IQWiG Reports – Commission No. A18-40

Nivolumab (melanoma) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Nivolumab (Melanom) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 13 September 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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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.

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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 15/06/2018.

Research question

The aim of this report is to assess the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as nivolumab + ipilimumab) in comparison with the appropriate comparator therapy (ACT) in adult, treatment-naïve patients with advanced (unresectable or metastatic) melanoma with rapidly accelerated fibrosarcoma – isoform B wild-type (BRAF-V600-wt) tumour.

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 + ipilimumab

Indication	**ACT[a]**
Treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma with a BRAF-V600-wt tumour.	**Nivolumab** or pembrolizumab
a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. BRAF: Rapidly Accelerated Fibrosarcoma – isoform B (serine/threonine protein kinase B-Raf); BRAF-V600-wt: BRAF-V600-wildtype; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT for the relevant subpopulation and selected nivolumab from the presented options.

The assessment is based on the comparison of the combination therapy (nivolumab + ipilimumab) with nivolumab monotherapy in treatment-naïve patients with advanced (unresectable or metastatic) melanoma with a BRAF-V600-wt tumour. In this constellation, no conclusions can be drawn on the drug nivolumab alone, particularly since the combination therapy and monotherapy used different dosages in the induction phase.

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

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

Results

For the benefit assessment, 2 relevant studies, CA209-067 and CA209-038 (study parts 3 and 4), were available. CA209-067 already served as the basis of the previous assessment of nivolumab + ipilimumab in comparison with nivolumab. The additional data presented by the company on CA209-170 are not suitable for this benefit assessment.

Study pool and patient characteristics

CA209-067 study

CA209-067 is a randomized, double-blind, actively controlled, 3-arm, parallel-group study. For this assessment, the study's nivolumab + ipilimumab arm and nivolumab arm are relevant. The study included patients with unresectable or metastatic melanoma (stage III or IV as classified by the American Joint Committee on Cancer [AJCC]), known BRAF-V600 mutation status, and good general condition (Eastern Cooperative Oncology Performance Status [ECOG-PS] grade 0 or 1).

Overall, 316 patients were randomly allocated to the nivolumab arm and 314 to the nivolumab + ipilimumab arm of the study. Randomization was conducted in a stratified manner according to the factors programmed death-ligand 1 (PD-L1) status (positive or negative, cannot be determined), BRAF-V600 mutation status as well as metastatic stage (M0, M1a, M1b or M1c).

In the 12-week induction phase, patients in the intervention group received1 mg/kg body weight nivolumab (intravenously [i.v.] for 60 minutes) in combination with 3 mg/kg body weight ipilimumab (i.v. for 90 minutes) every 3 weeks. The comparator group received 3 mg/kg body weight nivolumab (i.v. for 60 minutes) every 2 weeks. In the maintenance phase, both groups received 3 mg/kg body weight nivolumab (i.v. for 60 minutes) every 2 weeks.

Patients were treated until progression or the occurrence of unacceptable persistent toxicities. Under certain conditions, continued patient treatment beyond progression was allowed upon the investigator's discretion. In case of progression and at the end of study treatment, patients were unblinded.

Primary outcomes of the study are progression-free survival (PFS) and overall survival. Secondary outcomes comprise symptoms, health-related quality of life, and adverse events.

For the outcome overall survival, this benefit assessment is based on the results of the data cut-off date of 05/08/2018. For all other outcomes, the results at the data cut-off date 24/05/2017 were used.

CA209-038 study

CA209-038 is an open-label, actively controlled, phase I study which investigates different dosage regimens of nivolumab, including in combination with ipilimumab, in 4 different study parts. The study aims to evaluate the pharmacodynamic changes of treatment on various biomarkers. For this benefit assessment, only the randomized study parts 3 and 4 are relevant,

which each compare the combination of ipilimumab and nivolumab with nivolumab monotherapy.

CA209-038 included patients (≥16 years of age) with unresectable or metastatic melanoma, known BRAF-V600 status, and ECOG-PS ≤ 1.

For part 3 of the study, a total of 26 patients were randomly allocated to the nivolumab + ipilimumab arm and 12 to the nivolumab + ipilimumab arm, using a 2:1 ratio. For part 4 of the study, 11 patients were randomized to the combination arm and 11 to the nivolumab arm, using a 1:1 ratio.

Patient treatment was largely the same as in CA209-067.

Patients were treated until progression or the occurrence of unacceptable toxicities. Upon the discretion of the investigator, treatment continuation after progression was possible. There were no restrictions concerning follow-up therapy after progression.

The study's primary outcome measure is the effect on various biomarkers. Patient-relevant secondary outcomes are overall survival as well as adverse events. Outcomes on symptoms or health-related quality of life were not surveyed.

This assessment is based on the planned final analysis of PFS as of the data cut-off date of 08/11/2017.

Subpopulation relevant for the research question

The relevant subpopulation for answering this research question is the subpopulation of treatment-naïve patients with BRAF-V600-wt tumour in CA209-067 and CA209-038. For both studies, the company presented analyses on the total population and the subpopulation of patients with BRAF-V600-wt tumour. While CA209-067 included only treatment-naïve patients, CA209-038 included both treatment-naïve and pretreated patients. However, patients with prior therapy made up <20% of the relevant subpopulation in each of the two relevant parts of CA209-038.

In CA209-067, the relevant subpopulation used for this benefit assessment is N = 213 in the nivolumab + ipilimumab arm and N = 216 in the nivolumab arm. The relevant subpopulation of CA209-038 comprises N = 13 (study part 3) and N = 3 (study part 4) or N = 7 (study part 3) and N = 7 (study part 4) patients, respectively.

Risk of bias

The risk of bias on the study level is assessed as low for both studies. On the outcome level, the risk of bias is rated as high for all outcomes except for overall survival and discontinuation due to adverse events (AEs) in CA208-067. No usable data are available for specific AE outcomes – including immune-mediated AEs.

The results of CA209-067 and CA209-038 on the outcome overall survival and the outcomes on adverse events were combined in a meta-analysis, and the results of the meta-analysis were used to draw a conclusion on added benefit.

The available data allow for no more than indications (for example on added benefit) to be inferred in terms of the outcomes overall survival, SAEs, severe AEs (CTCAE Grade ≥ 3), and discontinuation due to AEs, which were investigated in the meta-analysis. For the outcomes on symptoms, health status, and health-related quality of life (which were investigated only in CA208-067), given the high risk of bias, no more than hints can be inferred.

Mortality

For the outcome overall survival, the meta-analysis of the event time analyses of CA209-067 (data cut-off for 48 months) and CA209-038 (study parts 3 and 4) was used. In the meta-analysis, no statistically significant difference between treatment groups was found. Hence there was no hint of an added benefit of nivolumab + ipilimumab in comparison with nivolumab; an added benefit is therefore not proven.

Morbidity

Symptoms (measured using the symptoms scales of the European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core-30 [QLQ-C30])

For the outcome regarding symptoms, as measured by the time to confirmed deterioration of the respective symptom scales of the EORTC QLC-C30, only data from CA209-067 are available. For the scales **fatigue, nausea and vomiting, pain, dyspnoea, insomnia, impaired appetite,** and **diarrhoea**, no statistically significant difference between treatment groups was found. For each of these scales, there is no hint of an added benefit of nivolumab + ipilimumab in comparison with nivolumab; an added benefit is therefore not proven for these symptom-related outcomes.

For the **constipation** scale, a statistically significant difference to the disadvantage of nivolumab + ipilimumab was found. The extent is no more than marginal. For the outcome constipation, there is consequently no hint of an added benefit of nivolumab + ipilimumab in comparison with nivolumab. An added benefit is therefore not proven.

Health status (measured using the European Quality of Life Questionnaire 5 Dimensions [EQ-5D] Visual Analogue Scale [VAS])

For health status as measured using the EQ-5D VAS, only data from CA209-067 are available. For this outcome, the mean difference (MD) is used from a mixed model for repeated measures (MMRM). A statistically significant difference was found to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab. The 95% CI of the standardized mean difference (Hedges' g) is, however, not fully outside the irrelevance range of −0.2 to 0.2. Hence, the effect cannot be rated as relevant. Consequently, there is no hint of added benefit of nivolumab + ipilimumab in comparison with nivolumab; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (measured using the EORTC QLQ-C30 functional scales)

For the outcome health-related quality of life, measured using the time to confirmed deterioration of the respective EORTC QLQ-C30 functional scales, only data from CA209-067 are available. For the scales **global health status, physical functioning, role functioning, emotional functioning,** and **social functioning**, no statistically significant difference between treatment groups was found. Consequently, for each of these scales, there is no hint of added benefit of nivolumab + ipilimumab in comparison with nivolumab; an added benefit is therefore not proven for any of these scales.

For the **cognitive function** scale, a statistically significant difference to the disadvantage of nivolumab + ipilimumab was found. This results in a hint of lesser benefit of nivolumab + ipilimumab in comparison with nivolumab.

Adverse events

Serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3–4), and discontinuation due to AEs

For each of the outcomes SAEs, severe AEs (CTCAE Grade ≥ 3), and discontinuation due to AEs, the meta-analysis shows statistically significant differences to the disadvantage of nivolumab + ipilimumab in comparison with nivolumab. For each of these outcomes, there is consequently an indication of greater harm of nivolumab + ipilimumab in comparison with nivolumab.

Immune-mediated AEs

For the outcome immune-mediated AEs, no usable data were available.

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

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

The overall analysis shows exclusively negative effects from the outcome categories health-related quality of life and adverse events.

[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].

Consequently, for treatment-naïve patients with advanced (unresectable or metastatic) melanoma and BRAF-V600-wt tumour, there is an indication of lesser benefit of nivolumab + ipilimumab in comparison with nivolumab.

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

Table 3: Nivolumab + ipilimumab – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment-naïve adult patients with advanced (unresectable or metastatic) melanoma with a BRAF-V600-wt tumour[b]	**Nivolumab** or pembrolizumab	Indication of lesser benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b: The studies on which the benefit assessment is based included patients with an ECOG-PS of 0 or 1. It is unclear whether the observed effects can be extrapolated to patients with ECOG-PS ≥ 2.
BRAF: Rapidly Accelerated Fibrosarcoma – isoform B (serine/threonine protein kinase B-Raf); BRAF-V600-wt: BRAF-V600-wildtype; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; 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.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 04 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. 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/a18-40-nivolumab-melanoma-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.10101.html.