IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-76

Nivolumab (classical Hodgkin lymphoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (klassisches Hodgkin-Lymphom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ASCT	autologous stem cell transplantation
BV	brentuximab vedotin
CI	confidence interval
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
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 nivolumab. 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 19 December 2016.

Research question

The aim of the present report was to assess the added benefit of nivolumab 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).

Two research questions resulted from the ACT specified by the G-BA for the present benefit assessment (see Table 2).

Table 2: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Patients who are candidates for further stem cell transplantation	▪ **Allogeneic stem cell transplantation** or ▪ **HDCT followed by ASCT (high-dose chemotherapy followed by autologous stem cell transplantation)**
2	Patients who are not candidates for further stem cell transplantation	▪ Treatment specified by the physician under consideration of the approval and prior therapies

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee; HDCT: high-dose chemotherapy

The company followed the ACT specified by the G-BA. The assessment was conducted in comparison with the 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.

Results for research question 1 (patients who are candidates for further stem cell transplantation)

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) on the comparison of nivolumab versus the ACT.

Since no randomized studies of direct comparisons were available, the company conducted an information retrieval for RCTs for indirect comparisons, for non-randomized comparative studies, and for further investigations. The company stated that it had not identified any suitable comparator data on the ACT on all evidence levels. Hence there were no data for the assessment of the added benefit of nivolumab in patients who are candidates for further stem cell transplantation (SCT).

Since the company presented no data for the assessment of the added benefit of nivolumab in patients who are candidates for further SCT in the dossier, there was no hint of an added benefit of nivolumab in comparison with the ACT. An added benefit is therefore not proven.

Results for research question 2 (patients who are not candidates for further stem cell transplantation)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the comparison of nivolumab versus the ACT.

Since no randomized studies of direct comparisons were available, the company conducted an information retrieval for RCTs for indirect comparisons, for non-randomized comparative studies, and for further investigations. Based on the search results, the company identified further investigations, which it used for the benefit assessment. These were the 2 single-arm studies CA209-205 and CA209-039 for nivolumab and the retrospective study Cheah 2016 for the ACT. The comparison of individual arms from different studies conducted on this basis was unsuitable to derive conclusions on the added benefit of nivolumab in comparison with the ACT. The following reasons were decisive for this:

- On the one hand, the suitability of the studies on nivolumab presented by the company is questionable. The reason for this is that the inclusion and exclusion criteria of the studies did not limit the populations to patients who are not candidates for further SCT. The company presented no data showing that these patients were not candidates for further SCT.
- On the other hand, there are justified doubts that the Cheah 2016 study is suitable for research question 2. It can be inferred that a relevant part of the patients had not received the required pretreatment (ASCT followed by treatment with BV). In addition, there were signs that further SCT was still an option for some of the patients in the Cheah 2016 study. Furthermore, a relevant proportion of the patients were treated with drugs that are not approved in the therapeutic indication.

Irrespective of the missing suitability of the comparison presented by the company, analyses on the comparison between nivolumab and the ACT were not available for all patient-relevant outcomes. In addition, the effects from the comparison of individual arms from different studies presented by the company were not of a magnitude that the effects were not explicable solely by the impact of confounding factors.

Since, overall, the company presented no relevant data for the assessment of the added benefit of nivolumab in patients who are not candidates for further SCT in the dossier, there was 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[4]

Table 3 presents a summary of the probability and extent of the 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	Patients who are candidates for further stem cell transplantation	▪ **Allogeneic stem cell transplantation** or ▪ **HDCT followed by ASCT (high-dose chemotherapy followed by autologous stem cell transplantation)**	Added benefit not proven
2	Patients who are not candidates for further stem cell transplantation	▪ 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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee; HDCT: high-dose chemotherapy

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of the present report was to assess the added benefit of nivolumab in comparison with the ACT in adults with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV.

The G-BA distinguished between 2 patient groups in its specification of the ACT. Two research questions resulted from this for the assessment; their therapeutic indications and ACTs are presented in Table 4.

Table 4: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Patients who are candidates for further stem cell transplantation	▪ **Allogeneic stem cell transplantation** or ▪ **HDCT followed by ASCT (high-dose chemotherapy followed by autologous stem cell transplantation)**
2	Patients who are not candidates for further stem cell transplantation	▪ Treatment specified by the physician under consideration of the approval and prior therapies

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee; HDCT: high-dose chemotherapy

The company followed the ACT specified by the G-BA. The assessment was conducted in comparison with the 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.

2.3 Research question 1: patients who are candidates for further stem cell transplantation

2.3.1 Information retrieval and study pool (research question 1)

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 nivolumab (status: 18 October 2016)
- bibliographical literature search on nivolumab (last search on 18 October 2016)
- search in trial registries for studies on nivolumab (last search on 17 October 2016)
- bibliographical literature search on the ACT (last search on 18 October 2016)

- search in trial registries for studies on the ACT (last search on 17 October 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 23 January 2017)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the comparison of nivolumab versus the ACT.

Since no randomized studies of direct comparisons were available, the company conducted an information retrieval for RCTs for indirect comparisons, for non-randomized comparative studies, and for further investigations. The company stated that it had not identified any suitable comparator data on the ACT on all evidence levels. Hence there were no data for the assessment of the added benefit of nivolumab in patients who are candidates for further SCT.

Although the company presented no comparator data, it still saw an advantage of nivolumab. It argued that treatment with nivolumab resulted in a survival advantage and in clinically relevant improvement. The company's reasoning was not followed (see Section 2.6.2.8.2 of the full dossier assessment).

2.3.2 Results on added benefit (research question 1)

The company presented no data for the assessment of the added benefit of nivolumab in comparison with the ACT for patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV who are candidates for further SCT. This resulted in no hint of an added benefit of nivolumab in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit (research question 1)

Since the company presented no data for the assessment of the added benefit of nivolumab for patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV who are candidates for further SCT, an added benefit of nivolumab for these patients is not proven.

2.3.4 List of included studies (research question 1)

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question 2: patients who are not candidates for further stem cell transplantation

2.4.1 Information retrieval and study pool (research question 2)

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 nivolumab (status: 18 October 2016)
- bibliographical literature search on nivolumab (last search on 18 October 2016)
- search in trial registries for studies on nivolumab (last search on 17 October 2016)
- bibliographical literature search on the ACT (last search on 18 October 2016)
- search in trial registries for studies on the ACT (last search on 17 October 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 23 January 2017)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the comparison of nivolumab versus the ACT.

Since no randomized studies of direct comparisons were available, the company conducted an information retrieval for RCTs for indirect comparisons, for non-randomized comparative studies, and for further investigations. Based on the search results, the company identified further investigations, which it used for the benefit assessment.

These were the 2 single-arm studies CA209-205 [3] and CA209-039 [4] for nivolumab and the retrospective study Cheah 2016 [5] for the ACT. The comparison of individual arms from different studies conducted on this basis was unsuitable to derive conclusions on the added benefit of nivolumab in comparison with the ACT. This is justified below.

Further investigations on nivolumab

Study CA209-205 was the approval study of nivolumab in the present therapeutic indication. Study CA209-039 was a dose-ranging study. Both studies were single-arm, open-label, non-comparative studies with a multicentre design. The CA209-205 study included patients with classical Hodgkin lymphoma after failure of ASCT. The company presented the data of a subpopulation of 137 patients who were pretreated with ASCT followed by BV treatment. According to the therapeutic indication [6], this subpopulation had failure of their last treatment or relapse or progression of the disease at study inclusion.

The CA209-039 study included patients with different therapy-refractory haematologic malignancies. The company presented the data of a subpopulation of 15 patients with classical Hodgkin lymphoma whose pretreatment included ASCT followed by BV treatment. These patients were also refractory or had recurrence.

Suitability for research question 2 unclear

Overall, the company presented data on 153 patients who were treated with nivolumab. It was unclear, however, whether these patients concurred with the population of research question 2 (patients who are not candidates for further SCT). The reason for this is that the inclusion and exclusion criteria of the studies did not limit the populations to patients who are not

candidates for further SCT. The company presented no data showing that these patients were not candidates for further SCT.

Study pool potentially incomplete

The company did not include the single-arm Japanese phase 2 study JapicCTI-142755 ([7,8], N = 17) in its study pool. It is unclear whether the patients included in the study fulfilled the approval criteria for nivolumab (ASCT followed by treatment with BV) and whether, concurring with research question 2, they were not candidates for further SCT (see Section 2.6.2.3.1 of the full dossier assessment). Due to this uncertainty, the study pool is potentially incomplete.

Further investigations on the appropriate comparator therapy

As further investigation on the ACT, the company identified the retrospective observational study Cheah 2016. This study included patients who

- had a histologically confirmed diagnosis of classical Hodgkin lymphoma
- between June 2007 and January 2015, received BV treatment at the MD Anderson Cancer Centre (Houston, Texas, USA) for recurrence or refractoriness
- had disease progression at any time after treatment with BV
- were treated with an individual therapeutic strategy after disease progression

The results reported in the publication on the Cheah 2016 study were not usable for research question 2. This is explained below.

Suitability of the population of the Cheah 2016 study for investigation of the research question not guaranteed

The company did not show that the population of the Cheah 2016 study was suitable for research question 2. On the contrary, there are justified doubts regarding the suitability of the population for research question 2. This concerns mainly 2 aspects. On the one hand, it is unclear how many patients had received the required pretreatment (ASCT followed by treatment with BV). On the other hand, it is unclear to what extent further SCT was not an option for the patients in the Cheah 2016 study.

It is not clear from the Cheah 2016 publication how many of the patients included had already received an ASCT at the time point of treatment with BV. The text of the publication only contains the information that 66 of 97 patients included received an ASCT at the time point of the second remission. This would be a proportion of 68% of the patients included. The abstract states that 100 patients were included in the study and that n = 71 of these patients had had an ASCT before treatment with BV. It can be inferred from this that at least 29% of the patients had received no ASCT before treatment with BV, but the exact proportion is unclear. ASCT before treatment with BV is a prerequisite for treatment with nivolumab and hence an inclusion criterion for the present research question.

According to the information provided in the Cheah 2016 publication, 26 of 97 patients received an SCT in the framework of subsequent therapies after BV (n = 8 received an ASCT and n = 18 an allogeneic SCT). Hence it was not assumed that these patients can be allocated to the present research question (patients who are not candidates for further SCT).

Unapproved therapies in Cheah 2016

It can be inferred from the Cheah 2016 publication that a relevant proportion of the patients (at least 28%) were treated with drugs that are not approved in the therapeutic indication; for example, at least 15 patients received gemcitabine, and at least 12 patients received bendamustine. Both drugs are not approved in the present therapeutic indication [9,10] and therefore do not concur with the ACT, according to which treatment was to be conducted under consideration of the approval status.

No proof of the similarity of the study populations

Neither for the studies CA209-205 and CA209-039, nor for the Cheah 2016 study did the company present data for the respective subpopulation of interest (patients with relapsed or refractory disease after ASCT and treatment with BV who were not candidates for further SCT). Hence it did not prove that the subpopulations of interest of these studies were sufficiently similar.

Results presented by the company

Overall survival

For the outcome "overall survival", the company used a comparison using individual arms from different studies (referred to by the company as "historical comparison") for the derivation of the added benefit. These were the total population of the Cheah 2016 study and the subpopulations – as cited by the company – of the studies CA209-205 and CA209-039.

The company claimed that a hazard ratio of 0.25 with a 95% confidence interval (CI) of [0.14; 0.46] in favour of nivolumab resulted from a Cox proportional hazards regression. Irrespective of the fact that the comparison conducted by the company was unsuitable per se (see above for justification), this effect was not so large that it is not explicable solely by the impact of confounding factors. An orientation for an observed effect that is not explicable solely by the impact of confounding factors is a significance level of 1% and a value of > 10 for the relative risk [1,11]. The company did not provide any further justification for its assessment that the effect it presented was not solely explicable by bias in the historical comparison. This assessment was therefore not followed.

B symptoms

For the outcome "B symptom resolution rate", the company only presented data for the patients treated with nivolumab. In addition, no data were available for the majority of these patients.

The company stated that 87.5% (95% CI [71.0%; 96.5%]) of the patients with B symptoms at the start of the study had complete resolution under nivolumab. This information was based on the analysis of 32 patients in the CA209-205 study with B symptoms in the therapeutic indication at the start of the study. Correspondingly, the vast majority of patients (106 of 138) did not have B symptoms at the start of the study. The company did not address the question whether B symptoms occurred during the study and, if so, how the course of these symptoms was.

The company argued that overall, due to the effect size, there was an advantage of nivolumab despite missing data for the ACT. Irrespective of the fact that the comparison conducted by the company was unsuitable per se (see above for justification), the company's reasoning was not followed.

Further patient-relevant outcomes

The company presented no analyses on the comparison of nivolumab with the ACT for further patient-relevant outcomes (e.g. health-related quality of life, adverse events).

Conclusion

No added benefit of nivolumab in comparison with the ACT could be derived from the comparison of individual study arms from different studies presented by the company. There are justified doubts regarding the suitability of the study on the comparator therapy for research question 2. The suitability of the studies on nivolumab presented by the company is also questionable.

Irrespective of the missing suitability of the comparison presented by the company, analyses on the comparison between nivolumab and the ACT were not available for all patient-relevant outcomes. In addition, the effects from the comparison of individual arms from different studies presented by the company were not of a magnitude that the effects were not explicable solely by the impact of confounding factors.

2.4.2 Results on added benefit (research question 2)

The company presented no relevant data for the assessment of the added benefit of nivolumab in comparison with the ACT for patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV who are not candidates for further SCT. This resulted in no hint of an added benefit of nivolumab in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit (research question 2)

Since the company presented no relevant data for the assessment of the added benefit of nivolumab for patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV who are not candidates for further SCT, an added benefit of nivolumab for these patients is not proven.

2.4.4 List of included studies (research question 2)

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of nivolumab in comparison with the ACT for any of the 2 research questions in the dossier, an added benefit of nivolumab is not proven.

This result deviates from the assessment of the company, which, on the basis of the data it presented for patients who are candidates for further SCT, derived a hint of a non-quantifiable added benefit. It derived a hint of a non-quantifiable, but at least considerable added benefit for patients who are not candidates for further SCT.

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	Appropriate comparator therapy[a]	Probability and extent of added benefit
1	Patients who are candidates for further stem cell transplantation	▪ **Allogeneic stem cell transplantation** or ▪ **HDCT followed by ASCT (high-dose chemotherapy followed by autologous stem cell transplantation)**	Added benefit not proven
2	Patients who are not candidates for further stem cell transplantation	▪ 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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee; HDCT: high-dose chemotherapy

The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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