Pembrolizumab (pleural mesothelioma)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A25-53 Version: 1.0 Status: 17 Jul 2025 DOI: 10.60584/A25-53_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Pembrolizumab (Pleuramesotheliom) – Nutzenbewertung gemäß § 35a SGB V*. 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Pembrolizumab (pleural mesothelioma) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

25 April 2025

Internal Project No.

A25-53

DOI-URL

https://doi.org/10.60584/A25-53_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Pembrolizumab (pleural mesothelioma); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-53_en.

Keywords

Pembrolizumab, Mesothelioma – Malignant, Benefit Assessment

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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
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 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 (in combination with pemetrexed and platinum chemotherapy). 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 25 April 2025.

Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy (hereinafter referred to as pembrolizumab + pemetrexed + platinum chemotherapy) in comparison with the appropriate comparator therapy (ACT) as first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of pembrolizumab + pemetrexed + platinum chemotherapy

Therapeutic indication	**ACT**[a]
First-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma	nivolumab in combination with ipilimumab
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

On 23 April 2025, the day on which the company submitted its dossier, the G-BA modified the ACT to that shown in Table 2. The ACT previously specified by the G-BA in 2022 was treatment of physician's choice. The company referred to this decision and named treatment of physician's choice as the ACT. This benefit assessment was carried out versus the current 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. Randomized controlled trials (RCTs) were used to derive the added benefit.

Results

A review of the completeness of the study pool did not identify any relevant studies.

This deviates from the company's view, which identified the RCT KEYNOTE 483 in its information retrieval and used this study to assess the added benefit.

The KEYNOTE 483 study [1] is a completed open-label phase 2/3 study. Patients with unresectable advanced and/or metastatic malignant pleural mesothelioma were enrolled. The study was initially designed as a phase 2 trial comparing pembrolizumab + pemetrexed + platinum chemotherapy versus pemetrexed + platinum chemotherapy and versus pembrolizumab monotherapy. The study arm for treatment with pembrolizumab monotherapy was discontinued after an interim analysis. The study was then converted to a phase 3 study comparing pembrolizumab + pemetrexed + platinum chemotherapy versus pemetrexed + platinum chemotherapy.

The G-BA determined nivolumab + ipilimumab to be the ACT for the first-line treatment of unresectable non-epithelioid malignant pleural mesothelioma in adults. In contrast, the patients enrolled in the comparator arms of KEYNOTE 483 received treatment with pemetrexed + platinum chemotherapy or pembrolizumab monotherapy. Thus, KEYNOTE 483 did not include a comparison with the ACT. KEYNOTE 483 was therefore not suitable for the assessment of the added benefit of pembrolizumab + pemetrexed + platinum chemotherapy versus the ACT of the G-BA as first-line treatment of unresectable non-epithelioid malignant pleural mesothelioma in adults.

Results on added benefit

Since no relevant study was available for the benefit assessment, there is no hint of an added benefit of pembrolizumab + pemetrexed + platinum chemotherapy in comparison with the ACT; an added benefit is 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 the added benefit of pembrolizumab + pemetrexed + platinum chemotherapy.

[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 [2,3].

Table 3: Pembrolizumab + pemetrexed + platinum chemotherapy – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma	nivolumab in combination with ipilimumab	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy (hereinafter referred to as pembrolizumab + pemetrexed + platinum chemotherapy) in comparison with the ACT as first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of pembrolizumab + pemetrexed + platinum chemotherapy

Therapeutic indication	**ACT**[a]
First-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma	nivolumab in combination with ipilimumab
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

On 23 April 2025, the day on which the company submitted its dossier, the G-BA modified the ACT to that shown in Table 4. The ACT previously specified by the G-BA in 2022 was treatment of physician's choice. The company referred to this decision and named treatment of physician's choice as the ACT. This benefit assessment was carried out versus the current 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. RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on pembrolizumab (status: 7 March 2025)
- Bibliographical literature search on pembrolizumab (last search on 28 February 2025)
- Search of trial registries/trial results databases for studies on pembrolizumab (last search on 18 March 2025)
- Search on the G-BA website for pembrolizumab (last search on 18 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on pembrolizumab (last search on 15 May 2025); for search strategies, see I Appendix A of the full dossier assessment

A review of the completeness of the study pool did not identify any relevant studies.

This deviates from the company's view, which identified the RCT KEYNOTE 483 [1] in its information retrieval and used this study to assess the added benefit.

The treatment in the comparator arm of KEYNOTE 483 did not concur with the ACT, so no data were available on the comparison of pembrolizumab + pemetrexed + platinum chemotherapy with the comparator therapy specified by the G-BA. This is justified below.

Evidence provided by the company

Study KEYNOTE 483

The KEYNOTE 483 study [1] is a completed open-label phase 2/3 study. Patients with unresectable advanced and/or metastatic malignant pleural mesothelioma were enrolled. There were no restrictions regarding the histology subtype of pleural mesothelioma (epithelioid, non-epithelioid). The study was initially designed as a phase 2 trial comparing pembrolizumab + pemetrexed + platinum chemotherapy versus pemetrexed + platinum chemotherapy and versus pembrolizumab monotherapy. The study arm for treatment with pembrolizumab monotherapy was discontinued after an interim analysis. The study was then converted to a phase 3 study comparing pembrolizumab + pemetrexed + platinum chemotherapy versus pemetrexed + platinum chemotherapy.

In accordance with the marketing authorization, the company only presented results from the KEYNOTE 483 study for a subpopulation of patients with non-epithelioid subtype for the benefit assessment.

No data on the comparison of pembrolizumab with the comparator therapy specified by the G-BA

The G-BA determined nivolumab + ipilimumab to be the ACT for the first-line treatment of unresectable non-epithelioid malignant pleural mesothelioma in adults. In contrast, the patients enrolled in the comparator arms of KEYNOTE 483 received treatment with pemetrexed + platinum chemotherapy or pembrolizumab monotherapy. Thus, KEYNOTE 483 did not include a comparison with the ACT. KEYNOTE 483 was therefore not suitable for the assessment of the added benefit of pembrolizumab + pemetrexed + platinum chemotherapy versus the ACT of the G-BA as first-line treatment of unresectable non-epithelioid malignant pleural mesothelioma in adults.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of pembrolizumab + pemetrexed + platinum chemotherapy for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma. There is no hint of an added benefit of pembrolizumab + pemetrexed + platinum chemotherapy 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 the added benefit of pembrolizumab + pemetrexed + platinum chemotherapy in comparison with the ACT.

Table 5: Pembrolizumab + pemetrexed + platinum chemotherapy – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma	nivolumab in combination with ipilimumab	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived an indication of a major added benefit.

The G-BA decides on the added benefit.

I 6 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. Chu Q, Perrone F, Greillier L et al. Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France; a phase 3, open-label, randomised controlled trial. Lancet 2023; 402(10419): 2295-2306. https://doi.org/10.1016/s0140-6736(23)01613-6.

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3. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

The full report (German version) is published under https://www.iqwig.de/en/projects/a25-53.html.