Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Nivolumab (Reassessment after the deadline (melanoma, adjuvant treatment)

of 16 September 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient nivolumab (Opdivo) to be assessed for the first time on 27 August 2018. For the resolution of 21 February 2019 made by the G-BA in this resolution, a time limit of 1 April 2021 was pronounced.

In accordance with Section 4, paragraph 3 paragraph 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Opdivo recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 31 March 2021. The G-BA commissioned the IQWiG to carry out the

assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 1 July 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of nivolumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nivolumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of nivolumab (Opdivo) in accordance with the product information

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Therapeutic indication of the resolution (resolution from 16.09.2021):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

Appropriate comparator therapy:

- pembrolizumab (only for patients with stage III tumours after complete resection)

or

- dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection)

or

- monitoring wait-and-see approach

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. About the authorisation status, in addition to nivolumab, the active ingredients pembrolizumab and interferon alfa-2b are available in the present indication. Furthermore, the combination therapy dabrafenib + trametinib is explicitly approved for the adjuvant treatment of BRAF V600 mutation-positive melanoma.

on 2. Adjuvant radiotherapy can be considered in principle in the present therapeutic indication.

on 3. Resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are:

- pembrolizumab - resolution of 19 September 2019
- dabrafenib - resolution of 22 March 2019
- trametinib - resolution of 22 March 2019
- nivolumab - resolution of 21 February 2019

on 4. The generally accepted state of medical knowledge for the indication was established using a search for guidelines and systematic reviews of clinical studies. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication.

As a non-medicinal treatment, adjuvant radiotherapy can, in principle, be considered in stage III. This serves to improve regional tumour control. Adjuvant radiotherapy is used on a patient-individual basis depending on the risk of relapse and taking into account possible therapy-related side effects. There are no data demonstrating a

positive impact of adjuvant radiotherapy on overall survival. A regular application cannot be derived, which is why adjuvant radiotherapy cannot be considered as an appropriate comparator therapy.

Interferon alfa-2b has been approved for the treatment of tumour-free patients but are at high risk of relapse after surgery. The underlying evidence no longer recommends interferon therapy for adjuvant treatment of cutaneous melanoma with lymph node involvement or metastasis after complete resection. Interferon alfa-2b is therefore not eligible as an appropriate comparator therapy.

In addition to interferon alfa-2b, the active ingredients dabrafenib + trametinib and pembrolizumab have also been approved for the adjuvant treatment of melanoma.

The combination of active ingredients dabrafenib + trametinib is indicated for the adjuvant treatment of adults with stage III melanoma with a BRAF V600 mutation after complete resection. For dabrafenib + trametinib, the G-BA found indication of a considerable additional benefit over the monitoring wait-and-see approach in its resolution of 22 March 2019. There were very clear advantages with regard to relapses and clear advantages in overall survival with simultaneously relevant disadvantages with regard to side effects. For the endpoint overall survival, median survival was not yet reached in either arm. Consequently, the validity of the resolution is limited to 1 April 2024.

Pembrolizumab is indicated for the adjuvant treatment of stage III melanoma with lymph node involvement after complete resection in adults. For pembrolizumab, an indication of non-quantifiable additional benefit over the monitoring wait-and-see approach was identified in a resolution dated 19 September 2019. There were clear advantages in terms of relapses with relevant disadvantages in terms of side effects. No results were available for the endpoint overall survival. Furthermore, the results on relapses were considered not yet conclusively assessable, as the duration of observation was not yet sufficiently long. Consequently, the validity of the resolution is limited to 1 April 2024.

Both the combination dabrafenib + trametinib and the anti-PD-1 antibodies pembrolizumab and nivolumab have been recommended in the guidelines. The statements of the scientific-medical societies and the AkdÄ, which participated in the comparative therapy, are consistent with this.

Accordingly, for patients with BRAF wild-type, the anti-PD-1 antibodies nivolumab and pembrolizumab are used, and for patients with BRAF V600 mutation, both the anti-PD-1 antibodies and the combination of active ingredients dabrafenib + trametinib are used. Nevertheless, relevant uncertainties with regard to the data basis arise from the benefit assessments conducted to date, both with regard to dabrafenib + trametinib and pembrolizumab, which resulted in the limitations for the resolutions.

Therefore, in addition to the therapy options mentioned - pembrolizumab (only for patients with tumour stage III after complete resection) and dabrafenib + trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection) - the "monitoring wait-and-see approach" is also determined as an equally appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab is assessed as follows:

Hint of a considerable additional benefit.

Justification:

For the new benefit assessment after the expiry of the limited validity period of the resolution of 21 February 2019, the pharmaceutical company submits an adjusted indirect comparison according to Bucher of nivolumab versus the appropriate comparator therapy consisting of the monitoring wait-and-see approach. For this indirect comparison via the bridge comparator ipilimumab, the pharmaceutical company includes study CA209-238 (nivolumab vs ipilimumab) and the study CA184-029 (placebo vs ipilimumab). The studies are randomised double-blind, controlled, multicentre Phase III studies. In addition, the pharmaceutical company presents the direct comparative, 3-arm study IMMUNED (nivolumab vs placebo vs nivolumab + ipilimumab).

CA209-238 study

The CA209-238 study included adult patients with completely resected melanoma in stage IIIB, IIIC or IV of the disease (classification according to AJCC2, version 7). Patients were considered free of disease and in good general condition (ECOG-PS: 0-1). Randomisation was 1:1 (453 patients per arm) stratified by PD-L1 status (positive [≥ 5%] vs negative [< 5%] / non-quantifiable) and disease stage according to AJCC. The study population received either treatment with nivolumab (3 mg/kg body weight) or treatment with ipilimumab (10 mg/kg body weight). In comparison to the current product information of nivolumab, this results in a discrepancy regarding the dosing scheme of nivolumab. This was adjusted after marketing authorisation and provides for the administration of nivolumab as a fixed dose. For the benefit assessment, it is assumed that this does not have a relevant influence on the observed effects.

The treatment duration was limited to 1 year in both study arms. Patients were treated until relapse or the occurrence of unacceptable persistent toxicity.

The study was conducted in 130 centres in South and North America, Europe and Asia, among others, and started in March 2015.

The primary endpoint of the CA209-238 study was relapse-free survival. Secondary endpoints include overall survival, symptomatology, health-related quality of life, and adverse events. For the adjusted indirect comparison, the final analysis from the 3rd. data cut-off of 29 January 2020 with an observation period of at least 48 months was used.

CA184-029 study

The CA184-029 study included adult patients with completely resected stage IIIA melanoma with metastases > 1 mm, IIIB or IIIC without in-transit metastases (classification according to AJCC2, version 6). Patients were considered free of disease and in good general condition (ECOG-PS: 0-1). In the study, 475 patients were randomised in the ipilimumab arm (10 mg/kg body weight) and 476 patients in the placebo arm in a 1:1 ratio. The placebo comparison performed corresponds sufficiently to an implementation of the appropriate comparator

therapy consisting of the monitoring wait-and-see approach (operationalised as a follow-up strategy that includes in particular the diagnosis of relapses according to the S3 guideline on the diagnosis, treatment and after-care of melanoma. Randomisation was stratified by stage of disease according to AJCC2 and region.

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

The study was conducted in 92 centres, primarily in North America and Europe (including Germany), and was carried out from 2006 to 2018.

The primary endpoint of the study was relapse-free survival. Secondary endpoints include overall survival, distant metastasis-free survival, symptomatology, health-related quality of life, and AEs.

The final analysis for the 2nd data cut-off from 13 May 2016 with an observation period of at least 53 months was taken as a basis for the benefit assessment.

On the similarities of the studies CA209-238 and CA184-029 in an indirect comparison

There are differences between the CA209-238 and CA184-029 studies, particularly concerning the disease stages included in the studies. There are no data on adults with stage-IV melanoma for study CA184-029 and no data on adults with stage-IIIA melanoma for study CA209-238. Against this background, evaluations of the sub-population of overlapping disease stage IIIB/IIIC populations are used for the adjusted indirect comparison.

Relevant differences between the two studies also arise concerning the available follow-up therapies after a relapse due to the different time periods of the study implementation. The majority of currently available active ingredients, in particular immunotherapies, were not approved at the time of the CA184-029 study, in contrast to the CA209-238 study, and were not available to the patients of the CA184-029 study to a relevant extent as follow-up therapy. The differences with regard to the time periods of the studies concern, in particular, the comparability of the results on overall survival.

However, no other differences challenge the similarity assumption for the indirect comparison across endpoints, so the adjusted indirect comparison for the overlapping sub-populations of patients with adjuvant therapy by disease stage IIIB/IIIC is used for the present evaluation.

IMMUNED study

The IMMUNED study is a 3-arm, multicentre, double-blind RCT comparing nivolumab to nivolumab in combination with ipilimumab and to placebo. This is an investigator-initiated study in which patients with stage IV melanoma were assigned in a 1:1:1 ratio to treatment with nivolumab (N=95), nivolumab in combination with ipilimumab (N=56), or placebo (N=52). The study started in 2015 and is conducted exclusively in Germany. Patients should be in good general condition at study entry (ECOG-PS: 0-1), had to have received surgery or radiotherapy to treat melanoma within 8 weeks prior to the start of the study, and had to have no subsequent evidence of disease (No Evidence of Disease [NED]). It is unclear which criteria define NED in the IMMUNED study and to what extent patients had a complete resection after surgery according to the criteria of the pivotal CA209-238 study.

The study's primary endpoint is relapse-free survival; secondary endpoints include overall survival and endpoints concerning side effects.

For the still ongoing study, only analyses for relapse-free survival and endpoints in the side effects category are available from a pre-specified interim analysis with a data cut-off of 2 July 2019. Final analyses are expected to be available in October 2021.

The IMMUNED study is not used for the benefit assessment because it is unclear to what extent patients had to fulfil the criteria of a complete surgical resection according to the marketing authorisation study 238 after surgery and thus correspond to the patient population relevant for the research question of the benefit assessment. In addition, a proportion of patients in both study arms received radiotherapy exclusively.

On the implementation of conditions for a time limit

According to the justification of the initial resolution of 21 February 2019, the limitation was that further clinical data from the CA209-238 study are expected, which may be relevant for assessing the benefit of the medicinal product. The initial resolution was based on the 12 June 2017 data cut-off results, which did not have evaluations for the endpoint overall survival. In addition, the endpoints on relapses were based on the results of an interim analysis conducted on 14 December 2017, with a minimum observation period of 24 months. For the reassessment of the benefit of nivolumab after the expiry date of the resolution on 1 April 2021, the results on all patient-relevant endpoints, in particular overall survival and relapses, should be presented in the dossier.

The pharmaceutical company resubmits an adjusted indirect comparison of the two studies CA209-238 and CA184-029 for the reassessment after the deadline. Here, the final data cut-offs of both studies are used, which also show results on overall survival and relapses with a sufficiently long observation period. The pharmaceutical company thus complies with the conditions of the limitation.

Extent and probability of the additional benefit

Mortality

For patients with stage IIIB/C disease, data are available from the adjusted indirect comparison of the CA209-238 and CA184-029 studies. Due to the differences mentioned above in the standard of care concerning the available follow-up therapies after relapse between the two studies, the results for the endpoint overall survival from the two studies are not comparable in terms of content and cannot be used for an indirect comparison.

In this respect, the pharmaceutical company shall submit sensitivity analyses to demonstrate the robustness of the observed effect. Although an adjustment was made by follow-up therapy, the type of follow-up therapy was not included in the analysis, which means that the newly approved options were not taken into account. Overall, the sensitivity analyses are not considered sufficient to be used for the indirect comparison.

Morbidity

Relapses / Relapse-free Survival (RFS)

Patients in the present therapeutic indication are treated with a curative therapy approach as part of the adjuvant treatment of melanoma after complete resection. Nevertheless, tumour cells might remain and cause a relapse in the further course. Relapse means that the attempt at a cure by the curative therapeutic approach was unsuccessful.

The occurrence of a relapse is patient-relevant. For the present evaluation of the endpoints relapse and RFS, the analyses for the final data cut-offs of 29 January 2020 (CA209-238) and

13 May 2016 (CA184-029) were used. The median observation durations for relapse-free survival were reached at the final data cut-offs in all study arms.

Both the operationalisation of the endpoints in the two studies CA209-238 and CA184-029 as well as the observation durations, differ, but the pharmaceutical company presents evaluations in the dossier for the benefit assessments that are considered as sufficiently similar for an adjusted indirect comparison.

The endpoints relapse and RFS include the following individual components:
- local relapse
- in-transit metastases (exclusively in study CA184-092)
- regional relapse
- remote relapse
- death (before relapse)

The endpoint relapse describes the percentage of patients with a relapse event or death at the corresponding data cut-off (event rate). In the endpoint RFS, the time to the event (recurrence or death) is also considered (time-to-event analysis).

Relapse (event rate)

There was a statistically significant advantage for nivolumab over placebo in the sub-population with stage IIIB/C disease for the endpoint relapse.

Relapse-free survival (RFS)

Nivolumab results in a statistically significant prolongation of time to relapse or death compared to placebo in the sub-population with stage IIIB/C disease.

Overall, about the endpoints relapses and RFS, the adjusted indirect comparison for patients with stage IIIB/C disease shows a clear, clinically relevant advantage of nivolumab compared to the appropriate comparator therapy consisting of the monitoring wait-and-see approach.

Symptomatology

Disease symptomatology was assessed in studies CA209-238 and CA184-029 using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30. The time until the occurrence of a deterioration of the respective score by at least 10 units was considered. The collection of data differs between studies: In the CA209-238 study, symptomatology was assessed regularly during treatment and at two follow-up visits after the end or discontinuation of therapy. Therefore, data from the CA209-238 study are only available for a limited time after the end or discontinuation of therapy. In contrast, symptomatology in the CA184-029 study was recorded regularly over 2 years, regardless of the end or discontinuation of therapy. Due to the planned treatment duration of 3 years, the duration of the assessment of disease symptomatology only partially covers the treatment period. As a consequence, data for patients in the CA184-029 study are partly not available for the period after the end or discontinuation of therapy, or no extensive data from the follow-up visits are available. Due to the different data collection strategies in the CA209-238 and CA184-029 studies, the data on disease symptomatology are not considered usable overall in the context of indirect comparison.

Health status

The endpoint health status assessed by EQ-5D VAS was only collected in the study CA209-238 so that no adjusted, indirect comparison can be performed based on this endpoint.

As a result, for the endpoint category morbidity, the adjusted indirect comparison provides usable data for the endpoints relapse and relapse-free survival, which show a clear, clinically relevant advantage of nivolumab for patients with stage IIIB/C disease compared to the appropriate comparator therapy consisting of the monitoring wait-and-see approach.

Quality of life

Health-related quality of life was assessed in studies CA209-238 and CA184-029 using the functional scales and the global health status scale of the EORTC QLQ-C30. The time until the occurrence of a deterioration of the respective score by at least 10 units was considered. The limitations of the data mentioned in connection with the assessment of disease symptomatology due to different measurement strategies in the CA209-238 and CA184-029 studies apply equally to the health-related quality of life assessment. Therefore, the results on health-related quality of life are not considered usable, in accordance with the explanations in section "Symptomatology".

Side effects

Adverse events (AEs) in total

Adverse events occurred in almost all study participants. Therefore, the results were only presented additionally.

Serious adverse events (SAEs), severe AEs (CTCAE grade 3-4)

For the endpoints SAEs and severe AEs (CTCAE grade ≥ 3), the adjusted indirect comparison showed no statistically significant differences between nivolumab versus placebo.

Therapy discontinuation due to AE

The adjusted indirect comparison shows a statistically significant disadvantage for nivolumab compared to placebo in the endpoint discontinuation due to AEs.

Immune-mediated AEs

Data on immune-mediated AE are considered unusable due to insufficient information to operationalise immune-mediated AE. In particular, it is unclear which events are included in the endpoint and whether there is sufficient similarity of operationalisation for indirect comparison.

Overall, regarding the side effects, there were no relevant differences in the endpoints serious adverse events (SAE) and severe adverse events (CTCAE grade ≥ 3) between the treatment arms. In contrast, there is a disadvantage for nivolumab compared to the monitoring wait-and-see approach in terms of treatment discontinuations due to adverse events.

Cross-endpoint observation from the indirect comparison

In the present specific assessment situation, the G-BA does not disregard the following facts in its assessment of the results:

There are advantages of nivolumab over placebo in the adjusted indirect comparison for the stage IIIB/C sub-population in the endpoints relapse and RFS. Although there are no subgroup analyses from the indirect comparison for the disease stage characteristic in the current dossier, the time-to-event analysis for relapse-free survival of study 238 at the final data cut-off for patient groups IIIB/C and IV support the assessment of transferability from the initial assessment. Subgroup analyses for the disease stage characteristic (stage IV vs IIIB/C) showed that there was no effect modification and comparable effect estimators for the comparison of nivolumab vs ipilimumab. Although there are no data for patients with stage IV disease from the CA184-029 study (ipilimumab vs placebo), in the present assessment situation, it is not expected that there will be such divergent effects for stage IV patients that these would significantly change the results of the indirect comparison of nivolumab vs placebo. This assessment is also supported by the data on patients with stage IV disease from the directly comparative IMMUNED study, which, however, is not used for the assessment of the extent of additional benefit for the reasons already mentioned.

In both stage IIIA and stage IIIB patients, up to three metastatically affected lymph nodes were diagnosed. The risk of relapse in both stages is high.

Against the background of the available data and the statements of scientific-medical societies, it is therefore considered medically plausible in the specific assessment situation to transfer the effects of patients in stage IIIB/C to stage IIIA and stage IV.

In summary, the statement on the additional benefit is therefore made for the entire population of patients with stage IIIA-C and IV disease covered by the therapeutic indication under assessment.

Overall assessment / conclusion

For the assessment of the additional benefit of nivolumab as monotherapy for the adjuvant treatment of melanoma with lymph node involvement or metastasis after complete resection,

results are available on morbidity, quality of life and side effects compared to the appropriate comparator therapy consisting of the monitoring wait-and-see approach.

The present assessment is based on an adjusted indirect comparison of the studies CA209-238 (nivolumab vs ipilimumab) and CA184-029 (placebo vs ipilimumab), according to Bucher. Nivolumab was compared to placebo (monitoring wait-and-see approach) via the bridge comparator ipilimumab. Because the disease stages encompassed by the CA209-238 (stage IIIB/C, IV) and CA184-029 (stage IIIA-C) studies are not completely congruent, the adjusted indirect comparison for the overlapping sub-populations of patients in stage IIIB/IIIC disease was used for the present evaluation.

No usable data are available for the endpoint overall survival.

In the endpoint category morbidity, nivolumab showed statistically significant, clear advantages compared to the monitoring wait-and-see approach in terms of relapse rate and relapse-free survival for the IIIB/C patient population.

The avoidance of relapses is an essential therapeutic goal in the present curative therapy situation.

The data submitted by the pharmaceutical company on patient-reported endpoints in the categories morbidity and health-related quality of life are not considered usable due to different data collection strategies in the studies CA209-238 and CA184-029 (EORTC QLQ-C30) or the exclusive collection in the study CA209-238 (EQ-5D VAS).

In terms of side effects, there were no relevant differences in the endpoints of serious adverse events (SAE) and severe adverse events (CTCAE grade 3-4) between the treatment arms. In contrast, there is a disadvantage for nivolumab compared to the monitoring wait-and-see approach in terms of treatment discontinuations due to adverse events.

Against the background of the available results of the indirect comparison for the sub-population of patients with disease stage IIIB/C and the statements of scientific-medical societies, it is considered plausible in the present specific assessment situation to transfer the results to patients with disease stages IIIA and IV.

In the overall analysis of the available results, nivolumab has an advantage over the monitoring wait-and-see approach exclusively for the endpoints relapse and relapse-free survival. The positive effect is clear and is based on significant data from a sufficiently long observation period. In the present adjuvant therapy situation, the avoidance of relapses is an essential therapeutic goal. The disadvantage in side effects is weighted against the background of the present right to a curative therapy and does not lead to a devaluation of the additional benefit.

The overall conclusion is that there is a hint of a considerable additional benefit for nivolumab compared with the monitoring wait-and-see approach.

Reliability of data (probability of additional benefit)

The present assessment is based on the adjusted indirect comparison of the phase III studies CA209-238 (nivolumab vs ipilimumab) and CA184-029 (placebo vs ipilimumab) according to Bucher. In the indirect comparison, nivolumab was compared to placebo (monitoring wait-and-see approach) via the bridge comparator ipilimumab. The risk of bias at the study level is rated as low for both studies. Due to the indirect comparison with one study per side, there are per se relevant uncertainties regarding the reliability of data.

Overall, the available data are subject to considerable uncertainty, which is why the reliability of data regarding the additional benefit identified is classified as hint.

2.1.4 Summary of the assessment

This assessment consists of the reassessment of the benefit of the active ingredient nivolumab after the expiry date of the resolution of 21 February 2019 in the therapeutic indication "OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection."

Pembrolizumab (only for patients with stage III tumours after complete resection), dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive stage III melanoma after complete resection) or "monitoring wait-and-see approach" was determined as the appropriate comparator therapy.

An adjusted indirect comparison according to Bucher of nivolumab versus placebo (monitoring wait-and-see approach) via the bridge comparator ipilimumab is used to prove the additional benefit.

There are no usable data for overall survival or patient-reported endpoints on morbidity or quality of life.

Regarding morbidity, nivolumab showed statistically significant, clear advantages over placebo concerning the endpoints relapse rate and relapse-free survival. The avoidance of relapses is an essential therapeutic goal in the present curative therapy situation.

In terms of side effects, there are relevant differences in therapy discontinuations due to adverse events to the disadvantage of nivolumab.

In the overall analysis, there are advantages of nivolumab over placebo exclusively for the endpoints on relapses. The positive effect is clear and based on significant data over a sufficiently long observation period. The disadvantage in side effects is weighted against the background of the present right to a curative therapy and does not lead to a devaluation of the additional benefit.

Due to the indirect comparison, there are per se relevant uncertainties about the reliability of data.

In the overall view, a hint of considerable additional benefit is identified.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The calculation of the target population by the pharmaceutical company is comprehensible and, despite uncertainty, lies in a largely plausible order of magnitude. Due to more recent sources and the additional consideration of some sub-patient groups compared to the patient numbers previously used in the therapeutic indication, this estimate represents a better approximation of the actual number of patients in the SHI target population.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 28 May 2021):

https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf

The initiation and monitoring of treatment with nivolumab must be carried out by a specialist experienced in the field of oncology and in the therapy of patients with melanoma (specialist in internal medicine, haematology and oncology, a specialist in skin and venereal diseases as well as other specialists participating in the Oncology Agreement).

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctor must discuss the risks of therapy with nivolumab with the patient. The patient card should be made available to the patient.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2021).

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

According to the product information, the recommended dosage of nivolumab as monotherapy is 240 mg every 2 weeks or 480 mg every 4 weeks.

The recommended dosage for pembrolizumab in monotherapy is 200 mg every 3 weeks or 400 mg every 6 weeks.

According to the product information, the recommended dose for dabrafenib in combination therapy with trametinib is 150 mg twice daily, and the recommended trametinib dose as part of this combination therapy is 2 mg once daily.

For the cost representation, only the doses of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information. The uses of nivolumab, pembrolizumab and dabrafenib in combination with trametinib for the treatment of adjuvant melanoma are limited to 12 months.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
nivolumab	1 x per 14 day cycle	26	1	26
	or			
	1 x per 28 day cycle	13	1	13
Appropriate comparator therapy				
Pembrolizumab	1 x per 21 day cycle	18	1	18
	or			
	1 x per 42 day cycle	9	1	9
Dabrafenib + trametinib				
Dabrafenib	2 x daily	365	1	365
+ trametinib	1 x daily	365	1	365
Monitoring wait-and-see approach	incalculable			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Consumption according to potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
nivolumab	240 mg	240 mg	2 x 100 mg 1 x 40 mg	26	52 x 100 mg + 26 x 40 mg
	or				
	480 mg	480 mg	4 x 100 mg 2 x 40 mg	13	52 x 100 mg + 26 x 40 mg
Appropriate comparator therapy					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	18	36 x 100 mg
	or				

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Consumption according to potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
	400 mg	400 mg	4 x 100 mg	9	36 x 100 mg
Dabrafenib + trametinib					
Dabrafenib	150 mg	300 mg	4 x 75 mg	365	1,460 x 75 mg
+ trametinib	2 mg	2 mg	1 x 2 mg	365	365 x 2 mg
Monitoring wait-and-see approach	incalculable				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nivolumab 100 mg	1 CIS	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Nivolumab 40 mg	1 CIS	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Appropriate comparator therapy					
Pembrolizumab 100 mg	1 CIS	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Dabrafenib 75 mg	120 HC	€ 5,831.71	€ 1.77	€ 0.00	€ 5,829.94
Trametinib 2 mg	30 FCT	€ 4,367.34	€ 1.77	€ 0.00	€ 4,365.57
Monitoring wait-and-see approach	incalculable				
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; HC = hard capsules					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be considered as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 28 July 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy defined by the G-BA took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 24 July 2018.

On 31 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5, sentence 2 VerfO.

By letter dated 1 April 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 9 August 2021.

By letter dated 10 August 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 27 August 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 7 September 2021, and the proposed resolution was approved.

At its session on 16 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	28 July 2020	Determination of the appropriate comparator therapy
Sub-committee Medicinal product	24 July 2018	New determination of the appropriate comparator therapy
Working group Section 35a	4 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	9 August 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 August 2021 1 September 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Sub-committee Medicinal product	7 September 2021	Final discussion of the draft resolution
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken