IQWiG Reports – Commission No. A16-64

Idelalisib (chronic lymphocytic leukaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Idelalisib (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 5 January 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Idelalisib (chronic lymphocytic leukaemia) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

4 October 2016

Internal Commission No.:

A16-64

Address of publisher:

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Keywords: idelalisib, rituximab, ofatumumab, leukemia – lymphocytic – chronic – B-cell, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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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
BSC	best supportive care
CLL	chronic lymphocytic leukaemia
EMA	European Medicines Agency
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)

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 idelalisib for the therapeutic indication that was newly approved in September 2016. 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 4 October 2016.

Research question

The aim of this report was to assess the added benefit of idelalisib in comparison with the appropriate comparator therapy (ACT) in the therapeutic indication that was newly approved in September 2016. This therapeutic indication comprised the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in the following subindications:

- in combination with ofatumumab for patients who have received at least one prior therapy
- in combination with ofatumumab or rituximab as first-line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies

In compliance with the approval of idelalisib, the G-BA differentiated between 2 subindications: pretreated patients (research question 1) and treatment-naive patients with 17p deletion or TP53 mutation (research question 2). The G-BA further distinguished the population of pretreated patients into 2 subpopulations (research questions 1a and 1b).

The research questions and the corresponding ACTs specified by the G-BA are shown in Table 2.

Table 2: Research questions of the benefit assessment of idelalisib

Research question	Subindication	Appropriate comparator therapy[a]
Adult patients with CLL who have received at least one prior therapy		
1a	Adult patients with relapsed or refractory CLL for whom chemotherapy is indicated (in combination with ofatumumab)[b]	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
1b	Adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated (in combination with ofatumumab)[b]	Ibrutinib or best supportive care[c]
Patients with treatment-naive CLL		
2	Adult patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies (in combination with rituximab or ofatumumab)	Best supportive care[c]

a: Presentation of the respective ACT specified by the G-BA.
b: The idelalisib + rituximab combination is not affected by the change in the therapeutic indication and is therefore not subject of the present dossier assessment.
c: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

Research question 1a: pretreated adult patients with relapsed or refractory CLL for whom chemotherapy is indicated

The company presented study GS-US-312-0119 (idelalisib + ofatumumab vs. ofatumumab) for research question 1 as a whole without using this study for the derivation of an added benefit. In the company's assessment, the patient population of the GS-US-312-0119 study can neither be allocated completely to research question 1a nor to research question 1b. Correspondingly, the company provided no additional analyses that address this aspect. Irrespective of this, the GS-US-312-0119 study was not relevant for research question 1a already because the comparator therapy (ofatumumab) does not concur with the ACT specified by the G-BA.

Overall, in its dossier the company presented no relevant data for the assessment of the added benefit of idelalisib in pretreated adult patients with relapsed or refractory CLL for whom chemotherapy is indicated.

This resulted in no hint of an added benefit of idelalisib in comparison with the ACT for research question 1a. An added benefit is therefore not proven.

Research question 1b: pretreated adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated

As for research question 1a, the company presented study GS-US-312-0119 (idelalisib + ofatumumab vs. ofatumumab) for research questions 1a and 1b as a whole without using this study for the derivation of an added benefit. Correspondingly, the company presented no additional analyses also for research question 1b; the comparator therapy chosen in the study also does not concur with the ACT specified by the G-BA.

Overall, in its dossier the company presented no relevant data for the assessment of the added benefit of idelalisib in pretreated adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated.

This resulted in no hint of an added benefit of idelalisib in comparison with the ACT for research question 1b. An added benefit is therefore not proven.

Research question 2: treatment-naive adult patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies

The company identified no randomized controlled trials (RCTs) for research question 2 and presented the one-arm study 101-08 and the corresponding extension study.

In addition, the company considered the results of subgroup analyses of the patients with 17p deletion and/or TP53 mutation from the 2 studies GS-US-312-0116 and GS-US-312-0119, which were only conducted in pretreated patients, however.

Study 101-08

Treatment-naive patients with CLL or small lymphocytic lymphoma were included in the one-arm phase 2 study 101-08. The patients in the study received idelalisib in combination with rituximab.

Being a one-arm study, study 101-08 by itself allowed no comparison with the ACT specified by the G-BA (best supportive care [BSC]). Irrespective of this, it was not clear from the inclusion criteria of study 101-08 that only patients were included for whom no other treatment than idelalisib is suitable (approval requirement of idelalisib). The study was therefore not relevant for research question 2 of the present benefit assessment.

Subgroup analyses of the studies GS-US-312-0116 and GS-US-312-0119

The company used the results of the subgroup of patients with 17p deletion or TP53 mutation from the studies GS-US-312-0116 and GS-US-312-0119 for the derivation of the added benefit. Only pretreated patients were investigated in both studies, however. Since, in addition, the patients in the comparator arms of both studies received rituximab (study GS-US-312-0116) or ofatumumab (study GS-US-312-0119), it can be assumed that the patients included were eligible for other treatments than idelalisib. This is another reason why both studies were unsuitable for research question 2.

Overall, in its dossier the company presented no relevant data for the assessment of the added benefit of idelalisib in treatment-naive adult patients with CLL in the presence of 17p deletion or TP53 mutation for whom no other treatments are suitable.

This resulted in no hint of an added benefit of idelalisib in comparison with the ACT for research question 2. An added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

The extent and probability of the added benefit of the drug idelalisib in comparison with the ACT is assessed on the basis of the results presented. Table 3 presents a summary of the extent and probability of the added benefit of idelalisib.

Table 3: Idelalisib – extent and probability of added benefit

Research question	Subindication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Adult patients with CLL who have received at least one prior therapy			
1a	Adult patients with relapsed or refractory CLL for whom chemotherapy is indicated (in combination with ofatumumab)	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	Added benefit not proven
1b	Adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated (in combination with ofatumumab)	Ibrutinib or best supportive care[b]	Added benefit not proven
Patients with treatment-naive CLL			
2	Adult patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies (in combination with rituximab or ofatumumab)	Best supportive care[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

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 this report was to assess the added benefit of idelalisib in comparison with the ACT in the therapeutic indication that was newly approved in September 2016. This therapeutic indication comprised the treatment of adult patients with CLL in the following subindications:

- in combination with ofatumumab for patients who have received at least one prior therapy
- in combination with ofatumumab or rituximab as first-line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies

In compliance with the approval of idelalisib, the G-BA differentiated between 2 subindications: pretreated patients (research question 1) and treatment-naive patients with 17p deletion or TP53 mutation (research question 2). The G-BA further distinguished the population of pretreated patients into 2 subpopulations (research questions 1a and 1b; see Table 4).

The research questions and the corresponding ACTs specified by the G-BA are shown in Table 4.

Table 4: Research questions of the benefit assessment of idelalisib

Research question	Subindication	Appropriate comparator therapy[a]
Adult patients with CLL who have received at least one prior therapy		
1a	Adult patients with relapsed or refractory CLL for whom chemotherapy is indicated (in combination with ofatumumab)[b]	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
1b	Adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated (in combination with ofatumumab)[b]	Ibrutinib or best supportive care[c]
Patients with treatment-naive CLL		
2	Adult patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies (in combination with rituximab or ofatumumab)	Best supportive care[c]

a: Presentation of the respective ACT specified by the G-BA.
b: The idelalisib + rituximab combination is not affected by the change in the therapeutic indication and is therefore not subject of the present dossier assessment.
c: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

In addition to the idelalisib + ofatumumab combination, the company also considered the idelalisib + rituximab combination for research questions 1a and 1b. The latter was not subject of the present assessment.

Regarding the ACT for research question 1a, the company deviated from the G-BA's specification and defined individually optimized treatment specified by the physician and under consideration of the approval status without further specification as comparator therapy. This was not followed (see Section 2.6.1 of the full dossier assessment).

For research questions 1b and 2, the company concurred with the ACTs specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

The company presented data for 2 of the 3 research questions. An overview of the data presented by the company is shown in Table 5.

Table 5: Idelalisib – data presented by the company

<table>
<tr><th>Research question</th><th>Subindication</th><th colspan="2">Data presented by the company</th></tr>
<tr><td colspan="4">Adult patients with CLL who have received at least one prior therapy</td></tr>
<tr><td>1a</td><td>Adult patients with relapsed or refractory CLL for whom chemotherapy is indicated
(in combination with ofatumumab)</td><td>No data</td><td rowspan="2">Study GS-US-312-0119 (idelalisib + ofatumumab vs. ofatumumab)
Presented by the company for research question 1 as a whole, but considered unsuitable by the company for the derivation of an added benefit for research question 1a or 1b</td></tr>
<tr><td>1b</td><td>Adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated
(in combination with ofatumumab)</td><td>No data</td></tr>
<tr><td colspan="4">Patients with treatment-naive CLL</td></tr>
<tr><td>2</td><td>Adult patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies
(in combination with rituximab or ofatumumab)</td><td colspan="2">Study 101-08[a] (one-arm study on the treatment with idelalisib + rituximab)
subgroup analyses of the studies GS-US-312-0116 (idelalisib + rituximab vs. rituximab) and GS-US-312-0119 (idelalisib + ofatumumab vs. ofatumumab)</td></tr>
<tr><td colspan="4">a: The results from the extension study 101-99 were partly included in the analyses of study 101-08.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee</td></tr>
</table>

2.3 Research question 1a: pretreated adult patients with relapsed or refractory CLL for whom chemotherapy is indicated

2.3.1 Information retrieval and study pool (research question 1a)

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 idelalisib (status: 27 July 2016)
- bibliographical literature search on idelalisib (last search on 26 July 2016)
- search in trial registries for studies on idelalisib (last search on 27 July 2016)

To check the completeness of the study pool:

- search in trial registries for studies on idelalisib (last search on 20 October 2016)

Concurring with the company, no relevant RCT on the direct comparison of idelalisib + ofatumumab versus the ACT was identified from the check of the completeness of the study pool for research question 1a.

In its information retrieval, the company additionally identified the GS-US-312-0119 study [3]. The GS-US-312-0119 study was a randomized, unblinded, phase 3 study on the comparison of idelalisib + ofatumumab with ofatumumab. Pretreated adult patients with CLL requiring treatment who had progressed within 24 months after their last prior therapy were included. In the company's assessment, the patient population of the study can neither be allocated completely to research question 1a nor to research question 1b because a reliable division of the study population in patients who are eligible for chemotherapy and those who are not is not possible. Correspondingly, the company provided no additional analyses that address this aspect. Irrespective of this, the GS-US-312-0119 study was not relevant for research question 1a already because the comparator therapy (ofatumumab) does not concur with the ACT specified by the G-BA.

2.3.2 Results on added benefit (research question 1a)

The company presented no data for the assessment of the added benefit of idelalisib + ofatumumab in adult patients with relapsed or refractory CLL for whom chemotherapy is indicated in its dossier. This resulted in no hint of an added benefit of idelalisib + ofatumumab in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit (research question 1a)

The company presented no data for the assessment of the added benefit of idelalisib + ofatumumab for adult patients with relapsed or refractory CLL for whom

chemotherapy is indicated. Hence an added benefit of idelalisib + ofatumumab is not proven for these patients. This concurs with the company's assessment.

The G-BA decides on the added benefit.

2.3.4 List of included studies (research question 1a)

Not applicable as no studies for this research question were included in the benefit assessment.

2.4 Research question 1b: pretreated adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated

2.4.1 Information retrieval and study pool (research question 1b)

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 idelalisib (status: 27 July 2016)
- bibliographical literature search on idelalisib (last search on 26 July 2016)
- search in trial registries for studies on idelalisib (last search on 27 July 2016)
- bibliographical literature search on the ACT (last search on 26 July 2016)
- search in trial registries for studies on the ACT (last search on 27 July 2016)

To check the completeness of the study pool:

- search in trial registries for studies on idelalisib (last search on 20 October 2016)

No relevant study was identified from the check. The company, in contrast, presented the GS-US-312-0116 study [4]. The combination of idelalisib and rituximab was investigated in this study. This combination in pretreated patients was not subject of the present benefit assessment, however.

As for research question 1a, the company additionally identified the GS-US-312-0119 study on the comparison of idelalisib + ofatumumab with ofatumumab. In the company's assessment, the patient population of the study can neither be allocated completely to research question 1a nor to research question 1b. Correspondingly, the company presented no additional analyses also for research question 1b; the comparator therapy chosen in the study also does not concur with the ACT specified by the G-BA.

2.4.2 Results on added benefit (research question 1b)

The company presented no relevant data for the assessment of the added benefit of idelalisib + ofatumumab for research question 1b. This resulted in no hint of an added benefit

of idelalisib + ofatumumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit (research question 1b)

The company presented no relevant data for the assessment of the added benefit of idelalisib + ofatumumab for patients with relapsed or refractory CLL for whom chemotherapy is not indicated. Hence an added benefit of idelalisib + ofatumumab is not proven for these patients.

This deviates from the assessment of the company, which derived a hint of a non-quantifiable added benefit on the basis of the evidence presented on the combination of idelalisib and rituximab.

The G-BA decides on the added benefit.

2.4.4 List of included studies (research question 1b)

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

2.5 Research question 2: treatment-naive adult patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies

2.5.1 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 list on idelalisib (status: 27 July 2016)
- bibliographical literature search on idelalisib (last search on 26 July 2016)
- search in trial registries for studies on idelalisib (last search on 27 July 2016)

To check the completeness of the study pool:

- search in trial registries for studies on idelalisib (last search on 20 October 2016)

No relevant study was identified from the check.

Since the company identified no RCTs for research question 2, it extended its search to non-randomized trials. In this extended search, the company identified the one-arm study 101-08 [5], which it had already presented for the first assessment of idelalisib, and the corresponding extension study.

In addition, the company considered the results of subgroup analyses of the patients with 17p deletion and/or TP53 mutation from the 2 studies GS-US-312-0116 and GS-US-312-0119, which were only conducted in pretreated patients, however.

Study 101-08

Treatment-naive patients with CLL or small lymphocytic lymphoma were included in the one-arm phase 2 study 101-08. In the first 8 weeks, the patients received idelalisib in combination with rituximab, and then idelalisib was administered until disease progression or occurrence of unacceptable adverse events up to a maximum of 48 weeks. Patients who had completed all 12 cycles of study 101-08 could participate in the extension study 101-99 to continue treatment with idelalisib.

The company analysed the data of 9 treatment-naive patients with 17p deletion or TP53 mutation from study 101-08 (14% of the total population). Data from the extension study 101-99 were partly included in this analysis.

Being a one-arm study, study 101-08 by itself allowed no comparison with the ACT specified by the G-BA (BSC). The company did not present data on the comparator therapy. Irrespective of this, it was not clear from the inclusion criteria of study 101-08 that only patients were included for whom no treatments other than idelalisib in combination with rituximab or ofatumumab were suitable (explicitly patients with contraindication to ibrutinib,

for example). The study was therefore not relevant for research question 2 of the present benefit assessment.

Subgroup analyses of the studies GS-US-312-0116 and GS-US-312-0119

The company used the results of the subgroup of patients with 17p deletion or TP53 mutation from the studies GS-US-312-0116 and GS-US-312-0119 for the derivation of the added benefit. Pretreated patients were investigated in both studies. These studies are therefore not relevant for the present research question 2 (first-line treatment).

Referring to the assessment report of the European Medicines Agency (EMA) [6] on idelalisib and on EMA's concept paper on extrapolation of study results [7], the company noted that transferability of the results to treatment-naive patients can be assumed for the subgroup of patients with 17p deletion or TP53 mutation from the studies GS-US-312-0116 and GS-US-312-0119 (pretreated patients). For transferability of the results it has to be demonstrated with sufficient certainty or plausibility in appropriate scientific studies that the effects of patient-relevant outcomes are not substantially influenced by the different treatment situations (in this case the different pretreatments). Such a demonstration is not contained in the EMA documents mentioned nor does the company present such proof.

In addition, the EMA statements refer to a time point at which the therapeutic indication was wider (patients for whom chemo-immunotherapy is unsuitable) and therefore not to the target population of research question 2 of the present assessment (patients who are not eligible for any other therapies). Since the patients in the comparator arms of both studies received rituximab (study GS-US-312-0116) or ofatumumab (study GS-US-312-0119), it can be assumed, on the contrary, that the patients included were eligible for other treatments than idelalisib.

Overall, the evidence provided by the company for research question 2 is not relevant for the derivation of an added benefit.

2.5.2 Results on added benefit (research question 2)

The company presented no relevant data for the assessment of the added benefit of idelalisib + rituximab or idelalisib + ofatumumab for research question 2.

This resulted in no hint of an added benefit of idelalisib + rituximab or idelalisib + ofatumumab in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit (research question 2)

The company presented no relevant data for the assessment of the added benefit of idelalisib + rituximab or idelalisib + ofatumumab for treatment-naive patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies. Hence an added benefit of idelalisib + rituximab or idelalisib + ofatumumab is not proven for these patients.

This deviates from the company's approach, which derived a hint of a non-quantifiable added benefit of idelalisib.

The G-BA decides on the added benefit.

2.5.4 List of included studies (research question 2)

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

2.5.5 Extent and probability of added benefit – summary

Table 6 presents a summary of the extent and probability of the added benefit of idelalisib.

Table 6: Idelalisib – extent and probability of added benefit

Research question	Subindication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Adult patients with CLL who have received at least one prior therapy			
1a	Adult patients with relapsed or refractory CLL for whom chemotherapy is indicated (in combination with ofatumumab)	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	Added benefit not proven
1b	Adult patients with relapsed or refractory CLL for whom chemotherapy is not indicated (in combination with ofatumumab)	Ibrutinib or best supportive care[b]	Added benefit not proven
Patients with treatment-naive CLL			
2	Adult patients with CLL in the presence of 17p deletion or TP53 mutation who are not eligible for any other therapies (in combination with rituximab or ofatumumab)	Best supportive care[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

An added benefit of idelalisib is not proven for any of the 3 research questions because the company presented no suitable data for any of the research questions.

This deviates from the assessment of the company, which derived a hint of a non-quantifiable added benefit for research questions 1b and 2.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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