

IQWiG Reports – Commission No. A14-35

**Idelalisib –  
Benefit assessment according  
to §35a Social Code Book V<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of Assessment module I, Sections I 2.1 to I 2.9, and Assessment module II, Sections II 2.1 to II 2.6, of the dossier assessment *Idelalisib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2014). 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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**Idelalisib**

**Assessment module I**

**Chronic lymphocytic  
leukaemia**

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### List of abbreviations

<b>Abbreviation</b>	<b>Meaning</b>
17p	short (p) arm of chromosome 17
ACT	appropriate comparator therapy
BSC	best supportive care
CD20	cluster of differentiation 20
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)
SPC	Summary of Product Characteristics
TP53	tumour protein 53

## **I 2 Benefit assessment**

### **I 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. 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 25 September 2014.

#### **Research question**

The aim of this report was to assess the added benefit of idelalisib compared with the appropriate comparator therapy (ACT) specified by the G-BA for adult patients with chronic lymphocytic leukaemia (CLL)

- who have received at least one prior therapy, or
- as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy

The assessment was conducted based on patient-relevant outcomes.

According to this approval of idelalisib, the G-BA distinguished between 2 subindications within the therapeutic indication CLL: pretreated patients and treatment-naive patients with 17p deletion and/or TP53 mutation. The G-BA further divided pretreated patients into 4 subpopulations. Accordingly, the assessment was conducted for a total of 5 research questions versus the ACT specified by the G-BA. The research questions and the corresponding ACTs are shown in Table 1.

Table 1: ACT specified by the G-BA for the benefit assessment of idelalisib in the therapeutic indication CLL

Research question	Subindication	ACT
<b>Research question 1: pretreated patients with CLL</b>		
<b>Patients with relapsed CLL (duration of remission &gt; 6 months)</b>		
1a	Patients for whom chemotherapy is indicated	Chemotherapy in combination with rituximab specified by the physician, under consideration of the approval status
1b	Patients for whom chemotherapy is not indicated	Best supportive care <sup>a</sup>
<b>Patients with refractory CLL (duration of remission ≤ 6 months)</b>		
1c	Patients for whom antineoplastic treatment is indicated <sup>b</sup>	Individually optimized treatment specified by the physician, under consideration of the approval status
1d	Patients for whom antineoplastic treatment is not indicated <sup>b</sup>	Best supportive care <sup>a</sup>
<b>Research question 2: treatment-naïve patients with CLL and 17p deletion or TP53 mutation</b>		
2	First-line treatment in patients with CLL unsuitable for chemo-immunotherapy	Best supportive care <sup>a</sup>
a: 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. b: Antineoplastic treatment refers to the totality of all CLL-targeted drug treatments. ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee		

For research questions 1a to 1d, the company deviated from the G-BA’s differentiation of the therapeutic indication. In contrast to the G-BA, the company summarized the populations of patients with relapsed and refractory CLL. This approach was not followed in the present benefit assessment. The following deviations versus the ACT specified by the G-BA result from the different division of the target population by the company for research question 1c:

- The company named chemotherapy in combination with rituximab specified by the physician and under consideration of the approval status as ACT for patients with refractory CLL for whom antineoplastic treatment including chemotherapy is indicated. This regimen is an option within the ACT defined by the G-BA, but it is not indicated in all patients eligible for chemotherapy in the population of research question 1c. For example, rituximab-refractory patients may be treated with a different, individually optimized treatment.
- For patients for whom antineoplastic treatment, but no chemotherapy is indicated, the company specified best supportive care (BSC) as comparator therapy. However, other antineoplastic treatments (except chemotherapy), which are to be used individually, are an option for these patients.

## Results

### ***Research question 1a: patients with relapsed CLL for whom chemotherapy is indicated***

There were no relevant data for idelalisib in comparison with the ACT (chemotherapy in combination with rituximab specified by the physician, under consideration of the approval status) for patients with relapsed CLL for whom chemotherapy is indicated.

The company presented data for this subpopulation from the non-comparative study 101-07. This study allowed no comparison of idelalisib with the ACT within the study. The company also conducted no adequate comparison of the results on idelalisib from the 101-07 study with results on the ACT from other studies.

There is no proof of added benefit of idelalisib versus the ACT specified by the G-BA (chemotherapy in combination with rituximab specified by the physician, under consideration of the approval status) for the treatment of patients with relapsed CLL for whom chemotherapy is indicated.

### ***Research question 1b: patients with relapsed CLL for whom chemotherapy is not indicated***

There were no relevant data for idelalisib in comparison with the ACT (BSC) for patients with relapsed CLL for whom chemotherapy is not indicated.

The company presented data from its direct comparative randomized approval study GS-US-312-0116 for this research question.

Pretreated patients with CLL that had progressed within 24 months after their last prior therapy were included in the study. Patients were allowed to be refractory to the last prior therapy if this refractoriness concerned no anti-cluster of differentiation 20 (CD20) antibodies (e.g. rituximab, ofatumumab). Hence both patients with relapsed and with refractory CLL were included in the study population. According to the inclusion criteria of the study, chemotherapy was unsuitable for the patients because of chemotherapy-induced bone marrow damage, renal dysfunction or comorbidities. 220 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms idelalisib + rituximab and placebo + rituximab. Patients of both treatment arms received drugs as needed to alleviate symptoms and for accompanying diseases.

The study was not relevant for the present benefit assessment. Patients according to research question 1b (relapsed CLL, no chemotherapy indicated) were also included in the study, but the study allowed no comparison of idelalisib with BSC (defined as best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life), which the G-BA had specified as ACT for this patient population. Instead, the patients of the comparator arm of the study received a uniform regimen with rituximab. Concomitant medication for necessary treatment of accompanying diseases and symptoms was allowed, but it had to be considered whether the administration of this medication compromised the result

or the integrity of the study. This is not compatible with individually optimized treatment in the sense of BSC.

Moreover, rituximab was administered as monotherapy in the comparator arm of the GS-US-312-0116 study. According to the specifications of the Summary of Product Characteristics (SPC), the use of rituximab in CLL is only approved in combination with chemotherapy. The G-BA explicitly pointed out the consideration of the approval status in its specification of the ACT for the individual subpopulations (see Table 1). However, since chemotherapy is not indicated for patients of research question 1b, the approval-compliant use of rituximab is also no treatment option for these patients.

There is no proof of added benefit of idelalisib versus the ACT specified by the G-BA (BSC) for the treatment of patients with relapsed CLL for whom chemotherapy is not indicated.

***Research question 1c: patients with refractory CLL for whom antineoplastic treatment is indicated***

There were no relevant data for idelalisib in comparison with the ACT (individually optimized treatment specified by the physician, under consideration of the approval status) for patients with refractory CLL for whom antineoplastic treatment is indicated.

The company presented data from its direct comparative randomized approval study GS-US-312-0116 for this research question. Patients of this study had progressed within 24 months after their last prior therapy. They were allowed to be refractory to the last prior therapy if this refractoriness concerned no anti-CD20 antibodies (e.g. rituximab, ofatumumab). Hence both patients with relapsed and with refractory CLL were included in the study population. Only patients were investigated in the study for whom chemotherapy was unsuitable. However, the patients could receive other antineoplastic treatments. Hence the study only covered a subgroup of the patients of research question 1c, i.e. the patient population for which no chemotherapy, but other antineoplastic treatments are suitable.

The study was not relevant for the present benefit assessment. A subgroup of patients according to research question 1c (refractory, antineoplastic treatment except chemotherapy indicated) was also included in the study, but the study allowed no comparison of idelalisib with individually optimized treatment specified by the physician, which the G-BA had specified as ACT for this patient population. Instead, the patients of the comparator arm of the study received a uniform regimen with rituximab. Concomitant medication for necessary treatment of accompanying diseases and symptoms was allowed, but it had to be considered whether the administration of this medication compromised the result or the integrity of the study. This is not compatible with individually optimized treatment.

Moreover, rituximab was administered as monotherapy in the comparator arm of the GS-US-312-0116 study. According to the specifications of the SPC, the use of rituximab in CLL is only approved in combination with chemotherapy. The G-BA explicitly pointed out the

consideration of the approval status in its specification of the ACT for this research question (see Table 1). Approval-compliant use of rituximab is no treatment option for the patients investigated in the study (chemotherapy is unsuitable for the patients). However, approval-compliant use would have been possible for a part of the patient population of research question 1c (those for whom chemotherapy is also an option as antineoplastic treatment).

There is no proof of added benefit of idelalisib versus the ACT specified by the G-BA (individually optimized treatment specified by the physician and under consideration of the approval status) for the treatment of patients with refractory CLL for whom antineoplastic treatment is indicated.

***Research question 1d: patients with refractory CLL for whom antineoplastic treatment is not indicated***

There were no data for idelalisib in comparison with the ACT (BSC) for patients with refractory CLL for whom antineoplastic treatment is not indicated. Hence there is no proof of added benefit of idelalisib versus the ACT specified by the G-BA.

**Research question 2: first-line treatment in the presence of 17p deletion or TP53 mutation in patients with CLL unsuitable for chemo-immunotherapy**

For patients of research question 2, there were no relevant data for a comparison of idelalisib with the ACT (BSC).

For this research question, the company used the one-arm phase 2 study 101-08, in which treatment-naïve patients with CLL or small lymphocytic lymphoma were included. This study allowed no comparison of idelalisib with the ACT within the study. The company also conducted no adequate comparison of the results on idelalisib from the 101-08 study with results on the ACT from other studies.

There is no proof of added benefit of idelalisib versus the ACT specified by the G-BA (BSC) for the treatment of CLL in first-line treatment in the presence of 17p deletion or TP53 mutation for patients unsuitable for chemo-immunotherapy.

**Extent and probability of added benefit, patient groups with therapeutically important added benefit<sup>2</sup>**

The company presented no suitable data in its dossier for any of the 5 research questions of the benefit assessment in the therapeutic indication CLL. Hence there is no proof of an added

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<sup>2</sup> 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), see [1]. 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), see [2].

benefit of idelalisib over the ACT specified by the G-BA for the respective subpopulations. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 2 presents a summary of the extent and probability of the added benefit of idelalisib in the therapeutic indication CLL for the different research questions.

Table 2: Idelalisib – extent and probability of added benefit

Subindication	ACT	Extent and probability of added benefit
<b>Research question 1: pretreated patients with CLL</b>		
<b>Patients with relapsed CLL (duration of remission &gt; 6 months)</b>		
Research question 1a ▫ patients for whom chemotherapy is indicated	Chemotherapy in combination with rituximab specified by the physician, under consideration of the approval status	Added benefit not proven
Research question 1b ▫ patients for whom chemotherapy is not indicated	Best supportive care <sup>a</sup>	Added benefit not proven
<b>Patients with refractory CLL (duration of remission ≤ 6 months)</b>		
Research question 1c ▫ patients for whom antineoplastic treatment <sup>b</sup> is indicated	Individually optimized treatment specified by the physician, under consideration of the approval status	Added benefit not proven
Research question 1d ▫ patients for whom antineoplastic treatment <sup>b</sup> is not indicated	Best supportive care <sup>a</sup>	Added benefit not proven
<b>Research question 2: treatment-naive patients with CLL and 17p deletion or TP53 mutation</b>		
First-line treatment in patients unsuitable for chemo-immunotherapy	Best supportive care <sup>a</sup>	Added benefit not proven
a: 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. b: Antineoplastic treatment refers to the totality of all CLL-targeted drug treatments. 17p: short (p) arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee; TP53: tumour protein 53		

The G-BA decides on the added benefit.

## I 2.2 Research question

The aim of this report was to assess the added benefit of idelalisib compared with the ACT specified by the G-BA for adult patients with CLL

- who have received at least one prior therapy, or
- as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy

The assessment was conducted based on patient-relevant outcomes.

According to the approval of idelalisib, the G-BA distinguished between 2 subindications within the therapeutic indication CLL: pretreated patients and treatment-naive patients with 17p deletion and/or TP53 mutation. The G-BA further divided pretreated patients into 4 subpopulations. Accordingly, the assessment was conducted for a total of 5 research questions versus the ACT specified by the G-BA. The research questions and the corresponding ACTs are shown in Table 3.

Table 3: ACT specified by the G-BA for the benefit assessment of idelalisib in the therapeutic indication CLL

Research question	Subindication	ACT
<b>Research question 1: pretreated patients with CLL</b>		
<b>Patients with relapsed CLL (duration of remission &gt; 6 months)</b>		
1a	Patients for whom chemotherapy is indicated	Chemotherapy in combination with rituximab specified by the physician, under consideration of the approval status
1b	Patients for whom chemotherapy is not indicated	Best supportive care <sup>a</sup>
<b>Patients with refractory CLL (duration of remission ≤ 6 months)</b>		
1c	Patients for whom antineoplastic treatment is indicated <sup>b</sup>	Individually optimized treatment specified by the physician, under consideration of the approval status
1d	Patients for whom antineoplastic treatment is not indicated <sup>b</sup>	Best supportive care <sup>a</sup>
<b>Research question 2: treatment-naive patients with CLL and 17p deletion or TP53 mutation</b>		
2	First-line treatment in patients with CLL unsuitable for chemo-immunotherapy.	Best supportive care <sup>a</sup>
a: 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. b: Antineoplastic treatment refers to the totality of all CLL-targeted drug treatments. 17p: short (p) arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee; TP53: tumour protein 53		

For research questions 1a to 1d, the company deviated from the G-BA's differentiation of the therapeutic indication (see I Appendix B of the full dossier assessment). In contrast to the G-BA, the company summarized the populations of patients with relapsed and refractory CLL. CLL is considered to be relapsed if the patient responded to treatment and progresses more than 6 months after that treatment. The disease is considered to be refractory if the patient either did not respond to treatment or progression occurs within 6 months after treatment [3]. The company's approach was not followed in the present benefit assessment.

The consequences resulting from the company's deviating division of the population is explained below for the individual research questions 1a to 1d. For research question 2, there was no deviation from the G-BA's specification.

### **Research question 1: pretreated patients with CLL**

#### ***Research question 1a: patients with relapsed CLL for whom chemotherapy is indicated***

According to the G-BA's specification, the benefit assessment for patients of research question 1a was conducted versus chemotherapy in combination with rituximab specified by the physician and under consideration of the approval status.

The ACT specified by the company for this patient population concurs with the G-BA's specification.

#### ***Research question 1b: patients with relapsed CLL for whom chemotherapy is not indicated***

According to the G-BA's specification, the benefit assessment for patients of research question 1b was conducted versus BSC.

The ACT specified by the company for this patient population concurs with the G-BA's specification.

#### ***Research question 1c: patients with refractory CLL for whom antineoplastic treatment is indicated***

According to the G-BA's specification, the benefit assessment for patients of research question 1c was conducted versus individually optimized treatment specified by the physician, under consideration of the approval status.

The following deviations versus the ACT specified by the G-BA result from the different division of the target population by the company:

- The company named chemotherapy in combination with rituximab specified by the physician and under consideration of the approval status as ACT for patients with refractory CLL for whom antineoplastic treatment including chemotherapy is indicated. This regimen is an option within the ACT defined by the G-BA, but it is not indicated in all patients eligible for chemotherapy in the population of research question 1c. It is

unsuitable for rituximab-refractory patients, for example, which, however, can be treated with another individually optimized treatment.

- For patients for whom antineoplastic treatment, but no chemotherapy is indicated, the company specified BSC as comparator therapy. However, other antineoplastic treatments (except chemotherapy), which are to be used individually, are an option for these patients.

The company was therefore not followed in its specification of the comparator therapy for the population of research question 1c.

***Research question 1d: patients with refractory CLL for whom antineoplastic treatment is not indicated***

According to the G-BA's specification, the benefit assessment for patients of research question 1d was conducted versus BSC.

The ACT specified by the company for this patient population concurs with the G-BA's specification.

**Research question 2: treatment-naive patients with CLL and 17p deletion or TP53 mutation**

According to the G-BA's specification, the benefit assessment for patients of research question 2 for whom chemo-immunotherapy is unsuitable was conducted versus BSC.

The ACT specified by the company for this patient population concurs with the G-BA's specification.

### **I 2.3 Research question 1a: patients with relapsed CLL for whom chemotherapy is indicated**

#### **I 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 lists on idelalisib (studies completed up to 19 August 2014)
- bibliographical literature search on idelalisib (last search on 7 July 2014)
- search in trial registries for studies on idelalisib (last search on 7 July 2014)

The company identified the phase 1 study 101-07, in which the patients of all treatment arms received idelalisib, which was administered in different dosages and in combination with other antineoplastic agents (including rituximab). The study allowed no comparison of idelalisib with the ACT specified by the G-BA. Hence the study was not used in the present benefit assessment to derive an added benefit of idelalisib.

This concurs with the company's approach, which, according to the company, presented the results of this study exclusively for reasons of transparency. It claimed no added benefit based on these data.

#### **I 2.3.2 Results on added benefit – research question 1a**

No relevant data were available for research question 1a. Hence an added benefit of idelalisib versus the ACT specified by the G-BA is not proven in patients with relapsed CLL for whom chemotherapy is indicated.

#### **I 2.3.3 Extent and probability of added benefit – research question 1a**

Since no relevant data for this research question were presented for the benefit assessment, there is no proof of added benefit of idelalisib versus the ACT specified by the G-BA (chemotherapy in combination with rituximab specified by the physician, under consideration of the approval status) for the treatment of patients with relapsed CLL for whom chemotherapy is indicated. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. The company also claimed no added benefit for this research question.

### **I 2.4 Research question 1b: patients with relapsed CLL for whom chemotherapy is not indicated**

#### **I 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 lists on idelalisib (studies completed up to 19 August 2014)
- bibliographical literature search on idelalisib (last search on 7 July 2014)
- search in trial registries for studies on idelalisib (last search on 7 July 2014)
- bibliographical literature search on the ACT (last search on 7 July 2014)
- search in trial registries for studies on the ACT (last search on 2 July 2014)

To check the completeness of the study pool regarding randomized controlled trials (RCT)s:

- bibliographical literature search on idelalisib (last search on 21 October 2014)
- search in trial registries for studies on idelalisib (last search on 21 October 2014)

No relevant study for the research question was identified from the steps of information retrieval mentioned. This deviates from the company's approach, which included the GS-US-312-0116 study [4] in its assessment. The company also cited the GS-US-312-0117 extension study, the data of which were partially included in the analyses of the GS-US-312-0116 study. Both studies were unsuitable for the assessment of the added benefit of idelalisib in comparison with the ACT specified by the G-BA. The studies GS-US-312-0116 and GS-US-312-0117 are described below and the reasons for exclusion are explained.

#### **Description and reasons for exclusion of the studies GS-US-312-0116 and GS-US-312-0117**

Study GS-US-312-0116 is presented in Table 4 and Table 5.

Table 4: Characteristics of the study included – idelalisib + rituximab vs. placebo + rituximab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes
GS-US-312-0116	RCT, double-blind, parallel	Adult patients with pretreated CLL; radiographically measurable lymphadenopathy; CLL requiring treatment; CLL progression within < 24 months since completion of the last CLL treatment; in case of prior therapy with an anti-CD20 antibody: improvement under this therapy or progression $\geq$ 6 months after completion; suitability for non-cytotoxic treatment (due to chemotherapy-associated bone marrow damage, creatinine clearance < 60 mL/min; or a CIRS score > 6); Karnofsky performance status $\geq$ 40	Idelalisib + rituximab (N = 110) Placebo + rituximab (N = 110)	Treatment duration: until progression or discontinuation of treatment or study 5-year follow-up for survival, 30 days after the end of study for adverse events data cut-off for overall survival 9 October 2013	Countries: 58 centres in the United States and in Europe (France, Great Britain, Italy, Germany) Period: 1 May 2012: randomization of the first patient 9 October 2013: last data cut-off before unblinding	Primary outcome: progression-free survival  Secondary outcomes: overall survival, morbidity, health-related quality of life, adverse events
<p>a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.</p> <p>CD20: cluster of differentiation 20; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus</p>						

Table 5: Characteristics of the interventions – RCT, direct comparison/indirect comparison – idelalisib + rituximab vs. placebo + rituximab

Study	Intervention	Comparison	Concomitant medication
GS-US-312-0116	Idelalisib 150 mg, orally, twice daily, dose reduction was allowed rituximab, intravenously; 375 mg/m <sup>2</sup> on day 1, 500 mg/m <sup>2</sup> in weeks 2, 4, 6, 8, 12, 16, 20; 8 infusions in total	Placebo, orally twice daily; rituximab, intravenously; 375 mg/m <sup>2</sup> on day 1, 500 mg/m <sup>2</sup> in weeks 2, 4, 6, 8, 12, 16, 20; 8 infusions in total	Not allowed: other antineoplastic substances except study medication Allowed: medication as needed to alleviate symptoms and for accompanying diseases

RCT: randomized controlled trial; vs.: versus

Study GS-US-312-0116 was a company-sponsored, randomized active-controlled, double-blind approval study.

Pretreated patients with CLL that had progressed within 24 months after their last prior therapy were included. According to the inclusion criteria, chemotherapy was unsuitable for these patients because of chemotherapy-induced bone marrow damage, renal dysfunction or comorbidities. Patients were allowed to be refractory to the last prior therapy if this refractoriness concerned no anti-CD20 antibodies (e.g. rituximab, ofatumumab). Hence both patients with relapsed and with refractory CLL were included in the study population.

220 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms idelalisib + rituximab and placebo + rituximab according to the treatment regimens specified in Table 5. Patients of both treatment arms received drugs as needed to alleviate symptoms and for accompanying diseases.

The study was not relevant for the present benefit assessment. Patients according to research question 1b (relapsed CLL, no chemotherapy indicated) were also included in the study, but the study allowed no comparison of idelalisib with BSC (defined as best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life), which the G-BA had specified as ACT for this patient population. Instead, the patients of the comparator arm of the study received a uniform regimen with rituximab. Concomitant medication for necessary treatment of accompanying diseases and symptoms was allowed, but it had to be considered whether the administration of this medication compromised the result or the integrity of the study. This is not compatible with individually optimized treatment in the sense of BSC. The guidelines also contain no indication that rituximab is to be used as a mandatory component of palliative/supportive treatment of patients with relapsed CLL [5-7]. Furthermore, according to the study documents, the study was designed in such a way that all patients in the study received potentially active treatment.

In addition, rituximab was administered as monotherapy in the comparator arm of the GS-US-312-0116 study. According to the specifications of the SPC, the use of rituximab in CLL is only approved in combination with chemotherapy [8]. However, since chemotherapy is not indicated for patients of research question 1b, the approval-compliant use of rituximab is also no treatment option for these patients.

Study GS-US-312-0117 was a company-sponsored, 2-arm extension study of the GS-US-312-0116 study. All patients of the GS-US-312-0116 study who had tolerated the study medication but had progressed could be enrolled in this study. The patients of the previous verum arm received idelalisib in a dosage of 300 mg and patients of the previous control arm received 150 mg (in each case twice daily). This study was not relevant for the benefit assessment because it allowed no comparison of idelalisib versus the ACT specified by the G-BA. However, it was mentioned by the company because data of patients who had already been included in the extension study at the time point of analysis were included in the analysis of GS-US-312-0116 in the framework of follow-up.

Both studies were not included in the present benefit assessment for the reasons mentioned.

#### **I 2.4.2 Results on added benefit – research question 1b**

No relevant data were available for research question 1b. Hence an added benefit of idelalisib versus the ACT specified by the G-BA is not proven in patients with relapsed CLL for whom chemotherapy is not indicated.

#### **I 2.4.3 Extent and probability of added benefit – research question 1b**

Since no relevant data for this research question were presented for the benefit assessment, there is no proof of added benefit of idelalisib versus the ACT specified by the G-BA in the treatment of patients with relapsed CLL for whom chemotherapy is not indicated. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's assessment, which derived an indication of a major added benefit for patients with relapsed CLL for whom chemotherapy is not indicated. Furthermore, the company derived proof of major added benefit on the basis of a subgroup analysis for pretreated CLL patients with 17p deletion and/or TP53 mutation.

### **I 2.5 Research question 1c: patients with refractory CLL for whom antineoplastic treatment is indicated**

#### **I 2.5.1 Information retrieval and study pool – research question 1c**

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 idelalisib (studies completed up to 19 August 2014)
- bibliographical literature search on idelalisib (last search on 7 July 2014)
- search in trial registries for studies on idelalisib (last search on 7 July 2014)
- bibliographical literature search on the ACT (last search on 7 July 2014)
- search in trial registries for studies on the ACT (last search on 2 July 2014)

To check the completeness of the study pool regarding RCTs:

- bibliographical literature search on idelalisib (last search on 21 October 2014)
- search in trial registries for studies on idelalisib (last search on 21 October 2014)

No relevant direct comparative study was identified for the present research question 1c. This deviates from the company's approach, which, in analogy to research question 1b, used the direct comparative randomized approval study GS-US-312-0116, in which both patients with relapsed and with refractory CLL were included. The company additionally cited the GS-US-312-0117 extension study. As described in I 2.4.1, this study was not relevant for the benefit assessment because all patients received idelalisib.

Further information on the study design and the interventions used in the GS-US-312-0116 study can be found in Section I 2.4.1.

The study was not relevant for the present benefit assessment. Since it exclusively investigated patients for whom chemotherapy is unsuitable, the study only covered a subgroup of the patients of research question 1c, i.e. the patient population for which no chemotherapy, but other antineoplastic treatments are suitable. Furthermore, it allowed no comparison of idelalisib with individually optimized treatment specified by the physician and under consideration of the approval status, which was the ACT specified by the G-BA for this population. Instead, the patients of the comparator arm of the study received a uniform regimen with rituximab. Concomitant medication for necessary treatment of accompanying diseases and symptoms was allowed, but it had to be considered whether the administration of this medication compromised the result or the integrity of the study. This is not compatible with individually optimized treatment.

Moreover, as described in Section I 2.4.1, rituximab was administered as monotherapy in the comparator arm of the GS-US-312-0116 study. According to the specifications of the SPC, the use of rituximab in CLL is only approved in combination with chemotherapy [8]. The G-BA explicitly pointed out the consideration of the approval status in its specification of the ACT for this research question (see Table 3). Approval-compliant use of rituximab is no treatment option for the patients investigated in the study (chemotherapy is unsuitable for the patients). However, approval-compliant use would have been possible for a part of the patient population of research question 1c (those for whom chemotherapy is also an option as antineoplastic treatment).

Study GS-US-312-0116, including its extension GS-US-312-0117, was not included in the present benefit assessment for the reasons mentioned.

### **I 2.5.2 Results on added benefit – research question 1c**

No relevant data were available for research question 1c. Hence an added benefit of idelalisib versus the ACT specified by the G-BA is not proven for patients with refractory CLL for whom antineoplastic treatment is indicated.

### **I 2.5.3 Extent and probability of added benefit – research question 1c**

Since no relevant data for this research question were presented for the benefit assessment, there is no proof of added benefit of idelalisib versus the ACT specified by the G-BA in the treatment of patients with refractory CLL for whom antineoplastic treatment is indicated. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. This assessment deviates from that of the company. The company derived an indication of major added benefit for the subpopulation of patients for whom antineoplastic treatment, but no chemotherapy is indicated. Furthermore, the company derived proof of major added benefit on the basis of a subgroup analysis for pretreated CLL patients with 17p deletion and/or TP53 mutation.

## **I 2.6 Research question 1d: patients with refractory CLL for whom antineoplastic treatment is not indicated**

### **I 2.6.1 Information retrieval and study pool – research question 1d**

The company conducted no information retrieval for the present research question 1d.

### **I 2.6.2 Results on added benefit – research question 1d**

The company presented no data for research question 1d. Hence an added benefit of idelalisib versus the ACT specified by the G-BA is not proven in patients with refractory CLL for whom antineoplastic treatment is not indicated.

### **I 2.6.3 Extent and probability of added benefit – research question 1d**

Since no relevant data were presented for the benefit assessment, there is no proof of added benefit of idelalisib versus the ACT specified by the G-BA in the treatment of patients with relapsed CLL for whom antineoplastic treatment is not indicated. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. The company also claimed no added benefit for this research question.

## **I 2.7 Research question 2: first-line treatment in the presence of 17p deletion or TP53 mutation in patients with CLL unsuitable for chemo-immunotherapy**

### **I 2.7.1 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 idelalisib (studies completed up to 19 August 2014)
- bibliographical literature search on idelalisib (last search on 7 July 2014)
- search in trial registries for studies on idelalisib (last search on 7 July 2014)
- bibliographical literature search on the ACT (last search on 7 July 2014)
- search in trial registries for studies on the ACT (last search on 2 July 2014)

To check the completeness of the study pool regarding RCTs:

- bibliographical literature search on idelalisib (last search on 21 October 2014)
- search in trial registries for studies on idelalisib (last search on 21 October 2014)

No relevant direct comparative study was identified for the present research question 2.

For research question 2, the company used the one-arm phase 2 study 101-08, in which treatment-naive patients with CLL or small lymphocytic lymphoma were included. 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. The company analysed the data of 9 treatment-naive patients with 17p deletion or TP53 mutation from this study.

The study itself allowed no comparison with the ACT specified by the G-BA. Hence the study was not relevant for the different research questions of the present benefit assessment. The company compared the results of the subpopulation of treatment-naive patients with 17p deletion or TP53 mutation with results of other studies with treatment-naive patients with CLL without considering the ACT specified by the G-BA. Moreover, the company itself claimed that the studies were a subjective choice; it did not conduct a systematic search.

Referring to the preliminary assessment report by the European Medicines Agency (EMA) [9], the company also noted that transferability of the results for the subgroup of patients with 17p deletion or TP53 mutation from the GS-US-312-0116 study (pretreated patients) to non-pretreated patients can be assumed. 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). This is not proven in the EMA document mentioned nor does the company present such a proof. In addition, the GS-US-312-0116 study was not relevant for the benefit assessment for the reasons described above (see I 2.4.1).

### **I 2.7.2 Results on added benefit – research question 2**

No relevant data were available for research question 2. Hence an added benefit of idelalisib versus the ACT specified by the G-BA is not proven in first-line treatment in the presence of 17p deletion or TP53 mutation for patients with CLL unsuitable for chemo-immunotherapy.

### **I 2.7.3 Extent and probability of added benefit – research question 2**

Since no relevant data were presented for the benefit assessment, there is no proof of added benefit of idelalisib versus the ACT specified by the G-BA in first-line treatment in the presence of 17p deletion or TP53 mutation for patients with CLL unsuitable for chemo-immunotherapy.

This deviates from the company's assessment, which claimed a hint of non-quantifiable added benefit for this patient group.

**I 2.8 Extent and probability of added benefit – summary**

The company presented no suitable data in its dossier for any of the 5 research questions of the benefit assessment in the therapeutic indication CLL, neither for a direct comparison nor from further investigations. Hence there is no proof of an added benefit of idelalisib over the ACT specified by the G-BA for the respective subpopulations. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 6 provides an overview of the extent and probability of the added benefit for the different research questions.

Table 6: Idelalisib – extent and probability of added benefit

Subindication	ACT	Extent and probability of added benefit
<b>Research question 1: pretreated patients with CLL</b>		
Patients with relapsed CLL (duration of remission > 6 months)		
Research question 1a ▫ patients for whom chemotherapy is indicated	Chemotherapy in combination with rituximab specified by the physician, under consideration of the approval status	Added benefit not proven
Research question 1b ▫ patients for whom chemotherapy is not indicated	Best supportive care <sup>a</sup>	Added benefit not proven
<b>Patients with refractory CLL (duration of remission ≤ 6 months)</b>		
Research question 1c ▫ patients for whom antineoplastic treatment <sup>b</sup> is indicated	Individually optimized treatment specified by the physician, under consideration of the approval status	Added benefit not proven
Research question 1d ▫ patients for whom antineoplastic treatment <sup>b</sup> is not indicated	Best supportive care <sup>a</sup>	Added benefit not proven
<b>Research question 2: treatment-naïve patients with CLL and 17p deletion or TP53 mutation</b>		
First-line treatment in patients unsuitable for chemo-immunotherapy	Best supportive care <sup>a</sup>	Added benefit not proven
a: 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. b: Antineoplastic treatment refers to the totality of all CLL-targeted drug treatments. 17p: short (p) arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee; TP53: tumour protein 53		

This deviates from the company’s result, which derived an added benefit of idelalisib from the data it submitted as follows:

Under research question 1c, the company considered separately the group of patients for whom antineoplastic treatment but no chemotherapy is indicated. The company claimed an indication of a major added benefit for this subpopulation. For the subgroup of patients of this subpopulation with 17p deletion and/or TP53 mutation, the company derived proof of major

added benefit. For the patients of research question 2, the company derived a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

## **I 2.9 List of included studies**

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of idelalisib versus the ACT specified by the G-BA could be derived.

## **References for English extract**

Please see full assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 1 August 2014]. URL: [https://www.iqwig.de/download/IQWiG\\_General\\_Methods\\_Version\\_%204-1.pdf](https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf).
2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: [https://www.iqwig.de/download/A11-02\\_Extract\\_of\\_dossier\\_assessment\\_Ticagrelor.pdf](https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf).
3. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008; 111(12): 5446-5456.
4. Gilead Sciences. A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated chronic lymphocytic leukemia: study GS-US-312-0116; second interim clinical study report [unpublished]. 2013.
5. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Chronische Lymphatische Leukämie (CLL): Leitlinie [online]. November 2014 [accessed: 18 December 2014]. URL: <https://www.dgho-onkopedia.de/de/onkopedia/leitlinien/cll/chronische-lymphatische-leuka-mie-ctl.pdf>.
6. Eichhorst B, Dreyling M, Robak T, Montserrat E, Hallek M. Chronic lymphocytic leukemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011; 22(Suppl 6): vi50-vi54.
7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas; version 1.2014 [online]. 20 December 2013 [accessed: 20 November 2014]. URL: <http://www.nccn.org>.
8. Roche. MabThera i.v.: Fachinformation [online]. May 2014 [accessed: 3 December 2014].

9. European Medicines Agency. Zydelig: European public assessment report [unpublished preliminary version]. 2014.

**Idelalisib**

**Assessment module II**

**Refractory follicular  
lymphoma**

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IQWiG thanks the medical and scientific advisor for her contribution to the assessment. However, the advisor was not involved in the actual preparation of the assessment. The responsibility for the contents of the assessment lies solely with IQWiG.

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**Keywords:** idelalisib, lymphoma – follicular, benefit assessment

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<sup>1</sup> Due to legal data protection regulations, employees have the right not to be named.

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**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

## **II 2 Benefit assessment**

### **II 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. 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 25 September 2014.

#### **Research question**

The aim of this report was to assess the added benefit of idelalisib as monotherapy in patients with follicular lymphoma that is refractory to 2 prior lines of treatment.

The benefit assessment was conducted in comparison with the appropriate comparator therapy (ACT) best supportive care (BSC) specified by the G-BA. BSC 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. The company followed the G-BA’s specification.

The assessment was based on patient-relevant outcomes.

#### **Results**

There were no relevant data for idelalisib in comparison with the ACT (BSC) for patients with follicular lymphoma that is refractory to 2 prior lines of treatment.

The company used the one-arm idelalisib study 101-09 to derive an added benefit of idelalisib. This study also included patients with follicular lymphoma who had received at least 2 prior chemotherapy- or immunotherapy-based treatments. All patients of this study received 150 mg idelalisib twice daily.

The 101-09 study allowed no comparison of idelalisib with the ACT specified by the G-BA (BSC) within the study. The company also conducted no adequate comparison of the results on idelalisib from the 101-09 study with results on the ACT from other studies. Hence the 101-09 study was not used in the present benefit assessment to derive an added benefit of idelalisib.

The added benefit of idelalisib as monotherapy over the ACT specified by the G-BA (BSC) in the treatment of patients with refractory follicular lymphoma is therefore not proven.

**Extent and probability of added benefit, patient groups with therapeutically important added benefit**

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of idelalisib versus the ACT specified by the G-BA (BSC) for the treatment of patients with refractory follicular lymphoma. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 1 presents a summary of the extent and probability of the added benefit of idelalisib in the therapeutic indication refractory follicular lymphoma.

Table 1: Idelalisib – extent and probability of added benefit

<b>Therapeutic indication</b>	<b>ACT</b>	<b>Extent and probability of added benefit</b>
Patients with follicular lymphoma that is refractory to 2 prior lines of treatments	Best supportive care <sup>a</sup>	Added benefit not proven
a: 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		

The G-BA decides on the added benefit.

## II 2.2 Research question

The aim of this report was to assess the added benefit of idelalisib as monotherapy in patients with follicular lymphoma that is refractory to 2 prior lines of treatment.

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

The assessment was based on patient-relevant outcomes.

## II 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 idelalisib (studies completed up to 19 August 2014)
- bibliographical literature search on idelalisib (last search on 7 July 2014)
- search in trial registries for studies on idelalisib (last search on 7 July 2014)
- bibliographical literature search on the ACT (last search on 7 July 2014)
- search in trial registries for studies on the ACT (last search on 7 July 2014)

To check the completeness of the study pool regarding randomized controlled trials:

- bibliographical literature search on idelalisib (last search on 21 October 2014)
- search in trial registries for studies on idelalisib (last search on 21 October 2014)

No relevant study for the research question was identified from the steps of information retrieval mentioned.

This approach deviates from that of the company. The company also identified no relevant direct comparative study with idelalisib, but used the one-arm idelalisib study 101-09 to derive an added benefit of idelalisib. This study included patients with follicular lymphoma, small B-cell lymphoma, Waldenström macroglobulinaemia, and mantle cell lymphoma who had received at least 2 prior chemotherapy- or immunotherapy-based treatments. All patients of this study received 150 mg idelalisib twice daily.

The 101-09 study allowed no comparison of idelalisib with the ACT specified by the G-BA (BSC) within the study. The company also conducted no adequate comparison of the results on idelalisib from the 101-09 study with results on the ACT from other studies. Hence the 101-09 study was not used in the present benefit assessment to derive an added benefit of idelalisib.

## II 2.4 Results on added benefit

No relevant studies were available for the research question on the added benefit of idelalisib as monotherapy versus BSC. The added benefit of idelalisib as monotherapy over the ACT specified by the G-BA (BSC) in the treatment of patients with refractory follicular lymphoma is therefore not proven.

## II 2.5 Extent and probability of added benefit

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of idelalisib versus the ACT specified by the G-BA (BSC). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived (see Table 2).

Table 2: Idelalisib – extent and probability of added benefit

Therapeutic indication	ACT	Extent and probability of added benefit
Patients with follicular lymphoma that is refractory to 2 prior lines of treatments	Best supportive care <sup>a</sup>	Added benefit not proven
a: 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		

This deviates from the company’s assessment, which derived a hint of non-quantifiable added benefit of idelalisib. The company made no statement about whether this added benefit, from the company’s point of view, refers to the comparator therapy specified by the G-BA.

The G-BA decides on the added benefit.

## II 2.6 List of included studies

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of idelalisib versus the ACT specified by the G-BA could be derived.

*The full report (German version) is published under <https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-35-idelalisib-nutzenbewertung-gemass-35a-sgb-v-dossierbewertung.6419.html>.*