IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pembrolizumab (classical Hodgkin lymphoma)

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Pembrolizumab (klassisches Hodgkin-Lymphom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 August 2017). 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.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AEs	adverse events
ASCT	autologous stem cell transplantation
BV	brentuximab vedotin
CTCAE	Common Terminology Criteria for AEs
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GHSG	German Hodgkin Study Group
HDCT	high-dose chemotherapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAEs	serious adverse events
SCT	stem cell transplantation
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 May 2017.

Research question

The aim of the present report was to assess the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) in adults with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplantation (ASCT) and treatment with brentuximab vedotin (BV), or after failure of a treatment with BV if ASCT is not an option.

The ACT specified by the G-BA is shown in the following Table 2.

Table 2: Research question of the benefit assessment of pembrolizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with recurring or refractory classical Hodgkin lymphoma after ASCT and treatment with BV, or after failure of a treatment with BV if ASCT is not an option.	Treatment specified by the physician under consideration of the approval and prior therapies
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; BV: brentuximab vedotin; G-BA: Federal Joint Committee		

On receipt of the dossier, the G-BA adjusted the ACT.

In the original comparator therapy, the G-BA differentiated between 2 patient groups (patients who are candidates for further stem cell transplantation [SCT] and patients who are not candidates for further SCT). The consolidation of the two patient groups performed by the G-BA had no consequence regarding the content for the present benefit assessment since the comparator therapy "individual treatment of physician's choice" also comprised allogenic or autologous SCT and the company had not assessed the individual patient groups separately in its dossier.

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

Results

Concurring with the company, the check of the completeness of the study pool showed no randomized controlled trial (RCT) on the comparison of pembrolizumab versus the ACT. Since no RCTs of direct comparisons were available, the company conducted an information retrieval for further investigations. Based on the search results, the company identified the single-arm study KEYNOTE 087 for pembrolizumab and the single-arm nivolumab study Checkmate 205 for the ACT.

The data presented by the company were incomplete and overall unsuitable for the derivation of conclusions on the added benefit of pembrolizumab in comparison with the ACT. The reasons are as follows:

- The data on nivolumab presented by the company were incomplete. The Checkmate 205 study included by the company was subject of the dossier assessment A16-76 on nivolumab in the same therapeutic indication. Several cohorts were included in the Checkmate 205 study. The therapeutic indication investigated in the present dossier concerned all patients in cohort B (N = 80) and 57 of 100 patients in cohort C. Moreover, 15 of 23 patients included in the CA209-039 study concurred with the investigated therapeutic indication. However, the company only presented the data on cohort B of the Checkmate 205 study in its dossier. In doing so, it referred, among other things, to Younes 2016 and to the European Public Assessment Report (EPAR) for nivolumab. As supplementary information, the company referred to the dossier published on 03 April 2017 and the dossier assessment on nivolumab. However, it did not use the information on the Checkmate 205 study provided by these documents for its dossier. Although the EPAR on nivolumab includes data on the relevant subpopulation of cohort C of the Checkmate 205 study as well as on the CA209-039 study, the company did not consider this information in its dossier. Moreover, the company did not include the publication "Ansell 2015" on the CA209-039 study in its assessment.
- Regardless of the incomplete data situation on nivolumab, the company's approach was no implementation of the ACT specified by the G-BA. The ACT in the present therapeutic indication was an individual treatment of physician's choice. All patients in the Checkmate 205 study were treated with nivolumab. In its dossier, the company did not explain that in the Checkmate 205 study nivolumab can be considered to be an implementation of an individual treatment specified by the physician.
- However, even a review of the data on pembrolizumab and nivolumab would not have revealed an added benefit of pembrolizumab. Altogether, there were no effects that were so large that they could not be caused by systematic bias alone.

Overall, in its dossier the company presented no suitable data for the assessment of the added benefit of pembrolizumab in patients with recurring or refractory classical Hodgkin lymphoma after ASCT and treatment with BV, or after failure of a treatment with BV if

ASCT is not an option; hence, there was no hint of an added benefit 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[4]

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

Table 3: Pembrolizumab – extent and probability of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV, or after failure of a treatment with BV if ASCT is not an option.	Treatment specified by the physician under consideration of the approval and prior therapies	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; BV: brentuximab vedotin; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) in adults with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplantation (ASCT) and treatment with brentuximab vedotin (BV), or after failure of a treatment with BV if ASCT is not an option.

The ACT specified by the G-BA is shown in the following Table 4.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 4: Research question of the benefit assessment of pembrolizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV, or after failure of a treatment with BV if ASCT is not an option.	Treatment specified by the physician under consideration of the approval and prior therapies
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; BV: brentuximab vedotin; G-BA: Federal Joint Committee		

After receipt of the dossier, the G-BA adjusted the ACT for the benefit assessment of pembrolizumab in patients with relapsed or refractory classical Hodgkin lymphoma during the assessment procedure [3].

In the original comparator therapy, the G-BA had distinguished between 2 patient groups. The ACT for patients who were candidates for further stem cell transplantation (SCT) was allogeneic SCT or high-dose chemotherapy (HDCT) followed by ASCT. The comparator therapy for patients who were not candidates for further SCT was a treatment specified by the physician under consideration of the approval and prior therapies.

The consolidation of the two patient groups performed by the G-BA had no consequence regarding the content for the present benefit assessment since the comparator therapy "individual treatment of physician's choice" also comprised allogenic or autologous SCT and the company had not assessed the individual patient groups separately in its dossier.

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

2.3 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 pembrolizumab (status: 23 March 2017)
- bibliographical literature search on pembrolizumab (last search on 9 March 2017)
- search in trial registries for studies on pembrolizumab (last search on 10 March 2017)
- bibliographical literature search on the ACT (last search on 9 March 2017)
- search in trial registries for studies on the ACT (last search on 10 March 2017)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 20 June 2017)

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trial (RCT) on the comparison of pembrolizumab versus the ACT.

Since no RCTs of direct comparisons were available, the company conducted an information retrieval for further investigations. Based on the search results, the company identified further investigations, which it used for the benefit assessment. This is the single-arm study KEYNOTE 087 [4] for pembrolizumab, and the single-arm nivolumab study Checkmate 205 [5] for the ACT. In addition to further investigations identified with its information retrieval, the company presented registry data of the German Hodgkin Study Group (GHSG) [6].

The data presented by the company were incomplete and overall unsuitable for the derivation of conclusions on the added benefit of pembrolizumab in comparison with the ACT. This is justified below.

Description of the studies used by the company

Studies on pembrolizumab

The KEYNOTE 087 study was the approval study in the present therapeutic indication. This was a single-arm, open-label, multicentre study that included several cohorts. 69 patients with classical Hodgkin lymphoma after ASCT and after failure of treatment with BV were included in cohort 1. Cohort 2 included 81 patients with classical Hodgkin lymphoma who were not candidates for ASCT, after failure of treatment with BV. The patients in both cohorts therefore met the inclusion criteria for the present therapeutic indication. The study started on 24 June 2015. In its dossier, the company presented analyses on the data cut-offs of 27 June 2016 and 25 September 2016.

Studies on nivolumab

The Checkmate 205 study included by the company was a single-arm, open-label, multicentre study. The study started in August 2014. This study was subject of the dossier assessment A16-76 on nivolumab in the same therapeutic indication [7]. Several cohorts were included in the Checkmate 205 study. The therapeutic indication investigated in the present dossier concerned all patients in cohort B (N = 80) and 57 of 100 patients in cohort C. Moreover, 15 of 23 patients included in the CA209-039 study concurred with the investigated therapeutic indication (see dossier assessment A16-76 on nivolumab for reasons).

However, in its dossier the company only presented data on cohort B of the study Checkmate 205, i.e. primarily on the data cut-off August 2015, supplemented by data on adverse events of the data cut-off February 2016. In doing so, it referred, among other things, to the publication “Younes 2016” [5] and to the European Public Assessment Report (EPAR) for nivolumab [8]. As supplementary information, the company referred to the dossier [9] published on 3 April 2017 and the dossier assessment [7] on nivolumab. However, it did not use the information on the Checkmate 205 study provided by these documents for its dossier. It justified this with the submission deadline for the dossier of the present benefit assessment (see also Section 2.7.2.3.2 of the full dossier assessment).

Although the EPAR on nivolumab includes data on the relevant subpopulation of cohort C of the Checkmate 205 study as well as on the CA209-039 study, the company did not consider this information in its dossier. Moreover, the company identified the publication "Ansell 2015" [10] on the CA209-039 study with its search, but excluded it based on erroneous arguments.

Overall, the data on nivolumab presented by the company were incomplete.

No implementation of the appropriate comparator therapy in the Checkmate 205 study

Regardless of the incomplete data situation on nivolumab, the company's approach was no implementation of the ACT specified by the G-BA.

The ACT in the present therapeutic indication was an individual treatment of physician's choice. All patients in the Checkmate 205 study were treated with nivolumab. In its dossier, the company did not explain that in the Checkmate 205 study nivolumab can be considered to be an implementation of an individual treatment of physician's choice. The company therefore also disregarded the consultation of the G-BA that, according to the written record, requests the company to explain in how far the therapy specified by the physician could still be represented after such limitation of the treatment options [11]. Irrespective of this, even a review of the data on pembrolizumab and nivolumab would not have revealed an added benefit of pembrolizumab (see below).

Further investigations – registry data of the German Hodgkin Study Group

In its dossier, the company presented data of a total of 58 patients from the GHSG registry. None of these patients had been pretreated with BV; they were therefore not relevant for the present benefit assessment (see also Section 2.7.2.3.2 of the full dossier assessment).

Results of the studies on pembrolizumab and nivolumab

In its dossier, the company only provided a descriptive presentation of the patient characteristics and the results of the studies KEYNOTE 087 and Checkmate 205; it calculated no effect measures to derive an added benefit of pembrolizumab. It justified this by claiming that the treatment duration in the Checkmate 205 study was unknown. However, the median observation period on overall survival for the data cut-off 08/2015 of cohort B used by the company can be inferred from the EPAR on nivolumab. It amounts to 8.9 month and is thus in the range of the median observation period of cohort 1 (10.7 months) or cohort 2 (9.9 months) of the pembrolizumab study KEYNOTE 087.

There were no noticeable differences in overall survival in these similar study periods:

- In cohort 1 of the KEYNOTE 087 study, 1 of 69 (1.4%) patients had died, 2 of 81 (2.5%) patients had died in cohort 2.
- In cohort B of the Checkmate 205 study, 3 of 80 (3.8%) patients had died.

The analyses on the mean change at week 24 or at week 25 presented by the company on symptoms and health-related quality of life were not meaningfully interpretable both for nivolumab and pembrolizumab, since a relevant proportion of the patients were not considered in the analysis (pembrolizumab: 30.4% in cohort 1, 33.3% in cohort 2; nivolumab: 36.3% in cohort B).

There was no information on the treatment and observation period for the data on nivolumab presented by the company for adverse events (AEs) (data cut-off February 2016). The dossier on nivolumab includes results on the data cut-off June 2016 including information on the treatment duration. In Table 5, the data on serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuations due to AEs are contrasted with the corresponding results on pembrolizumab at the data cut-off on 25 September 2016 from the KEYNOTE 087 study.

Table 5: Adverse events in the studies on pembrolizumab and nivolumab

Treatment duration **Outcome**	**Pembrolizumab: KEYNOTE 087, cohort 1** **(N = 69)**	**Pembrolizumab: KEYNOTE 087, cohort 2** **(N = 81)**	**Nivolumab: Checkmate 205, cohort B** **(N = 80)**
median treatment duration [months]	8.3	7.6	15.7
SAE n (%)	9 (13.0)	13 (16.0)	23 (28.8)
Severe AEs (CTCAE grade ≥ 3) n (%)	18 (26.1)	21 (25.9)	41 (51.3)
Discontinuation due to AEs n (%)	5 (7.2)	4 (4.9)	5 (6.3)
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event;			

For the outcomes “SAEs” and “severe AEs” (CTCAE grade ≥ 3) the event rates are about twice as high under nivolumab in comparison with pembrolizumab. However, the treatment duration is also about twice as long. Although the treatment duration is twice as long under nivolumab, there are no noticeable differences with regard to the discontinuations due to adverse events. Altogether, there were no effects that were so large that they could not be caused by systematic bias alone. An orientation for an effect that is not explicable solely by the impact of systematic bias is a significance level of 1% and a value of > 10 for the relative risk [1,12].

Summary

No added benefit of pembrolizumab in comparison with the ACT could be derived from the data of further investigations presented by the company. The data on nivolumab presented by the company were incomplete. Irrespective of this, administration of nivolumab in the Checkmate 205 study used by the company is no appropriate implementation of the ACT specified by the G-BA. Nevertheless, comparison of the data on pembrolizumab and nivolumab revealed no effects that were so large that they could not be caused by systematic bias alone.

2.4 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of pembrolizumab in comparison with the ACT for patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV, or after failure of a treatment with BV if ASCT is not an option. This resulted in no hint of an added benefit in comparison with the ACT. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 6.

Table 6: Pembrolizumab – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV, or after failure of a treatment with BV if ASCT is not an option.	Treatment specified by the physician under consideration of the approval and prior therapies	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; BV: brentuximab vedotin; G-BA: Federal Joint Committee		

Since the company presented no suitable data for the assessment of the added benefit of pembrolizumab in comparison with the ACT in the dossier, an added benefit of pembrolizumab is not proven.

This result deviates from the assessment of the company, which, on the basis of the data it presented, derived a hint of a non-quantifiable added benefit for all patients in the therapeutic indication.

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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