Nivolumab
(melanoma in adolescents, advanced)

Benefit assessment according to §35a SGB V1

EXTRACT

Project: A23-58 Version: 1.0 Status: 27 September 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Nivolumab (Melanom bei Jugendlichen, fortgeschritten) – 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

Nivolumab (melanoma in adolescents, advanced) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

30 June 2023

Internal Project No.

A23-58

Address of publisher

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Medical and scientific advice

No advisor on medical and scientific questions was involved in the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Anne Wispler.

IQWiG thanks the respondent for participating in the written exchange about how she experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Keywords

Nivolumab, Melanoma, Adolescent, Benefit Assessment

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
BRAF	rapidly-accelerated fibrosarcoma - isoform B
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 nivolumab as monotherapy or in combination with 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 30 June 2023.

Research question

The aim of this report was to assess the added benefit of nivolumab as monotherapy or in combination with ipilimumab in comparison with pembrolizumab as 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 nivolumab as monotherapy or in combination with ipilimumab

Therapeutic indication	**ACT**[a]
Treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older[b]	Pembrolizumab[c]

a. Presented is the ACT specified by the G-BA.
b. The target population is defined as those patients for whom resection and/or radiotherapy with a curative intent is not indicated.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents aged 12 years and older. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

The G-BA specified pembrolizumab as ACT. In doing so, it points out that present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents aged 12 years and older. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT

in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company departs from the ACT specified by the G-BA. It divides the research question and names several drugs in each case:

- Treatment with nivolumab as monotherapy or in combination with ipilimumab in first-line therapy: treatment of physician's choice (vemurafenib + cobimetinib [only for patients with rapidly-accelerated fibrosarcoma - isoform B [BRAF] V600 mutation], dabrafenib + trametinib [only for patients with BRAF V600 mutation], encorafenib + binimetinib [only for patients with BRAF V600 mutation], nivolumab [monotherapy; only for nivolumab in combination with ipilimumab], pembrolizumab [monotherapy]),
- treatment with nivolumab as monotherapy or in combination with ipilimumab after first-line therapy: a patient-specific therapy taking into account the respective pretreatment(s) and BRAF status (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], ipilimumab [monotherapy], nivolumab [monotherapy; only for nivolumab in combination with ipilimumab], pembrolizumab [monotherapy]).

The company's deviation from the ACT specified by the G-BA will not be further commented on below, as the company did not present any suitable data for the benefit assessment – neither versus a comparator therapy specified by the company nor versus the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier in comparison with the adjusted ACT specified by the G-BA.

Results

Concurring with the company, the check of the completeness of the study pool identified no relevant randomized controlled trial (RCT) that enables a direct comparison of nivolumab as monotherapy or in combination with ipilimumab versus the G-BA's ACT.

Overall, the company presented no data for the assessment of the added benefit of nivolumab in comparison with the ACT in its dossier.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of nivolumab as monotherapy or in combination with ipilimumab versus 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 nivolumab.

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older[b]	Pembrolizumab[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The target population is defined as those patients for whom resection and/or radiotherapy with a curative intent is not indicated.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents aged 12 years and older. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

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].

I 2 Research question

The aim of this report was to assess the added benefit of nivolumab as monotherapy or in combination with ipilimumab in comparison with pembrolizumab as (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 nivolumab as monotherapy or in combination with ipilimumab

Therapeutic indication	**ACT[a]**
Treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older[b]	Pembrolizumabc

a. Presented is the ACT specified by the G-BA.
b. The target population is defined as those patients for whom resection and/or radiotherapy with a curative intent is not indicated.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents aged 12 years and older. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

The G-BA specified pembrolizumab as ACT. In doing so, it points out that present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents aged 12 years and older. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company departs from the ACT specified by the G-BA. It distinguishes between treatment with nivolumab as monotherapy or in combination with ipilimumab, each in first-line therapy and after first-line therapy. The company considers the following ACTs to be adequate for these populations:

- treatment with nivolumab as monotherapy or in combination with ipilimumab, each in first-line therapy: treatment of physician's choice.

The company names the following as suitable comparators in the context of a clinical study:

- 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 (monotherapy; only for nivolumab in combination with ipilimumab),
- pembrolizumab (monotherapy).

- Treatment with nivolumab as monotherapy or in combination with ipilimumab, each after first-line treatment: individualized treatment taking into account the respective pretreatment(s) and the BRAF status.

  The company names the following as suitable comparators in the context of a clinical study:

  - 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),
  - ipilimumab (monotherapy),
  - nivolumab (monotherapy; only for nivolumab in combination with ipilimumab),
  - pembrolizumab (monotherapy).

The company's deviation from the ACT specified by the G-BA will not be further commented on below, as the company did not present any suitable data for the benefit assessment – neither versus a comparator therapy specified by the company nor versus the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier in comparison with the adjusted ACT specified by the G-BA.

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 list on nivolumab (status: 24 April 2023)
- bibliographical literature search on nivolumab (last search on 24 April 2023)
- search in trial registries/trial results databases for studies on nivolumab (last search on 17 April 2023)
- search on the G-BA website for nivolumab (last search on 24 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 13 July 2023); for search strategies, see I Appendix A of the full dossier assessment.

The check identified no relevant RCT that enables a direct comparison of nivolumab as monotherapy or in combination with ipilimumab versus the ACT pembrolizumab in the therapeutic indication. This concurs with the company's assessment.

The company stated that, regardless of the study design, it could not identify any relevant clinical study in the entire therapeutic indication that was suitable for answering the research question of the benefit assessment. For privacy reasons, it did not present an individual case study for the present therapeutic indication from the single-arm multi-cohort study CA209-070 [3], which was submitted to the regulatory authority in the approval process. The company further describes that it does not consider a transfer of evidence from the adult population to the population of adolescents aged 12 years and older to be feasible.

Overall, the company thus presented no data for the assessment of the added benefit of nivolumab in comparison with the ACT in its dossier.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of nivolumab as monotherapy or in combination with ipilimumab for the treatment of advanced (non-resectable or metastatic) melanoma in adolescents aged 12 years and older compared with the ACT pembrolizumab. There is no hint of an added benefit of nivolumab as monotherapy or in combination with ipilimumab versus 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 nivolumab as monotherapy or in combination with ipilimumab in comparison with the ACT.

Table 5: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older[b]	Pembrolizumab[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The target population is defined as those patients for whom resection and/or radiotherapy with a curative intent is not indicated.
c. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents aged 12 years and older. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

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The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit for all patients. This is not adequate, as the company did not present any data for a comparison of nivolumab as monotherapy or in combination with ipilimumab with the G-BA's ACT, but justified its approach with the positive benefit-risk profile of nivolumab confirmed by the European Medicines Agency (EMA) and the rarity of the disease in the relevant age segment.

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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-58.html.