the company is used in each case.
e. The following events were considered (MedDRA coding): "skin and subcutaneous tissue disorders (SOC, AEs)", "infections and infestations (SOC, SAEs)", "examinations (SOC, severe AEs)", "metabolism and nutrition disorders (SOC, severe AEs)" and "vascular disorders (SOC, severe AEs)".
f. For the previous data cut-offs, no analysis was planned for the outcome "overall survival" recorded in the study. However, the study report provides data on the total number of deaths per study arm up to the current data cut-off as part of the information on safety and AEs, which are used as all-cause mortality (see the following text section).
g. No suitable data available; for reasons, see the following text section.

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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; RFS: relapse-free survival; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Analyses on overall survival and all-cause mortality

The company presented no data on overall survival in Module 4 X of the dossier. In the present oncological research question, this is not appropriate in a curative therapy approach either. Although no analyses of overall survival were planned for the previous data cut-offs, the study documents provide information on the total number of deaths per study arm up to the current data cut-off as part of the information on safety and AEs. Even if event time analyses would be the adequate analyses for the outcome of overall survival, the data on deaths and the relative risk (RR) calculated from them are presented as all-cause mortality in the present situation.

Recurrence

The outcome of recurrence is a composite outcome and comprises the components of local recurrence, in-transit metastases, regional lymph node recurrence, distant metastases, new primary invasive melanoma, melanoma in situ, death from any cause and disease at baseline. The results of the operationalizations "proportion of patients with recurrence" (hereinafter referred to as "recurrence rate") and RFS are presented for the outcome of recurrence.

The patients considered in the present stage of the disease are a group of patients who were treated with a curative treatment approach. The occurrence of a recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful. At the time point of the data cut-off of 20 April 2023 used for the benefit assessment, the median observation period in the study was approximately 23 months. In malignant melanoma, the high-risk period for the occurrence of recurrences comprises the first 3 years after primary diagnosis [13]. The previous observation period does not fully cover this critical phase. In Module 4 X of the dossier, the company describes that the high-risk period for the occurrence of recurrences for stages IIB and IIC is limited to the first 2 years after primary diagnosis, however, the observation period to date covers this period also only for some of the patients. Thus, the effect of nivolumab on the outcome of recurrence cannot yet be assessed with sufficient certainty after this relatively short observation period. Consequently, the certainty of results for this outcome can only be assumed to be moderate.

Analyses on patient-reported outcomes of the categories of morbidity and health-related quality of life

In Module 4 X of the dossier, the company presents analyses of the change since the start of the study for patient-reported outcomes in the categories of morbidity and health-related quality of life recorded using the EORTC QLQ-C30 or EQ-5D VAS using a mixed-effects model repeated measures (MMRM). However, surveys after the end of treatment are not considered in these analyses.

For the EORTC QLQ-C30, 2 follow-up surveys were conducted on Day 30 and on Day 100 after the last dose of study medication, which are not considered in the analyses presented by the company. For the EQ-5D VAS moreover, surveys are also planned every 12 weeks up to 5 years after the start of treatment, which, like the 2 follow-up surveys on Day 30 and Day 100, are not considered in the analyses. However, the benefit assessment requires for the entire observation period to be included in the analyses. If treatment ends prematurely, values collected after the end of treatment must be transparently assigned to the corresponding time points from randomization (i.e. the corresponding visits) in a comprehensible manner. In the present data situation, consideration of the values from the follow-up surveys is of particular importance, as a high proportion of patients (39%) in the intervention arm and 27% of patients in the comparator arm discontinued treatment. The main reason for discontinuation of

treatment in the intervention arm was intolerance to the study medication, whereas in the comparator arm it was the occurrence of a recurrence (see Table 9 for details). These differences in the proportions of patients with the respective reasons for treatment discontinuation could potentially have different effects on the patient-reported outcomes for the follow-up surveys after the end of treatment. Therefore, the MMRM analyses presented by the company are not suitable for the benefit assessment and are accordingly not used.

According to the study design, only descriptive analyses were planned for the patient-reported outcomes in the CA209-76K study. Accordingly, Module 5 of the dossier presents no analyses with effect estimates. However, according to the study design, the descriptive presentation of results for patient-reported outcomes in the study was planned for both continuous data and response criteria. It remains unclear why the company only presents analyses on continuous data in Module 4 X of the dossier and no comparative analyses based on suitable response criteria. A change by 15% of the instrument's scale range is considered a suitable response criterion or, for analyses of the EORTC QLQ-C30, a change by 10 points [15]. For the patient-reported outcomes on symptoms and health-related quality of life recorded using the EORTC QLQ-C30, for example, event time analyses on the time to first deterioration would be conceivable, which consider the actual time point of the follow-up surveys after the end of treatment. For the outcome "health status" (recorded using EQ-5D VAS), on the other hand, comparative analyses based on response criteria would be conceivable due to the follow-up period of up to 5 years after the start of treatment, which take into account the surveys of all patients up to Month 12 or at later time points of the study with longer follow-up periods for all patients (e.g. over 24 months after the start of treatment).

Overall, no suitable data are available for patient-reported outcomes in the categories "morbidity" and "health-related quality of life" for the present benefit assessment.

Analyses on the outcomes of the side effects category

Types of analysis

Although the company describes that in the CA209-76K study there are almost identical median observation periods in the two treatment arms, it nevertheless only presents isolated analyses based on the RR for outcomes in the side effects category in Module 4 X of the dossier. Due to the sufficiently similar observation periods (see Table 10), analyses of the RR were used for all outcomes in the side effects category to derive the added benefit for the present assessment. This is due to the fact that in the assessment of side effects, the number of patients in whom an event occurred is primarily relevant. In addition, when analysing the time until occurrence of the event, effects may also result solely from an earlier or later occurrence of the event rather than on the basis of the proportions.

Follow-up and consideration of observations under subsequent therapies

According to the study design, analyses were planned in the CA209-76K study for all outcomes of the side effects category, with the exception of some selected specific AEs, which included a follow-up of 30 days after the last dose of the blinded study medication. However, within the framework of the study, follow-up for all outcomes in the side effects category was carried out over a period of 100 days after the last dose of blinded study medication. In the analyses planned according to the study design, the full follow-up period was therefore only taken into account for some selected specific AEs. In Module 4 X of the dossier, the company presents analyses on all outcomes of the side effects category that include the 100-day follow-up. However, in these analyses, patients with events who received nivolumab as subsequent therapy in the unblinded part 2 of the study were only considered for some of the outcomes. However, since nivolumab - as described in Section I 3.2 - is an adequate subsequent therapy for the majority of patients in relapse as part of the treatment strategy, it would be appropriate to consider events under subsequent therapy for all outcomes in the analyses. In addition, events that occur under other subsequent therapies are also taken into account, such as for the combination of nivolumab and ipilimumab. Thus, a subsequent therapy with nivolumab as monotherapy within the scope of the study is treated differently in the analyses presented by the company than a subsequent therapy with other drugs or drug combinations, such as the combination of nivolumab and ipilimumab. This approach is generally inadequate but remains of no consequence for the present benefit assessment in the present data situation. This is explained below.

For the overall rates of AEs, SAEs, severe AEs and discontinuations due to AEs, the company presented analyses with and without consideration of the corresponding events under nivolumab as subsequent therapy. The comparison of these analyses shows that the differences resulting from the company's approach are negligible. Only for SAEs is there a difference in patients with event (32 patients instead of 34 patients with at least 1 event in the comparator arm). For specific AEs, a direct comparison of the analyses with and without consideration of the corresponding events was only possible for treatment-related immune-mediated AEs (imAEs), but the results were identical. Overall, it is therefore assumed that analyses without consideration of events that occur under nivolumab as subsequent therapy are suitable for the benefit assessment for the specific AEs despite the uncertainty due to the company's approach. Analyses without consideration of the corresponding events are therefore used for the imAEs and other specific AEs.

ImAEs, immune-mediated severe AEs and immune-mediated SAEs

In Appendix 4 G of Module 4 X of the dossier, the company presents analyses on predefined specific imAEs, specific AEs (select AEs) as well as AEs of special interest (AESI). All of these outcomes represent potential operationalisations of imAEs. In addition, analyses of serious events and severe events (operationalized as CTCAE grade ≥ 3) are available for each of these

outcomes. Moreover, the company presents the lists of preferred terms (PTs) that are included as events in the respective analyses.

In the dossier, the company states that the AEs it referred to as "imAEs", with the exception of endocrine imAEs, were events requiring immunomodulatory therapy. This operationalization is unsuitable for fully representing imAEs. The outcome referred to by the company as "select AEs", however, represents a selection of System Organ Class (SOCs) and PTs which represent typical imAEs and for which AE treatment with immunosuppressants (e. g. with corticosteroids) could, but did not have to, be necessary. This operationalization is generally considered to be a sufficient operationalization for imAEs and is used for the present assessment. Both SAEs and severe AEs (CTCAE grade ≥ 3) are used for the benefit assessment. A list of the categories of immune-related AEs, immune-mediated SAEs, and immune-mediated severe AEs (CTCAE grade ≥ 3) which occurred in the CA209-76K study is provided as supplementary information in I Appendix D of the present benefit assessment.

In addition to the operationalization using select AEs, the outcome referred to by the company as AESI also potentially includes other immune-mediated PTs (e.g. in particular myocarditis, uveitis, rhabdomyolysis and pancreatitis). It would therefore make sense to consider both the PTs of the PT collection referred to by the company as select AEs and those of the AESI in the analyses of imAEs. In the present data situation, however, only a few events occurred for the other PTs of the AESI (see Table 15 for details). Therefore, the company’s approach remains without consequence for the present benefit assessment.

I 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, direct comparison: placebo versus nivolumab

Study	Study level	Outcomes										
		All-cause mortality	Recurrences[a]	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Immune-mediated SAEs[d]	Immune-mediated severe AEs[c, d]	Further specific AEs[c, e]
CA209-76K	L	L[f]	L	–[g]	–[g]	–[g]	H[h]	H[h]	L[i]	H[h]	H[h]	H[h]

a. Presented via recurrence rate and RFS, includes the events of local recurrence, in-transit metastases, regional lymph node recurrence, distant metastases, new primary invasive melanoma, melanoma in situ, death from any cause and disease at baseline.
b. Excludes progression events of the underlying disease (several PTs of the SOC "neoplasms benign, malignant and unspecified" [including cysts and polyps]" according to the company's list).
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. The operationalization of a specific MedDRA PT collection ("select AE") presented by the company is used in each case.
e. The following events were considered (MedDRA coding): "skin and subcutaneous tissue disorders (SOC, AEs)", "infections and infestations (SOC, SAEs)", "examinations (SOC, severe AEs)", "metabolism and nutrition disorders (SOC, severe AEs)" and "vascular disorders (SOC, severe AEs)".
f. For the previous data cut-offs, no analysis was planned for the outcome "overall survival" recorded in the study. However, the study report provides data on the total number of deaths per study arm up to the current data cut-off as part of the information on safety and AEs, which are used as overall mortality (see Section I 4.1).
g. No suitable data available; see Section I 4.1 for the reasoning.
h. Incomplete observations for potentially informative reasons.
e. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.

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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; RFS: recurrence-free survival; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias was rated as low for the results of the outcome "all-cause mortality".

Although there is a low risk of bias for the outcome of recurrence, the certainty of results for this outcome is limited, as the effect cannot yet be assessed with sufficient certainty due to the relatively short observation period (for reasoning, see Section I 4.1).

No suitable data are available for the outcomes of health status (recorded with the EQ-5D VAS), symptoms and health-related quality of life, (both recorded with the EORTC QLQ-C30) (for reasoning, see Section I 4.1).

The risk of bias of the results on the outcomes of SAEs, severe AEs as well as immune-mediated SAEs/severe AEs, and further specific AEs was rated as high. For the mentioned outcomes of the category of side effects, there are incomplete observations for potentially informative reasons due to the follow-up observation linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation (see also Table 8).

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias.

I 4.3 Results

Table 15 summarizes the results on the comparison of nivolumab with placebo in the adjuvant treatment of patients with stage IIB and IIC melanoma who have undergone complete resection. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. The Kaplan-Meier curves on the outcome of RFS are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment. I Appendix D of the full dossier assessment presents the results on imAEs, SAEs and severe AEs summarized in categories defined by the company.

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

Study outcome category outcome	Nivolumab N[a]	Nivolumab patients with event n (%)	Placebo N[a]	Placebo patients with event n (%)	Nivolumab vs. placebo RR [95% CI]; p-value[b]
CA209-76K					
Mortality					
All-cause mortality[c]	524	21 (4.0)	264	16 (6.1)	0.66 [0.35; 1.25]; 0.207
Morbidity					
Recurrence					
Recurrence rate[d]	526	102 (19.4)	264	84 (31.8)	0.61 [0.48; 0.78]; < 0.001
Local recurrence	526	10 (1.9)	264	10 (3.8)	–[e]
In-transit metastases	526	4 (0.8)	264	1 (0.4)	–[e]
Regional lymph node recurrence	526	16 (3.0)	264	23 (8.7)	–[e]
Distant metastases	526	44 (8.4)	264	39 (14.8)	–[e]
New invasive primary melanoma	526	6 (1.1)	264	3 (1.1)	–[e]
Melanoma in situ	526	8 (1.5)	264	5 (1.9)	–[e]
Death from any cause	526	14 (2.7)	264	3 (1.1)	–[e]
Disease at baseline	526	0	264	0	–
RFS	526	102 (19.4) Median time to event in months: NA	264	84 (31.8) Median time to event in months: 36.1 [24.8; NC]	HR: 0.53 [0.40; 0.71]; < 0.001[f]
Health status (EQ-5D VAS)				No suitable data[g]	
Symptoms (EORTC QLQ-C30)				No suitable data[g]	
Health-related quality of life					
EORTC QLQ-C30				No suitable data[g]	
Side effects					
AEs[h] (presented as supplementary information)	524	508 (96.9)	264	233 (88.3)	–
SAEs[h]	524	98 (18.7)	264	34 (12.9)	1.45 [1.01; 2.08]; 0.039
Severe AEs[h, i]	524	146 (27.9)	264	42 (15.9)	1.75 [1.28; 2.39]; < 0.001
Discontinuation due to AEs[h]	524	116 (22.1)	264	9 (3.4)	6.49 [3.35; 12.58]; < 0.001
imAEs[j, k, ll] (supplementary information)	524	399 (76.1)	264	131 (49.6)	–
Immune-mediated SAEs[j, k, l]	524	29 (5.5)	264	7 (2.7)	2.09 [0.93; 4.70]; 0.068

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

Study outcome category outcome	Nivolumab		Placebo		Nivolumab vs. placebo
	N[a]	patients with event n (%)	N[a]	patients with event n (%)	RR [95% CI]; p-value[b]
Immune-mediated severe AEs[i, j, k]	524	55 (10.5)	264	7 (2.7)	3.96 [1.83; 8.57]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs[k])	524	271 (51.7)	264	90 (34.1)	1.52 [1.26; 1.83]; < 0.001
Infections and infestations (SOC, SAEs[k])	524	23 (4.4)	264	2 (0.8)	5.79 [1.38; 24.39]; 0.006
Investigations (SOC, severe AEs[i, k]	524	43 (8.2)	264	9 (3.4)	2.41 [1.19; 4.86]; 0.011
Metabolism and nutrition disorders (SOC, severe AESI,[i, k])	524	16 (3.1)	264	2 (0.8)	4.03 [0.93; 17.40]; 0.042[m]
Vascular disorders (SOC, severe AEs[i, k])	524	15 (2.9)	264	1 (0.4)	7.56 [1.00; 56.90]; 0.020

a. As a rule, N is the number of all randomized patients. The analysis of the harm outcomes was based on the total number of all randomized patients who had received at least one dose of the study medication. 2 patients in the intervention arm received no study medication after randomization because they did not meet the inclusion criteria for the study. Data on all-cause mortality were taken from the safety analysis.
b. Institute's calculation: effect and CI (asymptotic): p-value (unconditional exact test, CSZ method according to [16]).
c. For the previous data cut-offs, no analysis was planned for the outcome of overall survival recorded in the study. However, the study report provides data on the total number of deaths per study arm up to the current data cut-off as part of the information on safety and AEs, which are used as overall mortality (see Section I 4.1). Here, the analysis population is the safety population with N = 524 patients in the intervention arm.
d. Proportion of patients with a qualifying event for the outcome "RFS". The individual components are presented in the lines below.
e. No calculation of the effect estimations. The presented events do not represent the outcome exhaustively. Only events that are relevant for the formation of the composite outcome are presented.
f. Effect and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by AJCC tumour stage at study inclusion.
g. No suitable data available; see Section I 4.1 for the reasoning.
h. Excludes progression events of the underlying disease (several PTs of the SOC "neoplasms benign, malignant and unspecified" [including cysts and polyps]" according to the company's list).
i. Operationalized as CTCAE grade ≥ 3.
j. The operationalization of a specific MedDRA PT collection ("select AE") presented by the company is used in each case.
k. Follow-up observation until 100 days after the last administration of the blinded study medication or until the start of treatment with nivolumab as subsequent therapy in part 2 of the study, whichever came first.
l. In addition, the following numbers of patients with events were reported for the outcome defined by the company as "AE of special interest (AESI)": 17 (3.2 %) vs. 2 (0.8 %) patients with any AESI; 8 (1.5 %) vs. 1 (0.4 %) patients with serious AESI; 7 (1.3 %) vs. 1 (0.4 %) patients with severe AESI (CTCAE grade ≥ 3). It cannot be ruled out that these patients are already included in the analyses on IMAEs.
m. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

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

Study outcome category outcome	Nivolumab		Placebo		Nivolumab vs. placebo
	N[a]	patients with event n (%)	N[a]	patients with event n (%)	RR [95% CI]; p-value[b]
AE: adverse event; AJCC: American Joint Committee on Cancer; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30; HR: Hazard Ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RFS: relapse-free survival; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale					

On the basis of the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of all-cause mortality, and at most hints can be derived for all other outcomes due to the high risk of bias and a limited certainty of results.

Mortality

All-cause mortality

An analysis of the outcome “overall survival” is not yet available at the current data cut-off. There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality", based on data on deaths that had occurred up to the data cut-off. There is no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

Regarding the outcome of recurrence, there was a statistically significant difference in favour of nivolumab in comparison with placebo for both “recurrence rate” and “relapse-free survival”. There is a hint of an added benefit of nivolumab in comparison with watchful waiting. However, the results of the operationalizations of recurrence rate and relapse-free survival differ in their extent. In the present data situation, taking into account the differences in the proportions of patients with event and the time courses (see I Appendix B), the overall extent of the added benefit is rated as “considerable” (see Section I 5.1).

Health status (EQ-5D VAS) and symptoms (EORTC QLQ-C30)

No suitable data are available for the outcomes of health status (recorded with the EQ-5D VAS) and symptoms (recorded with the EORTC QLQ-C30) (for reasoning, see Section I 4.1). In each case, there is no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No usable data are available the outcome of health-related quality of life (recorded using the EORTC QLQ-C30) (for reasons, see Section I 4.1). There is no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab in comparison with placebo was shown for each of the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". There was a hint of greater harm from nivolumab in comparison with watchful waiting.

Immune-mediated SAEs

No statistically significant difference between the treatment groups was shown for the outcome "immune-mediated SAEs". There was no hint of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Immune-mediated severe AEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of immune-mediated severe AEs. There was a hint of greater harm from nivolumab in comparison with watchful waiting.

Specific AEs

For each of the outcomes of skin and subcutaneous tissue disorders (SOC, AEs), infections and infestations (SOC, SAEs), examinations (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs) and vascular diseases (SOC, severe AEs), there was a statistically significant difference in favour of nivolumab compared to placebo. In each case, there was a hint of greater harm from nivolumab in comparison with watchful waiting.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65/≥ 65)
- sex (female versus male)
- AJCC tumour stage (T3b vs. T4a vs. T4b)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

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

For the outcome category of side effects, the company considered the time to event, using the hazard ratio (HR) as effect measure. The subgroup analyses conducted by the company for this category are also based on the HR. In contrast to the approach of the company, the present assessment uses analyses of the number of patients with event with the RR effect measure for the side effect outcomes to derive the added benefit. Analyses based on the RR are therefore also preferable for the subgroup analyses. Hence, the present benefit assessment checked whether a significant effect modification at the level of 0.2 was present using the HR. If this was the case, an interaction test was performed using the Q test, based on the RR.

Using the methods described above, the available subgroup analyses do not reveal any effect modifications.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [17].

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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 16).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Discontinuation due to AEs

In Module 4 X of the dossier, the company describes that more than 60% of the AEs that led to discontinuation were of CTCAE severity grade 1-2, but does not categorize the outcome. For the present assessment, the outcome “discontinuation due to AEs” is assigned to the category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: nivolumab versus watchful waiting (multipage table)

Outcome category **outcome**	**Nivolumab vs. placebo** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes observed over the entire study duration		
Mortality		
All-cause mortality	Proportion of events: 4.0 % vs. 6.1 % RR: 0.66 [0.35; 1.25] p = 0.207	Lesser/added benefit not proven
Morbidity		
Recurrence[c]		
Recurrence rate	Proportion of events: 19.4 % vs. 31.8 % RR: 0.61 [0.48; 0.78] p < 0.001 probability: hint	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit; extent: “considerable”
Relapse-free survival	Median: NA vs. 36.1 months HR: 0.53 [0.40; 0.71] p < 0.001 probability: hint	
Health status (EQ-5D VAS)[c]	No suitable data[d]	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)	No suitable data[d]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[d]	Lesser/added benefit not proven
Side effects		
SAEs	Proportion of events: 18.7 % vs. 12.9 % RR: 1.45 [1.01; 2.08] RR: 0.69 [0.48; 0.99][e] p = 0.039 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Severe AEs	Proportion of events: 27.9 % vs. 15.9 % RR: 1.75 [1.28; 2.39] RR: 0.57 [0.42; 0.78][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm; extent: “considerable”

Table 16: Extent of added benefit at outcome level: nivolumab versus watchful waiting (multipage table)

Outcome category **outcome**	**Nivolumab vs. placebo** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	Proportion of events: 22.1 % vs. 3.4 % RR: 6.49 [3.35; 12.58] RR: 0.15 [0.08; 0.30]e p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_U < 0.80 greater harm; extent: considerable
Immune-mediated SAEs	Proportion of events: 5.5 % vs. 2.7 % RR: 2.09 [0.93; 4.70] p = 0.068	Greater/lesser harm not proven
Immune-mediated severe AEs	Proportion of events: 10.5 % vs. 2.7 % RR: 3.96 [1.83; 8.57] RR: 0.25 [0.12; 0.55][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm; extent: “major”
Skin and subcutaneous tissue disorders (SOC, AE)	Proportion of events: 51.7 % vs. 34.1 % RR: 1.52 [1.26; 1.83] RR: 0.66 [0.55; 0.79][e] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_U < 0.80 greater harm; extent: “considerable”
Infections and infestations (SOC, SAE)	Proportion of events: 4.4 % vs. 0.8 % RR: 5.79 [1.38; 24.39] RR: 0.17 [0.04; 0.73][e] p = 0.006 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75; risk < 5% greater harm; extent: “considerable”
Examinations (SOC, severe AEs)	Proportion of events: 8.2 % vs. 3.4 % RR: 2.41 [1.19; 4.86] RR: 0.41 [0.21; 0.84][e] p = 0.011 probability: hint	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm; extent: considerable

Table 16: Extent of added benefit at outcome level: nivolumab versus watchful waiting (multipage table)

Outcome category **outcome**	**Nivolumab vs. placebo** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]** **p-value** **probability[a]**	**Derivation of extent[b]**
Metabolism and nutrition disorders (SOC, severe AEs)	Proportion of events: 3.1 % vs. 0.8 % RR: 4.03 [0.93; 17.40] RR: 0.25 [0.06; 1.07][e] p = 0.042 probability: hint	Outcome category: serious/severe side effects greater harm[f]; extent: minor[g]
Vascular disorders (SOC, severe AEs)	Proportion of events: 2.9 % vs. 0.4 % RR: 7.56 [1.004; 56.90] RR: 0.13 [0.02; 0.996][e] p = 0.020 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Follow-up planned for up to 5 years after the start of treatment. However, this observation period according, which was shortened as planned, has no consequences for the assessment based on the data cut-off used, at which no patient was observed for longer.
d. See Section I 4.1 of the present dossier assessment for the reasoning.
e. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. The result of the statistical test is decisive for the derivation of added benefit.
g. Discrepancy between CI and p-value; the extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire – Core 30; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of nivolumab in comparison with watchful waiting

Positive effects	Negative effects
Outcomes observed over the entire study duration	
Morbidity serious/severe symptoms/late complications ▪ recurrences: hint of an added benefit – extent: ”considerable”	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: “minor” ▫ *specific AEs (SAEs):* infections and infestations: hint of greater harm – extent: "considerable" ▪ severe AEs: hint of greater harm – extent: “considerable” ▫ immune-mediated severe AEs: hint of greater harm – extent: “major” ▫ specific AEs (severe AEs): examinations: hint of greater harm – extent: "considerable" - metabolism and nutrition disorders, vascular disorders: in each case hint of greater harm, extent: “minor”
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm - extent: “considerable” ▪ specific AEs: ▫ diseases of the skin and subcutaneous tissue (AEs): hint of greater harm – extent: considerable
No suitable data are available for the outcomes of symptoms, health status and health-related quality of life. AE: adverse event; SAE: serious adverse event	

Overall, both one positive and several negative effects of nivolumab were found in comparison with the ACT.

A hint of major considerable benefit was shown for the outcome "recurrence". This was offset by several negative effects: With regard to serious/severe side effects, there were several hints of greater harm with extents up to “major”. For non-serious/non-severe side effects, there are also several hints of greater harm; in each case, the extent is “considerable”. However, the effects observed for outcomes of the side effects category are based exclusively on the shortened observation period until treatment end plus up to 100 days. Therefore, the data available for these outcomes allow no conclusions about late-onset or longer-lasting events. There are no suitable analyses on “health-related quality of life”, “symptoms” and “health status”. In the overall weighing, however, the negative effects and the lack of data on

health-related quality of life, symptoms and health status do not completely call into question the advantage in recurrences.

In summary, there is a hint of minor added benefit of nivolumab versus the ACT watchful waiting for the adjuvant treatment of adults with stage IIB or IIC melanoma after complete resection.

The CA209-76K study provides no data for the assessment of the added benefit of nivolumab compared with the ACT for the adjuvant treatment of stage IIB or IIC melanoma after complete resection in adolescents aged 12 years and older. An added benefit of nivolumab versus the ACT is therefore not proven for adolescents aged 12 years and older.

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 18.

Table 18: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adjuvant treatment of stage IIB or IIC melanoma after complete resection in adults and adolescents 12 years of age or older.	Watchful waiting	▪ Adults: hint of minor added benefit[b] ▪ adolescents 12 years of age and older: added benefit not proven
a. Presented is the ACT specified by the G-BA. b. Only patients with an ECOG-PS of 0 or 1 were included in the CA209-76K study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which claims an indication of major added benefit regardless of the patients' age.

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

I 6 References for English extract

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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. University Hospital Essen. Adjuvant Nivolumab Treatment in Stage II (IIA, IIB, IIC) High-risk Melanoma (NivoMela) [online]. 2022 [Accessed: 11.10.2023]. URL: https://clinicaltrials.gov/study/NCT04309409.

4. Bristol Myers Squibb. A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy with Nivolumab versus Placebo after Complete Resection of Stage IIB/C Melanoma; study CA20976K; Primary Clinical Study Report [unpublished]. 2022.

5. Bristol Myers Squibb. A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy with Nivolumab versus Placebo after Complete Resection of Stage IIB/C Melanoma; study CA20976K; Addendum 1 to the Primary Clinical Study Report [unpublished]. 2023.

6. Bristol Myers Squibb. A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy with Nivolumab versus Placebo after Complete Resection of Stage IIB/C Melanoma; study CA20976K; Addendum 2 to the Primary Clinical Study Report [unpublished]. 2023.

7. Bristol-Myers Squibb. Effectiveness Study of Nivolumab Compared to Placebo in Prevention of Recurrent Melanoma After Complete Resection of Stage IIB/C Melanoma (CheckMate76K) [online]. 2023 [Accessed: 11.10.2023]. URL: https://clinicaltrials.gov/study/NCT04099251.

8. Bristol-Myers Squibb. A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy with Nivolumab versus Placebo after Complete Resection of Stage IIB/C Melanoma (CheckMate 76K: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 76K) [online]. [Accessed: 11.10.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001230-34.

9. European Medicines Agency. OPDIVO; Nivolumab; Procedure No. EMEA/H/C/003985/II/0130; Assessment report [online]. 2023. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo.

10. Kirkwood JM, Del Vecchio M, Weber J et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. Nat Med 2023; 29(11): 2835-2843. https://doi.org/10.1038/s41591-023-02583-2.

11. Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67(6): 472-492. https://doi.org/10.3322/caac.21409.

12. Bristol Myers Squibb. Fachinformation OPDIVO 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung; Stand: August 2023 [online]. URL: http://www.fachinfo.de.

13. Leitlinienprogramm Onkologie. S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms; Langversion 3.3; AWMF-Register-Nummer 032/024OL [online]. 2020. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Melanom/Melanom_Version_3/LL_Melanom_Langversion_3.3.pdf.

14. Michielin O, Van AACJ, Ascierto PA et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; 30(104): 1884-1901. https://doi.org/10.1093/annonc/mdz411.

15. Gemeinsamer Bundesausschuss. Antworten auf häufig gestellte Fragen zum Verfahren der Nutzenbewertung; Wie soll, vor dem Hintergrund der Veröffentlichung des Methodenpapiers 6.0 des IQWiG am 5. November 2020, derzeit in der Dossiererstellung mit der Bestimmung von klinischen Relevanzschwellen bei komplexen Skalen umgegangen werden? [online]. [Accessed: 05.08.2021]. URL: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/faqs.

16. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

17. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 27.11.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

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