IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ipilimumab (melanoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ipilimumab (Melanom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 9 May 2018). Please note: This translation 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
TPC	treatment of physician's choice

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 February 2018.

Research question

The aim of the present report was the assessment of the added benefit of ipilimumab in comparison with treatment of physician's choice (TPC) as appropriate comparator therapy (ACT) in the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

Concurring with the G-BA's specification, the company cited TPC as ACT. According to the company's subsequent explanation, all drugs approved and recommended for the treatment of advanced melanoma in adults are also used in the treatment of adolescents and are therefore an option as ACT. According to the company, the ACT includes the following drugs and drug combinations: dabrafenib, nivolumab, pembrolizumab, talimogene laherparepvec, trametinib, vemurafenib, as well as nivolumab + ipilimumab, cobimetinib + vemurafenib, and trametinib + dabrafenib.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

No direct comparative data on ipilimumab versus the ACT were available for the adolescent target population.

For the derivation of the added benefit, the company therefore tried to transfer the results of an ipilimumab study in adults (study CA184-169) to the target population of adolescents. It used the single-arm ipilimumab study CA184-178 for adolescents.

Study CA184-169 was a randomized, double-blind controlled study on the comparison of 2 different ipilimumab dosages (3 mg/kg body weight and 10 mg/kg body weight). The study included adults with pretreated or untreated advanced (unresectable or metastatic) stage III or stage IV melanoma. Study CA184-178 was a single-arm, open-label study with ipilimumab in adolescents (≥ 12 to < 18 years) with pretreated or untreated advanced (unresectable or metastatic) stage III or stage IV melanoma. A total of 12 patients between 12 and 16 years of age were treated with ipilimumab; 8 of them received ipilimumab at a dosage of 10 mg/kg body

weight, and 4 of them were treated with 3 mg/kg body weight, which is the dosage approved in Germany.

The company's approach to transfer study results from adults to adolescents is comprehensible as no comparative data for adolescents exist. The concrete approach adopted by the company was unsuitable, however. From the data presented by the company, an added benefit of ipilimumab versus the ACT for adolescents cannot be derived. This is justified below.

- To be able to transfer the added benefit to adolescents, studies in adults would have to produce comparative data between ipilimumab (3 mg/kg body weight) and the ACT for adolescents (TPC) that show an added benefit of ipilimumab for adults. The company interpreted the ACT to include all drugs approved and recommended for the treatment of advanced melanoma in adults, e.g. dabrafenib, nivolumab or pembrolizumab. However, the company presented no data for ipilimumab in comparison with these drugs in adults, but used only the CA184-169 study on the comparison of 2 different ipilimumab dosages (3 mg/kg body weight versus 10 mg/kg body weight) for the transfer of the results. Due to the missing comparative data versus the ACT, no added benefit of ipilimumab for adult patients can be derived on the basis of the CA184-169 study. Hence, subsequent transfer of the evidence presented from the CA184-169 study for the derivation of an added benefit in adolescents is also not possible.
- From the company's point of view, the CA184-169 study already constituted an adequate adult study for the transfer of study results, which is why it did not search for further potentially relevant studies with adults. This approach of the company was inadequate. Transfer of study results from adults to adolescents also requires complete processing of the available evidence. Restriction to one adult study is not comprehensible in particular as the European Medicines Agency (EMA) also used further studies for transfer of the results in the approval procedure. Since the company also interpreted the ACT in such a way that all drugs approved and recommended for the treatment of advanced melanoma in adults are also an option as ACT, a search for corresponding adult studies of direct comparison would have been logical. Corresponding studies are known also from prior benefit assessment procedures. The KEYNOTE 006 study on the comparison of pembrolizumab 10 mg/kg body weight versus ipilimumab 3 mg/kg body weight (see dossier assessment A15-33) or the CA209-067 study on the comparison of nivolumab 3 mg/kg body weight versus ipilimumab 3 mg/kg body weight are examples (see dossier assessment A15-27 and its addendum A15-50). It is not comprehensible why the company did not consider these (and possibly further) adult studies, which investigated a direct comparison between ipilimumab and the comparator therapies defined by the company in adults, for transfer of the study results.

In summary, the company's implementation of the transfer of study results from adults to adolescents was unsuitable for the derivation of the added benefit. The adult study CA184-169 presented by the company provided no results on the comparison of ipilimumab versus the ACT

or the treatment options understood by the company to be part of the ACT. In addition, the company did not consider further adult studies that compared ipilimumab with the comparator therapy considered suitable by the company (e.g. pembrolizumab) for the transfer of study results.

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 ipilimumab compared with the ACT is assessed as follows:

Table 2 presents a summary of the probability and extent of the added benefit of ipilimumab.

Table 2: Ipilimumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adolescents (between ≥ 12 and < 18 years of age) with advanced (unresectable or metastatic) melanoma	TPC	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TPC: treatment of physician's choice		

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 [1,2].

2.2 Research question

The aim of the present report was the assessment of the added benefit of ipilimumab in comparison with TPC as ACT in the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older.

Table 3 shows the therapeutic indication to be assessed and the corresponding ACT specified by the G-BA.

Table 3: Research question of the benefit assessment of ipilimumab

Therapeutic indication	**ACT[a]**
Adolescents (between ≥ 12 and < 18 years of age) with advanced (unresectable or metastatic) melanoma	TPC
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TPC: treatment of physician's choice	

Concurring with the G-BA's specification, the company cited TPC as ACT. According to the company's subsequent explanation, all drugs approved and recommended for the treatment of advanced melanoma in adults are also used in the treatment of adolescents and are therefore an option as ACT. According to the company, the ACT includes the following drugs and drug combinations: dabrafenib, nivolumab, pembrolizumab, talimogene laherparepvec, trametinib, vemurafenib, as well as nivolumab + ipilimumab, cobimetinib + vemurafenib, and trametinib + dabrafenib (see also Section 2.7.1 of the full dossier assessment).

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on ipilimumab (status: 3 January 2018)
- bibliographical literature search on ipilimumab (last search on 3 January 2018)
- search in trial registries for studies on ipilimumab (last search on 3 January 2018)

To check the completeness of the study pool:

- search in trial registries for studies on ipilimumab (last search on 22 February 2018)

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) with ipilimumab in the adolescent target population

(adolescents between ≥ 12 and < 18 years of age). Since no directly comparative data for the adolescent target population were available, the company, with reference to the EU regulation for children [3] and the EMA reflection paper on the extrapolation of study data on children [4], considered the possibility of transferring study results from adults to adolescents. For this purpose, the company tried to transfer the results of an ipilimumab study in adults (study CA184-169 [5]) to the target population of adolescents. It used the single-arm ipilimumab study CA184-178 for adolescents [6].

The company's approach to transfer study results from adults to adolescents is comprehensible as no comparative data for adolescents exist. The concrete approach adopted by the company was unsuitable, however. From the data presented by the company, an added benefit of ipilimumab versus the ACT for adolescents cannot be derived. This is justified below.

Ipilimumab study in adolescents (CA184-178)

Study CA184178 was a single-arm, open-label study with ipilimumab in adolescents (≥ 12 to < 18 years) with pretreated or untreated advanced (unresectable or metastatic) stage III or stage IV melanoma. A total of 12 patients between 12 and 16 years of age were treated with ipilimumab; 8 of them received ipilimumab at a dosage of 10 mg/kg body weight, and 4 of them were treated with 3 mg/kg body weight, which is the dosage approved in Germany [7][4]. Intravenous infusion was administered every 3 weeks for up to 4 cycles. Treatment with ipilimumab was continued until disease progression confirmed by the investigator, unacceptable toxicity, or discontinuation for other reasons. Following a recommendation by the Data Monitoring Committee, the study was ended prematurely in June 2016 because of recruitment problems due to the rareness of the disease in the investigated patient population and further available alternative treatment options (e.g. programmed cell death ligand 1 [PD-L1]-inhibiting antibodies) [8].

Approach of the company to transfer study results of adult patients to the adolescent target population

Besides the single-arm study CA184-178 in adolescents, the company used the adult study CA184-169 for the transfer of results of adult patients to the adolescent target population. Study CA184-169 was a randomized, double-blind controlled study on the comparison of 2 different ipilimumab dosages (3 mg/kg body weight and 10 mg/kg body weight). The study included adults with pretreated or untreated advanced (unresectable or metastatic) stage III or stage IV melanoma. The 727 patients were randomly allocated in a 1:1 ratio, 362 patients to the arm with the low, approved ipilimumab dosage (3 mg/kg body weight), and 365 patients to the arm with the high ipilimumab dosage (10 mg/kg body weight).

[4] Both groups were not planned a priori for comparison, but initially only the intervention with 10 mg/kg body weight ipilimumab was planned. With Amendment 04 in May 2014, the dosage was adjusted to the adult dosage of 3 mg/kg body weight, which was newly approved at this time point. The adolescents who were already being treated with 10 mg/kg body weight continued treatment with this dosage.

The company described that the results of the study in adults can be transferred to adolescents as there is adequate comparability between the initial population (adults) and the target population (adolescents) regarding mechanism of action, pharmacokinetics, disease manifestation, and efficacy and safety. The company also referred to the fact that the EMA also used a so-called evidence transfer [8].

Irrespective of whether or not the preconditions formulated by the company for a transfer of study results were sufficient and also fulfilled, the concrete approach used by the company in the present case was unsuitable to derive conclusions on the added benefit of ipilimumab in adolescents for the following reasons:

- To be able to transfer the added benefit to adolescents, studies in adults would have to produce comparative data between ipilimumab (3 mg/kg body weight) and the ACT for adolescents (TPC) that show an added benefit of ipilimumab for adults. The company interpreted the ACT to include all drugs approved and recommended for the treatment of advanced melanoma in adults, e.g. dabrafenib, nivolumab or pembrolizumab (see also Section 2.7.1 of the full dossier assessment). However, the company presented no data for ipilimumab in comparison with these drugs in adults, but used only the CA184-169 study on the comparison of 2 different ipilimumab dosages (3 mg/kg body weight versus 10 mg/kg body weight) for the transfer of the results. Due to the missing comparative data versus the ACT, no added benefit of ipilimumab for adult patients can be derived on the basis of the CA184-169 study. Hence, subsequent transfer of the evidence presented from the CA184-169 study for the derivation of an added benefit in adolescents is also not possible.
- From the company's point of view, the CA184-169 study already constituted an adequate adult study for the transfer of study results, which is why it did not search for further potentially relevant studies with adults (see also Section 2.7.2.3.2 of the full dossier assessment). This approach of the company was inadequate. Transfer of study results from adults to adolescents also requires complete processing of the available evidence. Restriction to one adult study is not comprehensible in particular as the EMA also used further studies for transfer of the results in the approval procedure ([8], see also Section 2.7.2.3.2 of the full dossier assessment). Since the company also interpreted the ACT in such a way that all drugs approved and recommended for the treatment of advanced melanoma in adults are also an option as ACT, a search for corresponding adult studies of direct comparison would have been logical. Corresponding studies are known also from prior benefit assessment procedures. The KEYNOTE 006 study on the comparison of pembrolizumab 10 mg/kg body weight versus ipilimumab 3 mg/kg body weight (see dossier assessment A15-33 [9]) or the CA209-067 study on the comparison of nivolumab 3 mg/kg body weight versus ipilimumab 3 mg/kg body weight are examples (see dossier assessment A15-27 [10] and its addendum A15-50 [11]). It is not comprehensible why the company did not consider these (and possibly further) adult studies, which investigated a direct comparison between ipilimumab and the comparator therapies defined by the company in adults, for transfer of the study results (see also Section 2.7.1 of the full dossier assessment).

In summary, the company's implementation of the transfer of study results from adults to adolescents was unsuitable for the derivation of the added benefit. The adult study CA184-169 presented by the company provided no results on the comparison of ipilimumab versus the ACT or the treatment options understood by the company to be part of the ACT. In addition, the company did not consider further adult studies that compared ipilimumab with the comparator therapy considered suitable by the company (e.g. pembrolizumab) for the transfer of study results.

2.4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of ipilimumab versus the ACT. This resulted in no hint of an added benefit of ipilimumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of ipilimumab in comparison with the ACT is presented in Table 4.

Table 4: Ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adolescents (between ≥ 12 and < 18 years of age) with advanced (unresectable or metastatic) melanoma	TPC	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TPC: treatment of physician's choice		

An added benefit of ipilimumab in adolescents (between ≥ 12 and < 18 years of age) is not proven because the company presented no suitable data.

This deviates from the approach of the company, which derived a hint of a non-quantifiable added benefit for ipilimumab in adolescents.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no suitable data for the benefit assessment.

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.

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