IQWiG Reports – Commission No. A22-73

Pembrolizumab (melanoma, advanced) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Pembrolizumab (Melanom, fortgeschritten) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 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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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.

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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
AE	adverse event
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 22 July 2022.

Research question

The aim of this report was to assess the added benefit of pembrolizumab in comparison with treatment of physician's choice as the appropriate comparator therapy (ACT) in adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT[a]**
Treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma	Treatment of physician's choice[b]

a. Presented is the ACT specified by the G-BA.
b. 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: vemurafenib + cobimetinib (only for patients with BRAF-V600 mutation), dabrafenib + trametinib (only for patients with BRAF-V600 mutation), encorafenib + binimetinib (only for patients with BRAF-V600 mutation), nivolumab. The choice of the used 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.

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

Results

Since the company found no randomized controlled trials (RCTs) directly comparing pembrolizumab versus the ACT in adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma, an information retrieval was conducted by the company for other investigations with pembrolizumab, which identified the KEYNOTE 051 study. The company did not conduct an information retrieval for other investigations on the ACT.

The KEYNOTE 051 study is an ongoing single-arm study treating children and adolescents aged ≥ 6 months to < 18 years suffering from various oncological diseases with

pembrolizumab. A total of 9 patients with advanced melanoma were included, of which 5 patients were in the age group in question, adolescents aged 12 years and older.

For the outcomes of treatment response and adverse events (AEs), the company presents the results for the 5 patients aged 12 years and older with advanced (unresectable or metastatic) melanoma from the KEYNOTE 051 study in descriptive form. The company argues that due to the small number of patients, no conclusions can be drawn regarding the effectiveness of pembrolizumab.

The KEYNOTE 051 study data which were descriptively presented by the company were unsuitable for deriving any added benefit of pembrolizumab in comparison with the ACT.

Results on added benefit

Since no relevant study is available for the benefit assessment, 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 presents a summary of the probability and extent of the added benefit of pembrolizumab.

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. 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: vemurafenib + cobimetinib (only for patients with BRAF-V600 mutation), dabrafenib + trametinib (only for patients with BRAF-V600 mutation), encorafenib + binimetinib (only for patients with BRAF-V600 mutation), nivolumab. The choice of the comparator used must be justified in the dossier.

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

[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].

The assessment described above deviates from the assessment by the company, which claims a hint of non-quantifiable added benefit, citing the granted marketing authorization.

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report was to assess the added benefit of pembrolizumab in comparison with treatment of physician's choice as the ACT in adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a]
Treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma	Treatment of physician's choice[b]
a. Presented is the ACT specified by the G-BA. b. 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: vemurafenib + cobimetinib (only for patients with BRAF-V600 mutation), dabrafenib + trametinib (only for patients with BRAF-V600 mutation), encorafenib + binimetinib (only for patients with BRAF-V600 mutation), nivolumab. The choice of the comparator used 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.

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

I 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 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 the completeness of the study pool for adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma identified no RCTs directly comparing pembrolizumab versus the ACT.

Since it identified no RCTs, the company conducted an information retrieval for other investigations with pembrolizumab, which resulted in the identification of the KEYNOTE 051 study [2]. The company conducted no information retrieval for other investigations on the ACT. The KEYNOTE 051 study data which were descriptively presented by the company were unsuitable for deriving any added benefit of pembrolizumab in comparison with the ACT. This is justified below.

Evidence presented by the company – KEYNOTE 051 study

The KEYNOTE 051 study is an ongoing single-arm study treating children and adolescents aged ≥ 6 months to < 18 years suffering from various oncological diseases with pembrolizumab. A total of 9 patients with advanced melanoma were included, of which 5 patients were in the age group in question, adolescents aged 12 years and older, and the oldest patient was 14 years of age.

Treatment with pembrolizumab was in line with the Summary of Product Characteristics (SPCs) [3]. Alongside pharmacokinetic outcomes, primary outcomes included the objective response rate as well as AEs. Overall survival was recorded as another patient-relevant outcome.

For the outcomes of treatment response and AEs, the company presents the results for the 5 patients aged 12 years and older with advanced (unresectable or metastatic) melanoma from

the KEYNOTE 051 study in descriptive form. The company argues that due to the small number of patients, no conclusions can be drawn regarding the effectiveness of pembrolizumab.

The company further argues that it is not appropriate to transfer evidence from adult patients with advanced (unresectable or metastatic) melanoma to adolescents aged 12 years and older with the same clinical picture. First, little evidence is reportedly available for the paediatric population, and second, there is no known study on adult patients comparing pembrolizumab with the ACT specified by the G-BA. However, the company did not carry out a corresponding information retrieval.

In summary, there is no proof of added benefit of pembrolizumab in comparison with the ACT in adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

I 4 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 adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. Consequently, there is no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 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

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. 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: vemurafenib + cobimetinib (only for patients with BRAF-V600 mutation), dabrafenib + trametinib (only for patients with BRAF-V600 mutation), encorafenib + binimetinib (only for patients with BRAF-V600 mutation), nivolumab. The choice of the comparator used must be justified in the dossier.

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

The assessment described above deviates from the assessment by the company, which claims a hint of non-quantifiable added benefit, citing the granted marketing authorization.

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

2. Geoerger B, Kang HJ, Yalon-Oren M et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1–2 trial. The Lancet Oncology 2020; 21(1): 121-133.

3. Merck Sharp Dohme. Fachinformation KEYTRUDA (Pembrolizumab) 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung. Stand: Juni. 2022.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-73.html.