Nivolumab
(melanoma in adolescents, adjuvant)

Benefit assessment according to §35a SGB V1

EXTRACT

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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
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. 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 the present report is the assessment of the added benefit of nivolumab as monotherapy in comparison with the appropriate comparator therapy (ACT) in the adjuvant treatment of adolescents aged 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

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

Table 2: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	ACT[a]
1	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma with involvement of lymph nodes who have undergone complete resection	Pembrolizumab[b]
2	Adjuvant treatment of adolescents aged 12 years and older with metastatic stage IV melanoma who have undergone complete resection	Watchful waiting[b]

a. Presented is the respective ACT specified by the G-BA.
b. 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 adjuvant treatment of 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

When specifying the ACT, the G-BA 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 adjuvant treatment of 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).

Deviating from the G-BA's specification, the company named a treatment of physician's choice in Module 3 A of the dossier, taking into account dabrafenib in combination with trametinib (only for patients with rapidly-accelerated fibrosarcoma - isoform B [BRAF] V600 mutation) and pembrolizumab as ACT. In doing so, it did not consider the breakdown by research question carried out by the G-BA.

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

The check identified no relevant randomized controlled trial (RCT) on the direct comparison of nivolumab in comparison with the ACT for the adjuvant treatment of adolescents aged 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. The company also did not identify any RCTs versus its ACT.

Overall, the company thus 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 data are available for the benefit assessment, there is no hint of an added benefit of nivolumab 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 nivolumab.

Table 3: Nivolumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma with involvement of lymph nodes who have undergone complete resection	Pembrolizumab[b]	Added benefit not proven
2	Adjuvant treatment of adolescents aged 12 years and older with metastatic stage IV melanoma who have undergone complete resection	Watchful waiting[b]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. 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 adjuvant treatment of 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 the present report is the assessment of the added benefit of nivolumab as monotherapy in comparison with the ACT in the adjuvant treatment of adolescents aged 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

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

Table 4: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	ACT[a]
1	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma with involvement of lymph nodes who have undergone complete resection	Pembrolizumab[b]
2	Adjuvant treatment of adolescents aged 12 years and older with metastatic stage IV melanoma who have undergone complete resection	Watchful waiting[b]

a. Presented is the respective ACT specified by the G-BA.
b. 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 adjuvant treatment of 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

When specifying the ACT, the G-BA 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 adjuvant treatment of 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).

Deviating from the G-BA's specification, the company named a treatment of physician's choice in Module 3 A of the dossier, taking into account dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation) and pembrolizumab as ACT. In doing so, it did not consider the breakdown by research question carried out by the G-BA.

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 on the direct comparison of nivolumab in comparison with the ACT for the adjuvant treatment of adolescents aged 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. The company also did not identify any RCTs versus its ACT.

The company also conducted an information retrieval for further studies with nivolumab. It also did not identify any relevant studies. Furthermore, the company pointed out that the approval in the present therapeutic indication was based on two individual case studies from the randomized, double-blind, phase III study CA209-915 [3], but that it did not present these case studies for privacy reasons. The company also categorized the possibility of an evidence transfer from the adult population to adolescents aged 12 years and older as not 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

There are no suitable data for the assessment of the added benefit of nivolumab as monotherapy in comparison with the ACT in the adjuvant treatment of adolescents aged 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. There is no hint of added benefit of nivolumab in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 5.

Table 5: Nivolumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment of adolescents aged 12 years and older with stage III melanoma with involvement of lymph nodes who have undergone complete resection	Pembrolizumab[b]	Added benefit not proven
2	Adjuvant treatment of adolescents aged 12 years and older with metastatic stage IV melanoma who have undergone complete resection	Watchful waiting[b]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. 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 adjuvant treatment of 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 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 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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Zugriff: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. 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://dx.doi.org/10.1002/bimj.201300274.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nivolumab – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2015 [Zugriff: 25.08.2023]. URL: https://www.iqwig.de/download/a15-27_nivolumab_nutzenbewertung-35a-sgb-v.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-59.html.