IQWiG Reports – Commission No. A18-53

Nivolumab (melanoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Nivolumab (Melanom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 27 August 2018.

Research question

This report aims to assess the added benefit of nivolumab monotherapy for the adjuvant treatment of melanoma with lymph node involvement or metastasis following complete resection in adults in comparison with the appropriate comparator therapy (ACT).

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2[2]: Research questions of the benefit assessment of nivolumab

Indication	ACT[a]
Adjuvant treatment of melanoma with lymph node involvement or metastasis following complete resection in adults	Watchful waiting[b]
a: Presentation of the ACT specified by the G-BA. b: The G-BA did not specify the ACT of watchful waiting. See Section 2.3.2.1 of the full report for the definition of the ACT in this assessment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

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

In clinical practice, the severity of the disease of melanoma is typically classified using the American Joint Committee on Cancer (AJCC) classification system. This classification system is also used in the S3 Guideline "Diagnosis, Therapy, and Follow-up of Melanoma" to categorize tumours and to structure the treatment and follow-up recommendations [1].

The therapeutic indication presented in Table 2 corresponds to disease stages III to IV in accordance with the current version 8 of the AJCC classification system, according to which melanoma stages III and above are characterized by lymph node involvement and stage IV by distant metastases [2].

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

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

Results

Study pool and study characteristics

No directly comparative RCTs were found to assess the added benefit of nivolumab in comparison with the ACT. Therefore, the company presented an adjusted indirect comparison of nivolumab and the ACT using the common comparator of ipilimumab. One RCT was included on each side of the indirect comparison.

CA209-238 study (nivolumab versus ipilimumab)

CA209-238 (hereinafter 238) is an ongoing, randomized, actively controlled, double-blind phase III study. The study examined nivolumab in comparison with ipilimumab. Included were patients ≥ 15 years of age who had undergone complete resection of a melanoma of stage IIIB, IIIC, or IV in accordance with AJCC (version 7), who were considered free of disease, and who were in good general health as measured by an Eastern Cooperative Oncology Performance Status (ECOG-PS) score of 0 or 1. Although adolescents < 18 years of age were eligible for inclusion in the study, only adults were actually included. In each study arm, 453 patients were randomized in a 1:1 ratio.

Primary outcome of the study was relapse-free survival (RFS). Secondary outcomes comprised overall survival, symptoms, health-related quality of life, and adverse events.

CA184-029 study (placebo versus ipilimumab)

CA184-029 (hereinafter 029) is an ongoing, randomized, actively controlled, double-blind phase III study. The study examined ipilimumab in comparison with placebo. Included were adult patients who underwent complete resection of a melanoma of stage

- IIIA with metastases > 1 mm,
- IIIB, or
- IIIC without in-transit metastases

according to the AJCC classification (version 6) and who were considered free of disease. Patients had to be in good general condition as measured by an ECOG-PS score of 0 or 1. The study randomized 457 patients to the ipilimumab arm and 476 patients to the placebo arm in a 1:1 ratio.

The primary outcome of the study was RFS. Secondary outcomes comprised overall survival, distant metastasis-free survival (DMFS), symptoms, health-related quality of life, and adverse events.

Operationalization and implementation of the ACT of watchful waiting

For this benefit assessment, the ACT of watchful waiting was operationalized as a follow-up strategy which particularly comprises relapse diagnostics in accordance with the S3 Guideline “Diagnosis, Therapy, and Follow-up of Melanoma”.

In study 029, placebo was used as the ACT. The study was not designed to be compared to watchful waiting, but it is nevertheless suitable for this comparison.

The examinations performed in study 029 fail to cover all recommendations of the S3 Guideline. In particular, sonography of lymph nodes and laboratory diagnostics of tumour marker S100B are recommended but were not performed. In contrast, tomography was conducted more often than recommended by the S3 Guideline.

Despite the deviations from the recommendations of the S3 Guideline, the patients in study 029 were closely and specifically examined in an effort to detect local, regional, and distant relapse; therefore, the examination regimen used in study 029 was considered a sufficient approximation of the above-described operationalization of watchful waiting.

Similarity of study populations and the resulting analysis population for indirect comparison

The demographic and clinical characteristics of the patients in studies 238 and 029 are sufficiently similar.

However, a particularly relevant difference in disease stages was found between the total populations of studies 238 and 029. Study 238 included patients in AJCC disease stages IIIB to IV, while study 029 included IIIA to IIIC.

Particularly the lack of data on disease stage IV, i.e. on patients with distant metastases, is considered a problem in study 029 since this means that no data on patients with distant metastases are available for the ACT. The company also failed to present any data to prove that the results of disease stages without distant metastases translate to stages with distant metastases. Consequently, the respective total populations are not comparable and unsuitable for performing an adjusted indirect comparison.

For this assessment, the subpopulation of patients in disease stages IIIB and IIIC was used to conduct the adjusted indirect comparison. However, this means that the therapeutic indication of nivolumab was not completely covered by this indirect comparison. Data were available only on patients with lymph node involvement (stage III), but not with distant metastases (stage IV). All results of the assessment therefore pertain to the subpopulation in disease stages IIIB and IIIC.

In addition, there are differences in study duration at the employed data cut-offs and in the application period of the common comparator.

Overall, the subpopulations of studies 238 and 029 are, however, considered sufficiently similar; therefore, the assumption of similarity regarding the included patient populations is not being called into question.

Risk of bias

The risk of bias at study level was rated as low for studies 238 and 029.

However, since only one study is available on either side of the indirect comparison and it was not possible to test either homogeneity or consistency (no direct comparative study), the indirect comparison can provide no more than a low certainty of results. Therefore, no more than hints, for instance of an added benefit, can be inferred in this situation.

Due to potential presence of informative censoring, the risk of bias at outcome level was rated as high in studies 238 and 029 for the outcomes of SAEs and severe AEs (CTCAE grade 3-4). For other outcomes, no usable data were available for indirect comparison.

Mortality

For the outcome of overall survival, results from the prescheduled final analysis at the data cut-off 13 May 2016 were available for study 029, but only for the total population. In study 238, the analysis of overall survival was not prescheduled for any of the available data cut-off dates. For this study, the dossier includes only information on the number of deaths in the study arms, again only for the total population. Hence, for the outcome of overall survival, sufficient data for an indirect comparison are not available.

Consequently, there is no hint of added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Relapse

The outcome of relapse is a combined outcome that comprises the following components: local, regional, and distant relapse or metastases and death due to any cause. The outcome of RFS, which was supplied as supplementary information, is comprised of the same components. In study 238, the occurrence of new primary melanoma was considered a relapse as well.

The components used for the combined outcome clearly differ in their relevance to patients. Therefore, information on the individual components is necessary to interpret the results of the combined outcome. However, only results of the combined outcome, but not on the individual components, were available for the assessment. In the absence of this information on the subpopulation used, the results on this outcome cannot be interpreted.

In addition, based on the information available in the study documents, it is assumed that the follow-up durations at the data cut-off dates used for studies 238 and 029 differ in a relevant way. No exact information is available on the actual follow-up periods. However, the data cut-offs are based on a planned minimum study duration for patients of 24 months (study 238) versus 53 months (study 029). Due to this large difference, the follow-up durations at the data cut-offs used for the outcome of relapse are too dissimilar to permit indirect comparison. Therefore, for study 029, the earlier data cut-off on 17 December 2013, with a median follow-

up duration of 2.7 years, would be relevant. The follow-up duration at this data cut-off date is likely to be closer to the follow-up duration in study 238.

This results in no hint of added benefit of nivolumab in comparison with placebo; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-C30)

For the outcome of symptoms, as measured by the time to deterioration in the respective symptom scales of the EORTC QLC-C30 by ≥ 10 points, no usable data are available. This is due to differences in measurement strategies for surveying the outcome in studies 238 and 029.

This results in no hint of added benefit of nivolumab in comparison with placebo; an added benefit is therefore not proven.

Health-related quality of life

For the outcome of health-related quality of life, as measured by the time to deterioration in the respective symptom scales of the EORTC QLC-C30 by ≥ 10 points, no usable data are available. The rationale is the same is as that for the outcome of symptoms.

This results in no hint of added benefit of nivolumab in comparison with placebo; an added benefit is therefore not proven.

Adverse events

In both studies, 238 and 029, the outcomes on adverse events, except for discontinuation due to AEs, have a high risk of bias; therefore, no hint of greater or lesser harm of nivolumab in comparison with placebo is derived for these outcomes in the indirect comparison. Greater or lesser harm is therefore not proven.

Consequently, there is no hint of greater or lesser harm of nivolumab in comparison with placebo; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

Unlike the other AE outcomes, the outcome of discontinuation due to AEs is free of potential informative censoring. However, the available data are not plausible and cannot be used to assess the added benefit of nivolumab.

Consequently, there is no hint of greater or lesser harm of nivolumab in comparison with placebo; greater or lesser harm is therefore not proven.

Specific AEs

No usable data are available on specific AE outcomes, particularly including immune-mediated AEs.

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 are assessed as follows:

The adjusted indirect comparison presented in the dossier is generally suitable for assessing the added benefit of nivolumab in comparison with watchful waiting. However, sufficient usable data are not available for any of the examined patient-relevant outcomes. For overall survival, data are available for only one of the two studies of the indirect comparison, and they are available not for the examined subpopulation, but only for the total population. An indirect comparison of nivolumab with watchful waiting is therefore not possible. For the combined outcome of relapse, data are available only on the overall result, but not on the individual components, which are also needed. Regarding outcomes in the adverse events category, no added benefit can be derived for SAEs and severe AEs (CTCAE grade ≥ 3) from the indirect comparison due to the high outcome-specific risk of bias. For other outcomes from the category of adverse events, no usable data were available.

In summary, an added benefit of nivolumab in comparison with the ACT of watchful waiting in adult patients with melanoma with lymph node involvement or metastasis after complete resection is not proven.

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

Table 3: Nivolumab – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of melanoma with lymph node involvement or metastasis following complete resection in adults	Watchful waiting	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

[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 [3,4].

Note:

An addendum (A19-01) to dossier assessment A18-53 has been published.

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. Leitlinienprogramm Onkologie der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutschen Krebsgesellschaft, Deutschen Krebshilfe. S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms: Version 3.1; AWMF-Register-Nummer 032/024OL [online]. [Accessed: 9 August 2018]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Melanom/Melanom_Version_3/LL_Melanom_Langversion_3.1.pdf.

2. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI 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.

3. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

4. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-53-nivolumab-melanoma-benefit-assessment-according-to-35a-social-code-book-v.10486.html.