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Pembrolizumab (melanoma, adjuvant) –

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

Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Pembrolizumab (Melanom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 6 December 2022). 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital

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.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Tobias Depke
- Christopher Kunigkeit
- Ulrike Lampert
- Katrin Nink
- Sabine Ostlender
- Min Ripoll
- Christoph Schürmann
- Ulrike Seay

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) 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 pembrolizumab. 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 25 July 2022.

Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) as adjuvant treatment in adults and adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection as well as in adolescents aged 12 years and older with stage III melanoma who have undergone complete resection.

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication	ACT[a]
1	Adjuvant treatment of adults with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]
2	Adjuvant treatment of adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]
3	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection	Treatment of physician's choice[c]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the drug interferon alfa might become unavailable in the foreseeable future, which in turn would require an adjustment of the ACT. Where interferon alfa is available, a single-comparator study is inadequate.
c. According to the G-BA, the following therapies, which are not approved for children or adolescents, are deemed suitable comparators in the context of clinical trials: dabrafenib in combination with trametinib (only for patients with BRAF-V600 mutation-positive stage III melanoma who have undergone complete resection); nivolumab. The choice of comparator must be justified in the dossier.

ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT for the adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection (research question 3). For the adjuvant treatment of adults as well as adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection

(research questions 1 and 2), the company departed from the specification by the G-BA by listing watchful waiting as the only ACT. The company justifies this choice by the drugs interferon alfa-2a and interferon alfa-2b having been taken off the market. The company concludes that interferon alfa is no longer available in practice, making watchful waiting the only possible ACT.

The availability of pharmaceuticals containing the drug interferon alfa in the German healthcare system cannot be conclusively determined in the context of this dossier assessment.

This benefit assessment used the respective ACT specified by the G-BA to answer each of its research questions. The placebo-controlled KEYNOTE 716 study, which was submitted by the company for answering research questions 1 and 2, is discussed as supplementary information in the appendix of the full dossier assessment.

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

Research question 1: Adjuvant treatment of adults with stage IIB or IIC melanoma who have undergone complete resection

Results

For its assessment, the company used the randomized controlled trial (RCT) KEYNOTE 716 comparing pembrolizumab versus placebo. The study enrolled patients aged 12 years and older who had undergone complete resection of a stage IIB or IIC melanoma (American Joint Committee on Cancer classification, version 8) within 12 weeks prior to randomization and who had received no further treatment of the melanoma. In the study's placebo arm, interferon alfa was not available. By failing to implement the ACT specified by the G-BA, this study is unsuitable for the benefit assessment of pembrolizumab.

The appendix of the full dossier assessment contains a supplementary discussion of the KEYNOTE 716 study and its results.

Results on added benefit

Because no relevant study is available for answering the present research question, there is no hint of added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Adjuvant treatment of adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection

Results

Rather than analysing adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection as a separate subpopulation, the company combined these patients with adults with stage IIB or IIC melanoma who have undergone complete resection and used the KEYNOTE 716 study to answer this research question as well. This study is

unsuitable for the benefit assessment of pembrolizumab because it failed to implement the ACT specified by the G-BA (see research question 1). Furthermore, only 1 person under the age of 18 years was enrolled in each treatment arm.

Hence, no relevant data are available for adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection.

Results on added benefit

Because no relevant study is available for answering the present research question, there is no hint of added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection

Results

The company did not submit any suitable data for assessing the added benefit of pembrolizumab in comparison with the ACT for the adjuvant treatment of adolescents 12 years and older with stage III melanoma who have undergone complete resection.

Results on added benefit

Because no relevant study is available for answering the present research question, there is no hint of added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of the probability and extent of added benefit of pembrolizumab.

[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: Pembrolizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment of adults with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]	Added benefit not proven
2	Adjuvant treatment of adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]	Added benefit not proven
3	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection	Treatment of physician's choice[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the drug interferon alfa might become unavailable in the foreseeable future, which in turn would require an adjustment of the ACT. Where interferon alfa is available, a single-comparator study is inadequate.
c. According to the G-BA, the following therapies, which are not approved for children or adolescents, are deemed suitable comparators in the context of clinical trials: dabrafenib in combination with trametinib (only for patients with BRAF-V600 mutation-positive stage III melanoma who have undergone complete resection); nivolumab. The choice of comparator must be justified in the dossier.

ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; G-BA: Federal Joint Committee

This assessment deviates from that by the company, which derived an indication of considerable added benefit for research questions 1 and 2 and a hint of non-quantifiable added benefit for research question 3.

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the ACT as adjuvant treatment in adults and adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection as well as in adolescents aged 12 years and older with stage III melanoma who have undergone complete resection.

The research questions shown in Table 4 were derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication	ACT[a]
1	Adjuvant treatment of adults with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]
2	Adjuvant treatment of adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]
3	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection	Treatment of physician's choice[c]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the drug interferon alfa might become unavailable in the foreseeable future, which in turn would require an adjustment of the ACT. Where interferon alfa is available, a single-comparator study is inadequate.
c. According to the G-BA, the following therapies, which are not approved for children or adolescents, are deemed suitable comparators in the context of clinical trials: dabrafenib in combination with trametinib (only for patients with BRAF-V600 mutation-positive stage III melanoma who have undergone complete resection); nivolumab. The choice of comparator must be justified in the dossier.

ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT for the adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection (research question 3). For the adjuvant treatment of adults as well as adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection (research questions 1 and 2), the company departed from the specification by the G-BA by listing watchful waiting as the only ACT. The company justifies this approach by arguing that the drug interferon alfa-2a has been discontinued since 15 October 2020 and the drug interferon alfa-2b was likewise taken off the market on 15 October 2020 [3,4]. The company concludes that interferon alfa is no longer available in practice, making watchful waiting the only possible ACT.

The availability of pharmaceuticals containing the drug interferon alfa in the German healthcare system cannot be conclusively determined in the context of this dossier assessment.

This benefit assessment used the respective ACT specified by the G-BA to answer each of its research questions. The placebo-controlled KEYNOTE 716 study, which was submitted by the company for answering research questions 1 and 2, is presented as supplementary information in I Appendix B of the full dossier assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

Research questions by the company

The company's dossier jointly assessed research questions 1 and 2 (adults [research question 1] and adolescents aged 12 years [research question 2] with stage IIB or IIC melanoma who have undergone complete resection). This approach remains without consequence for this benefit assessment because in any case, no data are available for adolescents aged 12 years and older in the therapeutic indication in question (see Section I 4).

I 3 Research question 1: Adjuvant treatment of adults with stage IIB or IIC melanoma who have undergone complete resection

I 3.1 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 pembrolizumab (status: 22 May 2022)
- bibliographical literature search on pembrolizumab (last search on 22 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 10 May 2022)
- search on the G-BA website for pembrolizumab (last search on 17 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 1 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check for completeness of the study pool revealed no relevant RCTs comparing pembrolizumab versus treatment of physician's choice, selecting from interferon alfa and watchful waiting as the ACT.

This departs from the company's approach, which included the KEYNOTE 716 RCT comparing pembrolizumab with placebo in its study pool and used it for the assessment.

The KEYNOTE 716 RCT was disregarded in the benefit assessment of pembrolizumab because the study failed to implement the ACT specified by the G-BA. This is explained below.

Evidence presented by the company – KEYNOTE 716 study

The KEYNOTE 716 study is an ongoing RCT comparing pembrolizumab with placebo in the adjuvant treatment of patients with stage IIB or IIC melanoma who have undergone complete resection. The study enrolled patients aged 12 years and older who had undergone complete resection of stage IIB or IIC melanoma (American Joint Committee on Cancer [AJCC] classification, version 8 [5]) within 12 weeks prior to randomization and who had received no further treatment of the melanoma. The KEYNOTE 716 study disallows the use of immunotherapies other than the experimental intervention (see Table 8 of the full dossier assessment). Hence, patients in the comparator arm cannot be treated with interferon alfa. Administering placebo in combination with close patient monitoring via physical examinations and imaging is a sufficient approximation to the ACT of watchful waiting (see Section I Appendix B.2 of the full dossier assessment). However, the absence of the option of interferon alfa treatment means that the study does not allow treatment of physician's choice, selecting from interferon alfa and watchful waiting. Instead, all comparator arm patients are treated with

placebo and, if necessary, supportive concomitant medication. The information on concomitant medication as provided in the study report confirms that the study does not use interferon alfa. Therefore, the KEYNOTE 716 study fails to adequately implement the ACT specified by the G-BA. Section I Appendix B of the full dossier assessment contains a supplementary presentation of the KEYNOTE 716 study and its results.

I 3.2 Results on added benefit

The company did not submit any suitable data for assessing the added benefit of pembrolizumab in comparison with the ACT for the adjuvant treatment of adults with stage IIB or IIC melanoma who have undergone complete resection. Consequently, there is no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived an indication of considerable added benefit.

I 4 Research question 2: Adjuvant treatment of adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection

I 4.1 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 pembrolizumab (status: 22 May 2022)
- bibliographical literature search on pembrolizumab (last search on 22 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 10 May 2022)
- search on the G-BA website for pembrolizumab (last search on 17 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 1 August 2022); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check. Rather than analysing adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection as a separate subpopulation, the company analysed it together with adults with stage IIB or IIC melanoma who have undergone complete resection (see Section I 2) and hence used the KEYNOTE 716 study also for the patients investigated in the latter research question.

Evidence presented by the company – KEYNOTE 716 study

Section I 3.1 and I Appendix B of the full dossier assessment contain a detailed description and discussion of the KEYNOTE 716 study.

According to the study protocol, the study allowed enrolment of adolescents aged 12 years and older. However, only 1 person under the age of 18 years was included in each treatment arm (see Table 10 of the full dossier assessment). A separate analysis of this subpopulation is neither meaningful nor available. Hence, no relevant data are available for adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection.

I 4.2 Results on added benefit

The company did not submit any suitable data for assessing the added benefit of pembrolizumab in comparison with the ACT in the adjuvant treatment of adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection. Consequently, there is no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the company's assessment, which has derived an indication of considerable added benefit.

I 5 Research question 3: Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection

I 5.1 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 pembrolizumab (status: 22 May 2022)
- bibliographical literature search on pembrolizumab (last search on 22 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 10 May 2022)
- search on the G-BA website for pembrolizumab (last search on 17 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 1 August 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool for adolescents aged 12 years and older with stage III melanoma who have undergone complete resection found no RCTs directly comparing pembrolizumab versus the ACT.

The company conducted an information retrieval for other investigations with pembrolizumab but did not find any relevant studies. The information retrieval for other studies was not reviewed.

I 5.2 Results on added benefit

The company did not submit any suitable data for assessing the added benefit of pembrolizumab in comparison with the ACT for the adjuvant treatment of adolescents 12 years and older with stage III melanoma who have undergone complete resection. Consequently, there is no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the company's evaluation, which claims a hint of non-quantifiable added benefit, citing the granted marketing authorization.

I 6 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of pembrolizumab in comparison with the ACT.

Table 5: Pembrolizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment of adults with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]	Added benefit not proven
2	Adjuvant treatment of adolescents aged 12 years and older with stage IIB or IIC melanoma who have undergone complete resection	Treatment of physician's choice, selecting from interferon alfa or watchful waiting[b]	Added benefit not proven
3	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma who have undergone complete resection	Treatment of physician's choice[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the drug interferon alfa might become unavailable in the foreseeable future, which in turn would require an adjustment of the ACT. Where interferon alfa is available, a single-comparator study is inadequate.
c. According to the G-BA, the following therapies, which are not approved for children or adolescents, are deemed suitable comparators in the context of clinical trials: dabrafenib in combination with trametinib (only for patients with BRAF-V600 mutation-positive stage III melanoma who have undergone complete resection); nivolumab. The choice of comparator must be justified in the dossier.

ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-72.html.