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Ipilimumab (melanoma) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Ipilimumab (Melanom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 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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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 ipilimumab. 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 June 2018.

Research question

The aim of this report is to assess the added benefit of ipilimumab in combination with nivolumab (hereinafter ipilimumab + nivolumab) in comparison with the appropriate comparator therapy (ACT) in adults with advanced unresectable or metastatic melanoma.

For this assessment, there are 3 resulting research questions, for which the G-BA specified the ACTs presented in Table 2.

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

Research question	Indication	ACT[a]
	Adults with advanced (unresectable or metastatic) melanoma	
1	Treatment-naïve adults with a BRAF-V600-mutated tumour	Vemurafenib + cobimetinib or dabrafenib + trametinib
2	Treatment-naïve adults with a BRAF-V600-wt tumour	**Nivolumab** or pembrolizumab
3	Pre-treated adults	Individualized therapy upon the treating physician's discretion based on the respective prior therapy and in consideration of the approval status[b]

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: Except dacarbazine and lomustine.
ACT: appropriate comparator therapy; BRAF: Rapidly Accelerated Fibrosarcoma – isoform B (serine/threonine protein kinase B-Raf); BRAF-V600-wt: BRAF-V600-wild type; G-BA: Federal Joint Committee

In deviation from the G-BA's specifications, the company chose nivolumab as the ACT for all patients with the therapeutic indication (adult patients with advanced [unresectable or metastatic] melanoma), regardless of rapidly accelerated fibrosarcoma isoform B (serine/threonine protein kinase B-Raf [BRAF]) mutation status and prior treatment. Despite

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

making this choice, the company additionally addressed the research questions which correspond to the G-BA's specifications regarding indication and ACT.

Using the ACTs specified by the G-BA for the various research questions, this 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 any added benefit.

Results regarding research question 1: treatment-naïve adults with BRAF-V600-mutated tumour

For research question 1 (treatment-naïve adults with BRAF-V600 mutation), no suitable directly comparative studies were identified. The company presented, as supplementary data, the results of a matching-adjusted indirect comparison (MAIC) for the comparison of ipilimumab + nivolumab with vemurafenib + cobimetinib and dabrafenib + trametinib.

The data provided by the company are not suitable for deriving an added benefit of ipilimumab + nivolumab. Since the company did not carry out a systematic search of studies on the ACT, it is entirely unclear to what extent the data underlying the MAIC are complete. Further, despite the similarities in name, a MAIC does not represent an adjusted indirect comparison in accordance with dossier templates. Based on a non-adjusted comparison of individual arms from different studies, conclusions on added benefit can, at best, be drawn if the effects are very large (dramatic effects). However, no such effect was found for any of the outcomes investigated by the company (overall survival, progression-free survival [PFS], and objective response rate [ORR]). Furthermore, the comparison presented by the company does not take into account any outcomes on adverse events and therefore does not provide a basis for weighing the benefit and harm of the ipilimumab + nivolumab combination in comparison with the ACT. The supplementary comparison presented by the company is therefore not suitable for deriving an added benefit.

Results on research question 2: treatment-naïve adults with BRAF-V600-wt tumour

For this research question, the 2 relevant studies CA209-067 and CA209-038 (study parts 3 and 4) are available. The supplementary data from study CA209-170, which were presented by the company, are not suitable for this research question.

Study pool and patient characteristics

Study CA209-067

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

Overall, 316 patients were randomly allocated to the study's nivolumab arm and 314 to the ipilimumab + nivolumab arm. Randomization was conducted in a stratified manner according to the factors: programmed death ligand 1 (PDL1) status (positive, negative, not assessable), BRAF-V600 mutation status, as well as metastasis classification (M0, M1a, M1b, M1c).

During the 12-week induction phase, patients in the intervention group received 3 mg/kg body weight ipilimumab (intravenous [i.v.] for 90 minutes) in combination with 1 mg/kg body weight nivolumab (i.v. for 60 minutes) every 3 weeks. The comparator group received 3 mg/kg body weight nivolumab (i.v. for 60 minutes) every 2 weeks. During 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.

The primary outcomes of the study are PFS as well as overall survival. Secondary outcomes comprise symptoms, health-related quality of life, and adverse events.

For the outcome of overall survival, this benefit assessment is based on the results of the data cut-off as per 5 August 2018. For all other outcomes, results of the data cut-off as per 24 May 2017 were used.

Study CA209-038

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 study's randomized 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, 26 patients were randomized to the ipilimumab + nivolumab arm and 12 to the nivolumab 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 essentially the same as in CA209-067.

Patients were treated until progression or the occurrence of unacceptable toxicities. Upon the investigator's discretion, 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 prescheduled final analysis of PFS as per the data cut-off of 8 November 2017.

Subpopulation relevant for the research question

The relevant subpopulation for this research question is 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 both relevant parts of CA209-038.

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

Risk of bias

The risk of bias at study level is assessed as low for both studies. At outcome level, the risk of bias is rated as high for all outcomes except for the outcomes overall survival and discontinuation due to adverse events (AEs) of the study 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 metaanalysis, and the results of the metaanalysis were used to draw a conclusion on added benefit.

On the basis of the available data, at most indications, for example of an added benefit, can be inferred for the outcomes investigated in the metaanalysis: overall survival, SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs. 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 of overall survival, the metaanalysis of the event time analyses for CA209-067 (data cut-off at 48 months) and CA209-038 (study parts 3 and 4) was used. In the metaanalysis, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of ipilimumab + nivolumab in comparison with nivolumab; an added benefit is therefore not proven.

Morbidity

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

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

For the **constipation** scale, a statistically significant difference to the disadvantage of ipilimumab + nivolumab was found. The extent is marginal at most. For the outcome of constipation, this does not result in a hint of added benefit of ipilimumab + nivolumab in comparison with nivolumab. An added benefit is therefore not proven.

Health status (as measured by the European Quality of Life Questionnaire 5 Dimensions [EQ-5D] visual analogue scale [VAS])

For health status, as measured by EQ-5D VAS, data are available only from CA209-067. For this outcome, the mean difference (MD) from a Mixed-effect Model Repeated-Measures (MMRM) analysis was used. A statistically significant difference was found to the disadvantage of ipilimumab + nivolumab 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, this does not result in a hint of added benefit of ipilimumab + nivolumab in comparison with nivolumab; an added benefit is therefore not proven.

Health-related quality of life

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

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

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

Adverse events

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

For the outcomes SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs, the metaanalysis shows statistically significant differences to the disadvantage of ipilimumab + nivolumab in comparison with nivolumab. For each of these outcomes, this results in an indication of greater harm of ipilimumab + nivolumab in comparison with nivolumab.

Immune-mediated AEs

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

Results for research question 3: pre-treated adults

For research question 3, no data are available for the comparison of ipilimumab + nivolumab with the ACT.

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 drugs ipilimumab + nivolumab in comparison with the ACT is assessed as follows:

No usable data were available for research questions 1 and 3. An added benefit of ipilimumab + nivolumab in comparison with the ACT is therefore not proven for patients with advanced (unresectable or metastatic) melanoma and BRAF-V600-mutated tumour or for pre-treated patients with advanced (unresectable or metastatic) melanoma.

For research question 2, the overall analysis shows exclusively negative effects from the outcome categories of health-related quality of life and adverse events. Consequently, for treatment-naïve patients with advanced (unresectable or metastatic) melanoma and BRAF-V600-wt tumour, there is an indication of lesser benefit of ipilimumab + nivolumab in comparison with nivolumab.

Table 3 presents a summary of the probability and extent of the added benefit of ipilimumab + 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: Ipilimumab + Nivolumab – probability and extent of added benefit

Research question	**Indication**	**ACT**[a]	**Probability and extent of added benefit**
	Adults with advanced (unresectable or metastatic) melanoma		
1	Treatment-naïve adults with a BRAF-V600-mutated tumour[b]	Vemurafenib + cobimetinib or dabrafenib + trametinib	Added benefit not proven
2	Treatment-naïve adults with a BRAF-V600-wt tumour	**Nivolumab** or pembrolizumab	Indication of lesser benefit
3	Pre-treated adults	Individualized therapy upon the discretion of the treating physician depending on the respective prior therapy and taking into account the approval status[c]	Added benefit not proven

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 ECOGPS of 0 or 1. It is unclear whether the observed effects are transferable to patients with ECOG-PS ≥ 2.
c: Except dacarbazine and lomustine.
ACT: appropriate comparator therapy; BRAF: Rapidly Accelerated Fibrosarcoma – isoform B (serine/threonine protein kinase B-Raf); BRAF-V600-wt: BRAF-V600-wild type; 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.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-44-ipilimumab-melanoma-benefit-assessment-according-to-35a-social-code-book-v.10222.html.