IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of Modules I to III of the dossier assessment *Ibrutinib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2016). 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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Ibrutinib

Assessment module I

Chronic lymphocytic leukaemia

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IQWiG thanks the medical and scientific advisor for his 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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[1] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
B-R	bendamustine + rituximab
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BSC	best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society of Haematology and Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life-5 Dimensions
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MID	minimally important difference
MMRM	mixed-effects model repeated measures
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small lymphocytic lymphoma
SPC	Summary of Product Characteristics
VAS	visual analogue scale

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 ibrutinib. 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 1 February 2016.

The drug ibrutinib is approved for several therapeutic indications. The present assessment module I contains the assessment of the therapeutic indication chronic lymphocytic leukaemia (CLL).

Research question

The aim of this report was to assess the added benefit of ibrutinib compared with the appropriate comparator therapy (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.

According to the approval of ibrutinib, the G-BA distinguished between 2 subindications within the therapeutic indication CLL: pretreated patients and treatment-naive patients with 17p deletion or TP53 mutation. The G-BA further divided pretreated patients into 2 subpopulations. Accordingly, the assessment was conducted for a total of 3 research questions. 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 ibrutinib in the therapeutic indication CLL

Research question	Subindication	Appropriate comparator therapy[a]
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
1b	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	Idelalisib or **best supportive care**[b]
2	First-line treatment of the CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy	Idelalisib[c] or **best supportive care**[b]

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.
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.
c: The approval of idelalisib was changed in the course of the benefit assessment. Following this change, idelalisib in first-line treatment is now only approved for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment [1]. This had no consequences for the present benefit assessment, however, because the company had not chosen idelalisib as comparator therapy.
CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The company accepted the ACT specified by the G-BA within the respective research question.

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

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

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

The company presented one direct and 3 indirect comparisons for research question 1a, which were not relevant for the present benefit assessment for the reasons stated below.

Direct comparison

The company presented study CLL3001 (ibrutinib + bendamustine + rituximab [B-R] versus placebo + B-R), in which the comparator therapy was not chosen for the individual patient, but in which all patients were uniformly receiving B-R. None of the guidelines names B-R as

the preferred choice over other treatment options mentioned in the guidelines for the target population. The company provided no proof that B-R constituted the most suitable treatment for a majority of the study population.

In addition, the therapy used in both treatment groups was not in compliance with the approval because, according to the Federal Institute for Drugs and Medical Devices (BfArM), bendamustine is not approved for second-line treatment in patients with CLL in monotherapy or in the framework of combination therapies.

Unadjusted indirect comparison

The company presented an unadjusted indirect comparison of the ibrutinib arm of study PCYC-1112-CA (ibrutinib + best supportive care [BSC] versus ofatumumab + BSC) with the placebo + B-R arm of the CLL3001 study. Since the CLL3001 study was unsuitable for the derivation of an added benefit of ibrutinib for research question 1a (see above), the unadjusted indirect comparison in which this study was included was also not relevant.

Indirect comparison according to Bucher

The company conducted an indirect comparison according to Bucher between the studies PCYC-1112-CA (ibrutinib + BSC versus ofatumumab + BSC) and OMB114242 (ofatumumab versus physician´s choice) using the ofatumumab arms of both studies as common comparator.

For several reasons, the indirect comparison presented by the company was not usable.

The maximum treatment duration in the ofatumumab arm of the PCYC-1112-CA study was 24 weeks. Patients in the ofatumumab arm of the OMB114242 study were treated for a period of up to 48 weeks. Due to the important differences in treatment duration in the data cut-offs presented by the company, there was therefore no sufficient similarity between the ofatumumab arms of both studies, which is required for a common comparator. In addition, a 48-week administration of ofatumumab does not comply with the approval. The approval specifies a maximum period of ofatumumab administration of 24 weeks.

Furthermore, the total populations of both studies differed particularly regarding the number of prior therapies. Under the assumption that the vast majority of patients in the OMB114242 study were at least double-refractory, this proportion, according to the company's definition, was unsuitable for chemotherapy and therefore did not concur with the population of research question 1a (chemotherapy indicated). Nonetheless, the company used the OMB114242 study in the indirect comparison for research question 1a. The company did not address this contradiction. The matching-adjusted indirect comparison (MAIC) conducted by the company to adjust the study populations did not solve this problem, either.

In addition, the OMB114242 study publication contained contradictory information on the outcome "overall survival". The results on overall survival were therefore not interpretable.

Network meta-analysis

The company presented a network meta-analysis to represent a sensitivity analysis on the indirect comparison according to Bucher (see above). For this purpose, the company included study GS-1101 (idelalisib + ofatumumab versus ofatumumab) in addition to the studies PCYC-1112-CA and OMB114242. Information on the GS-1101 study was only available in the form of a poster presentation. This constitutes no suitable data set for the assessment of the study results. In addition, including the GS-1101 study did not eliminate the principal lack of usability due to unsuitability of the ofatumumab arms as common comparator described for the indirect comparison.

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

No relevant randomized controlled trials (RCTs) on the direct comparison of ibrutinib versus the ACT (idelalisib or BSC) were identified for patients with relapsed or refractory CLL for whom chemotherapy is not indicated.

The company included study PCYC-1112-CA for research question 1b. This study compared the administration of ibrutinib with ofatumumab, each in addition to BSC.

The PCYC-1112-CA study did not concur with the inclusion criteria for research question 1b. The reason for this was that treatment in the comparator arm of the study was conducted with ofatumumab so that the comparator arm did not concur with the ACT specified by the G-BA (idelalisib or BSC). Nevertheless it was investigated in how far the results of the PCYC-1112-CA study were transferable to research question 1b. The prerequisite for this was that the concomitant medication administered in addition to ibrutinib or ofatumumab in both study arms corresponded to BSC. Hence the study constituted a comparison of ibrutinib + BSC versus ofatumumab + BSC. The potential influence of the additional administration of ofatumumab in the comparator arm was estimated at outcome level.

The company presented results for 3 populations. None of these populations completely represented the patient group of research question 1b (chemotherapy indicated): The total population of the PCYC-1112-CA study comprised an unknown number of patients for whom chemotherapy was indicated. It was assumed for the subpopulation of double-refractory patients defined by the company that chemotherapy was not indicated. An unknown proportion of the relevant patient population was not considered, however. For example, the company did not address the question why the results of the subpopulation of patients with 17p deletion were not considered for research question 1b. It was therefore also examined whether the results of the different populations formed by the company deviated from one another.

Study characteristics

Adult patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) were included in the PCYC-1112-CA study.

A total of 391 patients were randomly assigned to treatment with ibrutinib + BSC (195 patients) or to ofatumumab + BSC (196 patients).

Treatment was administered until disease progression or occurrence of unacceptable toxicity occurred. In the ofatumumab + BSC arm, ofatumumab treatment was administered for a maximum of 24 weeks.

Subpopulation of double-refractory patients defined by the company

From the total population, the company formed the subpopulation of patients who were refractory to at least 2 prior therapies (subpopulation of double-refractory patients) to represent the subpopulation of patients unsuitable for chemotherapy according to research question 1b. The subpopulation of double-refractory patients comprised 34 patients in the ibrutinib + BSC arm and 25 patients in the ofatumumab + BSC arm.

In the subpopulation of double-refractory patients, considerably more patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or a tumour mass of < 5 cm in the ibrutinib + BSC arm than in the ofatumumab + BSC arm. In addition, the proportion of patients with cytopenia was higher in the ofatumumab + BSC arm than in the ibrutinib + BSC arm. Hence the formation of subgroups resulted in an uneven distribution of important prognostic factors between the groups.

Influence of the additional administration of ofatumumab in the comparator arm

The uniform mandatory administration of ofatumumab was not a meaningful component of individual BSC for all patients in the comparator arm. The question arises in how far the additional administration of ofatumumab influenced the results of the study (in comparison with BSC alone).

The influence of additional administration of ofatumumab on the outcome “overall survival” was considered to be small. Assuming a life-prolonging effect of ofatumumab, at least the effect would be biased to the disadvantage of ibrutinib. Hence conclusions on the added benefit of ibrutinib were possible for this outcome, but the size of the effect remained unclear.

Bias in favour of ibrutinib was possible for the outcomes “symptoms”, “health-related quality of life” and “adverse events (AEs)”. Ofatumumab-related AEs could have occurred in the ofatumumab + BSC arm, which would not have occurred under BSC alone. This might be accompanied by a more negative evaluation of health-related quality of life by the patients and with an increased incidence of symptoms. Overall, a relevant influence of ofatumumab on the study results for the outcomes mentioned could not be excluded.

Results

Apart from the outcome “overall survival”, the results on all other outcomes were not usable for the comparison with BSC. The reason for this was that it could not be estimated for the outcomes of the categories “morbidity”, “health-related quality of life” and “side effects” in

how far the data were influenced by the additional administration of ofatumumab in the comparator arm.

Furthermore, the results on the data on morbidity and health-related quality of life recorded with the instruments Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Quality of Life-5 Dimensions (EQ-5D) had the following deficiencies. On the one hand, there was no information on the response rates of the completed questionnaires in the subpopulation of double-refractory patients. On the other, the company provided no information on mixed-effects model repeated measures (MMRM) or the information was unclear.

Mortality

For the outcome "overall survival", there was a statistically significant prolongation under ibrutinib + BSC in comparison with ofatumumab + BSC for the subpopulation of double-refractory patients. It was assumed for this outcome that the effect of ibrutinib in comparison with BSC was not overestimated by the additional administration of ofatumumab in the comparator arm. Based on this, there was a hint of an added benefit for ibrutinib for the outcome "overall survival" in the subpopulation of double-refractory patients.

The prolongation in overall survival differed between the populations for which the company provided results. This indicates that the prolongation in overall survival might differ between the subpopulation of double-refractory patients and all other patients for whom chemotherapy is not indicated. Hence the extent of the added benefit for the outcome "overall survival" was non-quantifiable for the totality of the study patients for whom chemotherapy is not indicated.

Morbidity and health-related quality of life

Bias in favour of ibrutinib could not be excluded for the outcomes of the categories "morbidity" and "health-related quality of life". The comparison of ibrutinib + BSC with ofatumumab + BSC may therefore lead to an underestimation of the negative effects of ibrutinib in comparison with the ACT (BSC).

Despite the potential underestimation of the negative effects of ibrutinib in comparison with BSC, negative results for the symptom scales of appetite loss and diarrhoea as well as for role functioning and time to improvement of emotional perception were additionally observed. It was unclear in which magnitude these disadvantages would exist in usable analyses for all pretreated patients for whom chemotherapy is not indicated. However, it could not be excluded overall that the positive effect for the outcome "overall survival" was accompanied by important negative effects in morbidity and health-related quality of life for ibrutinib + BSC in comparison with ofatumumab + BSC.

Side effects (SAEs, discontinuation due to AEs and severe AEs CTCAE grade ≥ 3)

AEs that might not have occurred under BSC alone may have occurred under the additional administration of ofatumumab in the comparator arm of the study. The proportions of the overall rates of serious adverse events (SAEs) and severe AEs Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 as well as of the discontinuations due to AEs that were caused only by the administration of ofatumumab were unknown. Considering the results on the ibrutinib + BSC arm, greater harm of ibrutinib + BSC in comparison with BSC alone could not be excluded: For the outcomes "SAEs" and "severe AEs CTCAE grade ≥ 3", more than half of the patients in the ibrutinib + BSC arm in the subpopulation of double-refractory patients had at least one event; 8.8% of the patients had discontinued treatment due to AEs.

Overall, greater harm from ibrutinib + BSC in comparison with BSC could not be excluded; greater or lesser harm is therefore not proven.

Balancing of positive and negative effects

The mortality advantage (extent "non-quantifiable") was accompanied by potentially lesser benefit in morbidity (disadvantage for the outcomes "appetite loss" and "diarrhoea") and in health-related quality of life (disadvantage for the outcomes "role functioning" and "emotional perception") as well as potentially greater harm (SAEs/severe AEs CTCAE grade ≥ 3) of ibrutinib in comparison with the ACT BSC. Greater harm can outweigh an advantage in mortality. Hence an added benefit of ibrutinib is not proven for patients with relapsed or refractory CLL for whom chemotherapy is not indicated.

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

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

The company used the PCYC-1112-CA study also for this research question and presented the results for the subpopulation of patients with 17p deletion.

The study was not relevant for research question 2 (first-line treatment) of the present benefit assessment. This resulted particularly from the fact that patients with at least one prior systemic therapy were included in the study. Correspondingly, the dosage in the comparator arm (ofatumumab + BSC) after the first infusion was considerably higher (week 2 to 8 and then in monthly intervals, 2000 mg for each infusion) than recommended in the Summary of Product Characteristics (SPC) for treatment-naive patients (1000 mg for each infusion on day 8 of the first cycle, and on day 1 of the subsequent cycles; 28-day cycles).

The company presented no adequate scientific investigations that proved with sufficient certainty or plausibility that the effects of patient-relevant outcomes were not influenced to an

important degree by the different treatment situations (in this case differences in pretreatment and dosage).

Moreover, the interpretation of the result of the study carries the same problems as research question 1b. The comparator therapy (ofatumumab + BSC) used in the study did not concur with the ACT specified by the G-BA (idelalisib or BSC).

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

The company presented no suitable data in its dossier for the research questions 1a and 2 of the benefit assessment in the therapeutic indication CLL.

In research question 1b, the mortality advantage (extent "non-quantifiable") is accompanied by potentially lesser benefit in morbidity and health-related quality of life as well as potentially greater harm of ibrutinib in comparison with the ACT BSC. Greater harm can outweigh an advantage in mortality. Hence an added benefit of ibrutinib for patients of research question 1b is not proven.

Overall, there was no hint of an added benefit of ibrutinib in comparison with the ACT specified by the G-BA for any of the 3 research questions; an added benefit of ibrutinib is therefore not proven for any of the 3 patient groups.

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

[2] 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 [2,3].

Table 2: Ibrutinib – extent and probability of added benefit

Research question		**ACT**[a]	**Extent and probability of added benefit**
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	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	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	Idelalisib or **best supportive care**[b]	Added benefit not proven
2	First-line treatment of the CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy	Idelalisib[c] or **best supportive care**[b]	Added benefit not proven

a: Presentation of the appropriate comparator therapy 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.
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.
c: The approval of idelalisib was changed in the course of the benefit assessment. Following this change, idelalisib in first-line treatment is now only approved for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment [1]. This had no consequences for the present benefit assessment, however, because the company had not chosen idelalisib as comparator therapy.
CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

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 ibrutinib 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

According to the approval of ibrutinib, the G-BA distinguished between 2 subindications within the therapeutic indication CLL: pretreated patients and treatment-naive patients with 17p deletion or TP53 mutation. The G-BA further divided pretreated patients into 2 subpopulations. Accordingly, the assessment was conducted for a total of 3 research questions. 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 ibrutinib in the therapeutic indication CLL

Research question	Subindication	Appropriate comparator therapy[a]
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
1b	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	Idelalisib or **best supportive care**[b]
2	First-line treatment of the CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy	Idelalisib[c] or **best supportive care**[b]

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.
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.
c: The approval of idelalisib was changed in the course of the benefit assessment. Following this change, idelalisib in first-line treatment is now only approved for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment [1]. This had no consequences for the present benefit assessment, however, because the company had not chosen idelalisib as comparator therapy.
CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The company accepted the ACT specified by the G-BA within the respective research question.

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

I 2.3 Research question 1a: patients with relapsed or refractory 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 list on ibrutinib (status: 12 November 2015)
- bibliographical literature search on ibrutinib (last search on 12 November 2015)
- search in trial registries for studies on ibrutinib (last search on 2 November 2015)
- bibliographical literature search on the ACT (last search on 1 December 2015)
- search in trial registries for studies on the ACT (last search on 19 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 12 February 2016)

The check of the completeness of the study pool produced no relevant RCTs on the comparison of ibrutinib versus the ACT. This deviates from the company's approach, which included RCTs both on a direct comparison and on indirect comparisons for research question 1a.

Direct comparison

Study CLL3001 [4] was a double-blind RCT on the comparison of ibrutinib + bendamustine + rituximab (B-R) with placebo + B-R. Concomitant therapies were allowed in both treatment arms. Adult patients with relapsed or refractory CLL or SLL with at least one prior systemic therapy were included. 578 patients were randomized in a ratio of 1:1, 289 patients to the ibrutinib + B-R arm and 289 patients to the placebo + B-R arm.

The CLL3001 study was unsuitable for the assessment of the added benefit of ibrutinib in comparison with the ACT specified by the G-BA. The reason for this was that the comparator therapy was not chosen individually for the patients in the study, but that all patients were uniformly receiving B-R. The B-R combination may have been an option for some of the patients in the study, but the guidelines [5-7] list B-R as one of several treatment options for the target population. None of the guidelines names B-R as the preferred choice over other treatment options mentioned in the guidelines for the target population. In the guideline of the German Society of Haematology and Oncology [DGHO] [5], the administration of B-R is limited to the treatment of patients with late relapse, and also constitutes only one of several options in this subindication. The company provided no proof that B-R constituted the most suitable treatment for a majority of the study population. The company also did not discuss in

how far other principally suitable treatment options were not preferable under clinical aspects. These further treatment options were excluded in the comparator arm.

In addition, the therapy used in both treatment groups was not in compliance with the approval. According to BfArM [8], bendamustine is not approved for second-line treatment in patients with CLL in monotherapy or in the framework of combination therapies. Hence neither the comparator arm (placebo + B-R) nor the intervention arm (ibrutinib + B-R) concurred with the approval requirements.

Overall, the CLL3001 study allowed no comparison of ibrutinib with the ACT specified by the G-BA.

Unadjusted indirect comparison

The company presented an unadjusted indirect comparison of the ibrutinib arm of study PCYC-1112-CA (ibrutinib + BSC versus ofatumumab + BSC) [9] with the placebo + B-R arm of the CLL3001 study. Since the CLL3001 study was unsuitable for the derivation of an added benefit of ibrutinib for research question 1a (see above), the unadjusted indirect comparison in which this study was included was also not relevant.

Indirect comparison according to Bucher

The company conducted an indirect comparison according to Bucher [10] between the studies PCYC-1112-CA (ibrutinib + BSC versus ofatumumab + BSC) and OMB114242 (ofatumumab versus physician´s choice) [11] using the ofatumumab arms of both studies as common comparator.

The company used the PCYC-1112-CA study also for research question 1b. The design and the patient characteristics of this study are therefore described in Section I 2.4.1.2.

Study OMB114242 was an open-label RCT on the comparison of ofatumumab with individual treatment (physician's choice). Adult patients with fludarabine-refractory CLL and at least 2 prior therapies were included. 122 patients were randomized in a ratio of 2:1, 79 patients to the ofatumumab arm and 43 patients to the physician's choice arm. In the ofatumumab arm of the OMB114242 study, patients who had no disease progression after 24 weeks of treatment underwent a second randomization and either continued treatment for up to another 24 weeks or were observed without further administration of ofatumumab. The patients were followed-up until study withdrawal or end of the study (60 months).

The indirect comparison according to Bucher presented by the company was not usable for the assessment of the added benefit of ibrutinib in comparison with the ACT specified by the G-BA for several reasons. These are explained below.

Treatment duration and observation period

There was no sufficient similarity between the ofatumumab arms of both studies, which is required for a common comparator. An important reason for this was the different treatment duration: The maximum treatment duration in the ofatumumab arm of the PCYC-1112-CA study was 24 weeks. In the ofatumumab arm of the OMB114242 study, 24 of 79 (about 30%) of the patients were treated with ofatumumab for up to 48 weeks due to the second randomization described above.

For the OMB114242 study, the company only presented the data cut-off after 48 weeks, at which 21 of 79 (about 27%) of the patients in the ofatumumab arm had already continued treatment after week 24 either until week 48 or until disease progression or death. The company did not present data for the time point after 24 weeks, i.e. the time point of the second randomization. Due to the different documentation periods, the results of both studies – for example on side effects – were also not comparable. Time-adjusted analyses were not available.

In addition, a 48-week administration of ofatumumab does not comply with the approval. The approval specifies a maximum period of ofatumumab administration of 24 weeks [12].

Moreover, the OMB114242 study publication contained no clear information on the outcome "overall survival". The publication stated 10 (flow chart), 24 (text) or a maximum of 23 (Kaplan-Meier analysis) deaths for the ofatumumab arm before the second randomization [11].

Prior therapies and suitability for chemotherapy

The total populations of both studies differed particularly in the number of prior therapies (median [minimum; maximum] PCYC-1112-CA: 2 [1; 13] in the ofatumumab arm, 3 [1; 12] in the ibrutinib arm; OMB114242: 4 [2; 16] in the ofatumumab arm, 3 [2; 11] in the physician´s choice arm). Assuming that the patients generally were refractory to prior therapies, the vast majority of the patients in the OMB114242 study were at least double-refractory. According to the company's definition, double-refractory patients are unsuitable for chemotherapy (see Section I 2.4.1.2) and therefore do not concur with the population of research question 1a (chemotherapy indicated). Nonetheless, the company used the OMB114242 study in the indirect comparison for research question 1a. The company did not address this contradiction.

Matching-adjusted indirect comparison

The company also conducted a MAIC using a so-called MAIC population, in which, according to the company, it only considered the patients concurring with the inclusion criteria of the OMB114242 study. A new weighting was conducted for this population. The company did not explain which patient characteristics were used for the weighting, and which weights it derived from the OMB114242 study. It therefore remained unclear whether and regarding which characteristics the MAIC population was comparable with the population of

the OMB114242 study. Irrespective of this, differences between the populations of the studies can still remain if they are inevitably not considered due to unrecorded or unreported characteristics. It was unclear whether the patients differed in prognostic factors such as the type of pretreatment in the ofatumumab arms or the allowed or disallowed concomitant treatments because, the dossier contained no information on this for the OMB114242 study.

It should be noted that a MAIC analysis cannot solve the problem that patients for whom chemotherapy was unsuitable (see above), and who therefore did not concur with the population of research question 1a, were included in the OMB114242 study.

Overall assessment

For the reasons stated above, the indirect comparison according to Bucher presented by the company was not usable. Further aspects regarding the usability of the indirect comparison were not investigated.

Network meta-analysis

The company presented a network meta-analysis to represent a sensitivity analysis on the indirect comparison according to Bucher (see above). For this purpose, the company included study GS-1101 [13] in addition to the studies PCYC-1112-CA and OMB114242. The GS-1101 study is an ongoing open-label phase 3 RCT comparing idelalisib + ofatumumab with ofatumumab. 261 adult patients with relapsed CLL were enrolled.

Information on the GS-1101 study was only available in the form of a poster presentation. This constitutes no suitable data set for the assessment of the study results. In addition, including the GS-1101 study did not eliminate the principal lack of usability due to unsuitability of the ofatumumab arms as common comparator described for the indirect comparison.

The network meta-analysis presented by the company was therefore not used for the assessment of the added benefit of ibrutinib.

Summary

Overall, no relevant direct or indirect comparisons of ibrutinib versus the ACT were presented for research question 1a.

I 2.3.2 Results on added benefit (research question 1a)

The company presented no relevant data for the assessment of the added benefit of ibrutinib for research question 1a. This resulted in no hint of an added benefit of ibrutinib in comparison with the ACT (individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated). An added benefit is therefore not proven.

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

The company presented no suitable data for the assessment of the added benefit of ibrutinib in patients with relapsed or refractory CLL for whom chemotherapy is indicated. Hence an added benefit of ibrutinib is not proven for these patients.

This deviates from the company's assessment, which derived an indication of considerable added benefit on the basis of the data presented by the company.

The G-BA decides on the added benefit.

I 2.3.4 List of included studies (research question 1a)

Not applicable as no studies for research question 1a were included in the benefit assessment.

I 2.4 Research question 1b: patients with relapsed or refractory 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 list on ibrutinib (status: 12 November 2015)
- bibliographical literature search on ibrutinib (last search on 12 November 2015)
- search in trial registries for studies on ibrutinib (last search on 2 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 12 February 2016)

No relevant RCTs on the direct comparison of ibrutinib versus the ACT (idelalisib or BSC) were identified from the check of the completeness of the study pool. This deviates from the company's approach, which for research question 1b included study PCYC-1112-CA for the direct comparison. This study compared the administration of ibrutinib with ofatumumab.

The PCYC-1112-CA study did not concur with the inclusion criteria for research question 1b. The reason for this was that treatment in the comparator arm of the study was conducted with ofatumumab so that the comparator arm did not concur with the ACT specified by the G-BA (idelalisib or BSC). Nevertheless it was investigated in how far the results of the PCYC-1112-CA study were transferable to research question 1b. The prerequisite for this was that the concomitant medication administered in addition to ibrutinib or ofatumumab in both study arms corresponded to BSC. Hence the study constituted a comparison of ibrutinib + BSC versus ofatumumab + BSC. The potential influence of the additional administration of ofatumumab in the comparator arm was estimated at outcome level.

I 2.4.1.1 Study pool of the company (research question 1b)

The study listed in the following tables was considered in the benefit assessment.

Table 4: Study pool of the company – RCT, direct comparison: ibrutinib + BSC vs. ofatumumab + BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PCYC-1112-CA	Yes	Yes	No
a: Study for which the company was sponsor. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

Section I 2.4.4 contains a reference list for the PCYC-1112-CA study.

The study characteristics and the results (if usable analyses were available) are presented and described below. The presentation refers to the subpopulation of double-refractory patients defined by the company because it was assumed that this was a better approximation to the relevant patient population of research question 1b than the total population.

The company presented results for 3 populations. None of these populations completely represented the patient group of research question 1b (chemotherapy indicated): The total population of the PCYC-1112-CA study comprised an unknown number of patients for whom chemotherapy was indicated. It was assumed for the subpopulation of double-refractory patients defined by the company that chemotherapy was not indicated. An unknown proportion of the relevant patient population was not considered, however; the company itself noted that further patients in the total population might have been unsuitable for chemotherapy. However, the company did not address the question why the results of the subpopulation of patients with 17p deletion were not considered for research question 1b. It was therefore also examined whether the results of the different populations formed by the company deviated from one another. Due to possibly relevant deviations between the effect estimates for the populations mentioned, the results of the subpopulation of double-refractory patients defined by the company might deviate to a relevant degree from the results of all patients for whom chemotherapy was not indicated. In this case, the extent of the effect for the patients according to research question 1b was non-quantifiable.

I 2.4.1.2 Study characteristics (research question 1b)

Table 5 and Table 6 describe the studies included by the company for the benefit assessment.

Table 5: Characteristics of the study of the company – RCT, direct comparison: ibrutinib + BSC vs. ofatumumab + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PCYC-1112-CA	RCT, open-label, parallel	Adult patients with relapsed or refractory CLL or SLL, active disease, at least one prior systemic therapy, unsuitable for purine analogue-based treatment, ECOG PS ≤ 1, measurable node disease (at least one lymph node > 1.5 cm)	Ibrutinib + BSC (N = 195) ofatumumab + BSC (N = 196) Subpopulation of double-refractory patients[b]: ibrutinib + BSC (n = 34) ofatumumab + BSC (n = 25)	Screening: ≤ 28 days before the first administration of the study medication Treatment duration: until disease progression or occurrence of unacceptable toxicity; 24 weeks[c] maximum in the ofatumumab arm Follow-up: until death, loss to follow-up, withdrawal of consent or end of study	67 study centres in Australia, Austria, France, Italy, Ireland, Poland, Spain, United Kingdom, USA 6/2012–ongoing Data cut-offs: 18 Dec 2013[d] 6 Oct 2014	Primary: progression-free survival Secondary: overall survival, morbidity, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The company defined this subpopulation as unsuitable for chemotherapy. Further patients in the total population who may be considered unsuitable for chemotherapy for other reasons remained unconsidered. This subpopulation therefore does not represent the complete relevant subpopulation of all patients unsuitable for chemotherapy in the PCYC-1112-CA study.
c: After confirmed disease progression possibility of treatment switching to ibrutinib + BSC.
d: Date of database extraction. The clinical data cut-off was on 6 November 2013.

AE: adverse event; BSC: best supportive care; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; n: number of patients in the subpopulation; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; vs.: versus

Table 6: Characteristics of the interventions – RCT, direct comparison: ibrutinib + BSC vs. ofatumumab + BSC

Study	Intervention	Comparison	Prior and concomitant medication
PCYC-1112-CA	Ibrutinib 420 mg/day orally[a]	Ofatumumab IV[a] ▪ week 1: 300 mg as starting dose ▪ weeks 2 – 8: 2000 mg weekly ▪ weeks 12 – 24: 2000 mg every 4 weeks	Concomitant medication allowed: ▪ antiemetics ▪ standard medication for supportive treatment ▪ growth factors (filgrastim and pegfilgrastim) ▪ patients at risk of TLS: treatment for lowering uric acid levels (allopurinol or febuxostat) Non-permitted concomitant medication: ▪ chemotherapy ▪ immunotherapy ▪ corticosteroids (> 20 mg/day prednisone equivalent) ▪ radiotherapy

a: Treatment withheld in case of toxicity up to grade ≤ 3 until grade ≤ 1 achieved; treatment stopped if grade ≤ 1 not achieved until day 28; treatment stopped in case of grade 4.

BSC: best supportive care; IV: intravenous; RCT: randomized controlled trial; TLS: tumour lysis syndrome; vs.: versus

Study design

The PCYC-1112-CA study was a randomized, open-label approval study. Adult patients with relapsed or refractory CLL or SLL who had at least one prior systemic therapy, were unsuitable for purine analogue-based treatment, and who had measurable node disease were included.

A total of 391 patients were randomly assigned to treatment with ibrutinib + BSC (195 patients) or to ofatumumab + BSC (196 patients). Supportive therapy was additionally allowed for all patients. Chemotherapy, immunotherapy, corticosteroids (> 20 mg/day prednisone equivalent) and radiotherapy were excluded from this. The patients had to have an ECOG PS of 0 or 1 at the start of the study. Patients with an ECOG PS of 2 or higher were not included.

The patients were stratified based on the 2 factors refractoriness to a purine analogue- and anti-CD20-containing chemo-immunotherapy regimen and presence of 17p deletion.

Treatment was administered until disease progression or occurrence of unacceptable toxicity occurred. In the ofatumumab + BSC arm, ofatumumab treatment was administered for a maximum of 24 weeks. On confirmed disease progression, patients in the ofatumumab + BSC arm had the possibility to switch to ibrutinib + BSC treatment. In the total population,

57 (29.1%) patients had switched to the ibrutinib + BSC arm at the first data cut-off (18 December 2013), and at the second data cut-off (6 October 2014) 123 (62.8%) of 196 patients in the ofatumumab + BSC arm had switched to the ibrutinib + BSC arm. No corresponding information was available for the subpopulation of double-refractory patients.

Assessment of the study for the consideration for the derivation of an added benefit

Subpopulation of double-refractory patients defined by the company

From the total population, the company formed the subpopulation of patients who were refractory to at least 2 prior therapies (subpopulation of double-refractory patients) to represent the subpopulation of patients unsuitable for chemotherapy according to research question 1b. The subpopulation of double-refractory patients comprised 34 patients in the ibrutinib + BSC arm and 25 patients in the ofatumumab + BSC arm. The company noted that chemotherapy might have been unsuitable for further patients in the total population of the study.

The subpopulation of double-refractory patients did not represent the complete relevant patient population for research question 1b (see also Section I 2.7.2.4.1 of the full dossier assessment).

Additional administration of ofatumumab in the comparator arm

Influence on the results

The comparator therapy (ofatumumab + BSC) used in the PCYC-1112-CA study did not concur with the ACT (idelalisib or BSC). From the company's point of view, treatment with ofatumumab is principally an option for the population of research question 1b. Referring to the PCYC-1112-CA study included by the company, the company argued that the comparator therapy is to be considered as BSC because of the supportive therapy administered in addition to ofatumumab, and did not constitute a less suitable therapy.

The aim of the study was not to compare the administration of ibrutinib with BSC alone. A uniform mandatory administration of ofatumumab was not a meaningful component of individual BSC for all patients in the comparator arm. However, the question arises in how far the additional administration of ofatumumab influenced the results of the study (in comparison with BSC alone). The direction of the influence may differ between the outcomes.

The influence of additional administration of ofatumumab on the outcome "overall survival" was rather considered to be small. Assuming a life-prolonging effect of ofatumumab, at least the effect would be biased to the disadvantage of ibrutinib. Hence conclusions on the added benefit of ibrutinib were possible for this outcome, but the size of the effect remained unclear.

Estimating an influence was more complex for the outcomes "symptoms", "health-related quality of life" and "AEs", however. Neither positive nor negative effects of ofatumumab in the comparator arm of the study could be excluded for these outcomes. Bias in favour of

ibrutinib was possible. Ofatumumab-related AEs (particularly SAEs and severe AEs CTCAE grade ≥ 3) could have occurred in the ofatumumab + BSC arm, which would not have occurred under BSC alone. The increased incidence of AEs might be accompanied by a more negative evaluation of health-related quality of life by the patients and with an increased incidence of symptoms. The additional administration of ofatumumab could have also had a positive influence on the morbidity outcomes, however. Overall, a relevant influence of ofatumumab on the study results for the outcomes mentioned could not be excluded.

It should also be noted that BSC – in combination with ofatumumab – may also be constituted of other components or their dosages than BSC alone.

These deliberations were taken into account in the consideration of the study and the results in the present benefit assessment. Section I 2.4.2.3 contains a description in how far conclusions on the added benefit are possible on the basis of the available data for the individual outcomes.

Supplementary note on the restriction of approval of ofatumumab

According to the information provided in the SPC [12], ofatumumab is only indicated in patients with refractory CLL who are refractory both to fludarabine and to alemtuzumab. In the total population, only 33 of 196 (about 17%) patients in the ofatumumab + BSC arm had received alemtuzumab as prior therapy. At least 163 (83%) patients in the ofatumumab + BSC arm did therefore not fulfil the approval requirement of refractoriness to both fludarabine and alemtuzumab. No corresponding information was available on the number of patients in the subpopulation of double-refractory patients who were not treated in compliance with the approval.

It should be noted that alemtuzumab is no longer approved in Germany, and therefore is of low importance in everyday practice in Germany. The company itself noted in the dossier that alemtuzumab is no longer freely available for the treatment of CLL outside a hardship programme.

Planned duration of follow-up

Table 7 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 7: Planned duration of follow up – RCT, direct comparison: ibrutinib + BSC vs. ofatumumab + BSC

Study **Outcome category** **Outcome**	**Planned follow-up**
PCYC-1112-CA	
Mortality	
Overall survival	Until death, end of study, withdrawal of consent or loss to follow-up
Morbidity	
Symptoms (EORTC QLQ-C30)	After end of treatment until progression or end of study
Health status (EQ-5D VAS)	After end of treatment until progression or end of study
Fatigue (FACIT-Fatigue)	After end of treatment until progression or end of study
Health-related quality of life	
Recorded with the EORTC QLQ-C30 functional scales	After end of treatment until progression or end of study
Side effects	
All AE outcomes	Until 30 days after the last treatment

AE: adverse event; BSC: best supportive care; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The planned follow-up of the patients for the outcome “overall survival” was conducted until death, end of study, withdrawal of consent or loss to follow-up. It was planned for the other outcomes to observe the patients after the end of the study treatment until disease progression or until the end of the study – except AEs, for which the patients were observed up to 30 days after the last study treatment.

Characteristics of the study population

Table 8 shows the characteristics of the subpopulation of double-refractory patients in the PCYC-1112-CA study.

Table 8: Characteristics of the study populations – RCT, direct comparison: ibrutinib + BSC vs. ofatumumab + BSC

Study **Characteristics** **Category**	**Ibrutinib + BSC**	**Ofatumumab + BSC**
Subpopulation of double-refractory patients	**N = 34**	**N = 25**
Age [years]: median [min; max]	66 [44; 79]	64 [37; 78]
Sex [F/M], %	38/62	36/64
Ethnicity, %		
White	76	88
Black	9	8
Asian/multiple	6[a]	0[a]
Unknown	9	4
Time since diagnosis [months], median [min; max]	92 [15; 316]	97 [9; 260]
Histology at diagnosis, n (%)		
CLL	32 (94.1)	22 (88.0)
SLL	2 (5.9)	3 (12.0)
Rai stage at screening, n (%)		
0	1 (2.9)	0 (0)
I	12 (35.3)	10 (40.0)
II	5 (14.7)	2 (8.0)
III	1 (2.9)	2 (8.0)
IV	15 (44.1)	11 (44.0)
ECOG PS, n (%)		
0	20 (58.8)	5 (20.0)
1	14 (41.2)	20 (80.0)
Tumour mass, n (%)		
< 5 cm	16 (47.1)	7 (28.0)
≥ 5 cm	18 (52.9)	18 (72.0)
Chromosome anomaly del11q, n (%)	12 (35.3)	5 (20.0)
Chromosome anomaly del17p, n (%)	9 (26.5)	7 (28.0)
Cytopenia total, n (%)	20 (58.8)	19 (76.0)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Institute's calculation.

BSC: best supportive care; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; max: maximum; min: minimum; N: number of included patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; vs.: versus

The characteristics between the treatment arms were largely balanced in the subpopulation of double-refractory patients in the PCYC-1112-CA study.

The mean age of the patients was 65 years. About 2 thirds of the patients were men. Patients in the ibrutinib + BSC arm had been diagnosed 92 months, and patients in the ofatumumab + BSC arm 97 months before the start of the study. The patients in both treatment groups mainly had Rai stage I or IV at screening.

A notably higher proportion of patients had ECOG PS 0 in the ibrutinib + BSC arm (about 59%) than in the ofatumumab + BSC arm (20%). In addition, in the ofatumumab + BSC arm, the proportion of patients with a tumour mass ≥ 5 cm was notably higher (72%) than the proportion of patients with a tumour mass < 5 cm (28%). In the ibrutinib + BSC arm, in contrast, the proportions of patients in both categories were similar (about 53% versus about 47%). The proportion of patients with cytopenia was higher in the ofatumumab + BSC arm (76%) than in the ibrutinib + BSC arm (about 59%). Hence the formation of subgroups resulted in an uneven distribution of important prognostic factors between the groups.

There was no information on treatment and study discontinuations for the subpopulation of double-refractory patients.

Treatment duration and observation period

Neither data on the treatment duration nor data on the follow-up period were available for the subpopulation of double-refractory patients.

I 2.4.2 Results on added benefit (research question 1b)

I 2.4.2.1 Outcomes considered (research question 1b)

The following patient-relevant outcomes were to be considered in the assessment (for reasons, see Section I 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, measured with the symptom scales of the EORTC QLQ-C30
  - health status, measured with the EQ-5D visual analogue scale (VAS)
  - fatigue, measured with FACIT-Fatigue
- Health-related quality of life
  - measured with the functional scales and the global health status of the EORTC QLQ-C30

- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of considered outcomes deviated from that of the company, which used further outcomes in Module 4 A (see Section I 2.7.2.4.3 of the full dossier assessment). Reasons for the choice of the considered outcomes for the present benefit assessment can be found in Section I 2.7.2.4.3 of the full dossier assessment.

Table 9 shows for which outcomes data were available in the study considered in the assessment.

Table 9: Matrix of outcomes – RCT, direct comparison: ibrutinib + BSC vs. ofatumumab + BSC

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30)[a]	Health status (EQ-5D VAS)	Fatigue (FACIT-Fatigue)	Health-related quality of life (EORTC QLQ-C30)[b]	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
PCYC-1112-CA								
Subpopulation of double-refractory patients	Yes	No[c, d]	No[c, d]	No[c, d]	No[c, d]	No[c]	No[c]	No[c]

a: Measured with the symptom scales of the EORTC QLQ-C30 questionnaire version 3.
b: Measured with the functional scales of the EORTC QLQ-C30 questionnaire version 3.
c: No data usable for the comparison with BSC available because it could not be estimated in how far the data were influenced by the additional administration of ofatumumab in the comparator arm.
d: No usable data available due to missing information on response rates.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Apart from the outcome “overall survival”, the results on all other outcomes were not usable for the comparison with BSC. The reason for this was that it could not be estimated for the outcomes of the categories “morbidity”, “health-related quality of life” and “side effects” in

how far the data were influenced by the additional administration of ofatumumab in the comparator arm (see Section I 2.4.2.3 for an explanation of the assessment of the usability of the data).

Furthermore, the results on the data on morbidity and health-related quality of life recorded with the instruments FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D had the following deficiencies. There was no information on the response rates of the completed questionnaires in the subpopulation of double-refractory patients defined by the company. It was unclear which time period was used for the MMRM calculations. Furthermore, there were discrepancies in the MMRM information, which were not explained by the company. For example, the number of patients for whom results on the EQ-5D VAS at the start of the study were available for the total population was stated as 147 for the ofatumumab + BSC arm in Module 4 A, whereas for 158 patients results of later dates of analysis were included in the MMRM calculations for the calculation of change in comparison with the start of the study. Furthermore, the mean value of the EQ-5D VAS at the start of the study was stated as 71.5 (ibrutinib + BSC arm) and 71.1 (ofatumumab + BSC) arm in the MMRM calculation in Module 4 A, and as 65.8 (ibrutinib + BSC arm) and 65.9 (ofatumumab + BSC arm) – thus considerably lower – in the clinical study report (CSR).

I 2.4.2.2 Risk of bias (research question 1b)

A clear assessment of the risk of bias (both on study and on outcome level) was not meaningful in the present situation (deviation of the comparator arm [ofatumumab + BSC] from the ACT [BSC]).

The company's approach deviated in so far as it assessed the risk of bias both on study and outcome level and derived indications of an added benefit based on its assessment.

I 2.4.2.3 Results of study PCYC-1112-CA (research question 1b)

Table 10 summarizes the results on the comparison of ibrutinib + BSC with ofatumumab + BSC in patients with relapsed or refractory CLL. The company presented no Kaplan-Meier curves for the subpopulations of double-refractory patients and patients with 17p deletion. The Kaplan-Meier curves on overall survival in the total population can be found in I Appendix A of the full dossier assessment.

Table 10: Results (survival time) – RCT, direct comparison: ibrutinib + BSC vs. ofatumumab + BSC

Study Outcome Population	Ibrutinib + BSC N	Median survival time in months [95% CI] Patients with event n (%)	Ofatumumab + BSC N	Median survival time in months [95% CI] Patients with event n (%)	Ibrutinib + BSC vs. ofatumumab + BSC HR [95% CI]; p-value[a]
PCYC-1112-CA					
Mortality					
Overall survival (data cut-off on 6 Oct 2014)					
Subpopulation of double-refractory patients	34	NA ND	25	NA ND	0.19 [0.06; 0.62]; 0.002[b]
Subpopulation of patients with 17p deletion[c]	63	NA ND	64	NA ND	0.49 [0.23; 1.01]; 0.0496[d]
Total population[c]	195	NA ND	196	NA ND	0.52 [0.32; 0.84]; 0.007[e]
Morbidity	No usable data[f, g]				
Health-related quality of life	No usable data[f, g]				
Side effects	No usable data[f]				

a: Log-rank test.
b: Result with censoring at treatment switching: HR [95% CI]: 0.11 [0.03; 0.39]; p < 0.001.
c: Additional information; the subpopulation of double-refractory patients does not include all patients for whom chemotherapy is not indicated.
d: Result with censoring at treatment switching: HR [95% CI]: 0.42 [0.20; 0.91]; p = 0.023.
e: Result with censoring at treatment switching: HR [95% CI]: 0.48 [0.28; 0.80]; p = 0.005.
f: Because it cannot be estimated in how far the data for the relevant comparison (ibrutinib vs. BSC) are influenced by the additional administration of ofatumumab in the comparator arm.
g: Due to missing information on response rates of the questionnaires and on the period of analysis for the subpopulation of double-refractory patients.

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

Hereinafter, it is estimated for the individual outcomes in how far the results are transferable to research question 1b despite the problems mentioned (deviation from the ACT by additional administration of ofatumumab; incomplete consideration of the patient population for research question 1b).

Mortality

Overall survival

For the outcome "overall survival", there was a statistically significant prolongation under ibrutinib + BSC in comparison with ofatumumab + BSC for the subpopulation of double-

refractory patients. It was assumed for this outcome that the effect of ibrutinib in comparison with BSC was not overestimated by the additional administration of ofatumumab in the comparator arm. Based on this, there was a hint of an added benefit for ibrutinib for the outcome "overall survival" in the subpopulation of double-refractory patients. The company claimed an indication of an added benefit for this outcome.

The estimated effect size for overall survival differed between the populations. The reduction in risk of death was notably higher in the subpopulation of double-refractory patients (hazard ratio [HR] [95% confidence interval, CI]: 0.19 [0.06; 0.62]; p = 0.002) than in the subpopulation of patients with 17p deletion (HR [95% CI]: 0.49 [0.23; 1.01]; p = 0.0496) and in the total population (HR [95% CI]: 0.52 [0.32; 0.84]; p = 0.007). This indicates that the prolongation in overall survival might differ between the subpopulation of double-refractory patients and all other patients for whom chemotherapy is not indicated. Hence based on the results for the subpopulation of double-refractory patients, the extent of the added benefit for the outcome "overall survival" was non-quantifiable for the totality of the study patients for whom chemotherapy is not indicated.

Further outcomes

No usable data for the comparison with BSC were available for further outcomes from the categories of morbidity, health-related quality of life and side effects. It was decisive that, depending on the outcome, both positive and negative effects of ofatumumab on the results could not be excluded for the comparator arm of the study. Bias in favour of ibrutinib from the additional administration of ofatumumab in the comparator arm could not be excluded for these outcomes.

Morbidity and health-related quality of life

Bias in favour of ibrutinib could not be excluded for the outcomes of the categories "morbidity" and "health-related quality of life". It is highly probable that the additional administration of ofatumumab in the comparator arm of the study caused AEs that would not have occurred under BSC alone. Accompanying this, worsening of morbidity and of health-related quality of life for the patients in the comparator arm is conceivable. The comparison of ibrutinib + BSC with ofatumumab + BSC may therefore lead to an underestimation of the negative effects of ibrutinib in comparison with the ACT (BSC).

Despite the potential underestimation of negative effects of ibrutinib versus BSC, negative results were additionally observed in the PCYC-1112-CA study. For instance, with a minimally important difference (MID) of 10 points, there was a statistically significantly shorter time to increase in the symptom scales of appetite loss (HR [95% CI]: 1.69 [1.06; 2.68]; p = 0.027) and diarrhoea (HR [95% CI]: 1.77 [1.17; 2.67]; p = 0.007) for the total population in the ibrutinib + BSC arm in comparison with the ofatumumab + BSC arm. With an MID of 15 points, worsening of role functioning was present in 50% of the double-refractory patients in the ibrutinib + BSC arm versus 24% in the ofatumumab + BSC arm. Moreover, with an MID of 20 points, a statistically significantly longer time to improvement

of emotional perception was observed for these patients in the ibrutinib + BSC arm versus the ofatumumab + BSC arm (HR [95% CI]: 0.22 [0.06; 0.85]; p = 0.028).

It was unclear in which magnitude these disadvantages would exist in usable analyses (see Section I 2.4.2.1 for information on the problems) for all pretreated patients for whom chemotherapy is not indicated. However, it could not be excluded overall that the positive effect for the outcome "overall survival" was accompanied by important negative effects in morbidity and health-related quality of life for ibrutinib + BSC in comparison with ofatumumab + BSC.

This deviates from the company's approach, which included data on the outcomes mentioned above in its assessment, but then derived neither lesser benefit nor added benefit of ibrutinib based on these data.

Side effects

SAEs, discontinuation due to AEs and severe AEs CTCAE grade ≥ 3

AEs that might not have occurred under BSC alone may have occurred under the additional administration of ofatumumab in the comparator arm of the study. The proportions of the overall rates of SAEs and severe AEs CTCAE grade ≥ 3 as well as of the discontinuations due to AEs that were caused only by the administration of ofatumumab were unknown. Considering the results on the ibrutinib + BSC arm, greater harm of ibrutinib + BSC in comparison with BSC alone could not be excluded: For the outcomes "SAEs" and "severe AEs CTCAE grade ≥ 3", more than half of the patients in the ibrutinib + BSC arm in the subpopulation of double-refractory patients had at least one event; 8.8% of the patients had discontinued treatment due to AEs (see Table 15 in I Appendix B of the full dossier assessment).

Overall, greater harm from ibrutinib + BSC in comparison with BSC could not be excluded; greater or lesser harm is therefore not proven. This deviates from the company's approach, which included the data on the outcomes "SAEs", "discontinuation due to AEs" and "severe AEs CTCAE grade ≥ 3" in its assessment, and derived no greater or lesser harm based on these data.

I 2.4.2.4 Subgroups and other effect modifiers (research question 1b)

Indications or proof of effect modifications in comparisons of ibrutinib + BSC versus ofatumumab + BSC were not usable. One reason for this was that no conclusions on effect modifications could be derived for comparisons with BSC alone because of the unknown influence of ofatumumab. The subgroup analyses were therefore not considered.

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

On the side of positive effects, the data presented in Section I 2.4.2 resulted in a hint of a non-quantifiable added benefit of ibrutinib in the category "mortality" for the outcome "overall survival".

The mortality advantage (extent "non-quantifiable") was accompanied by potentially lesser benefit in morbidity (disadvantage for the outcomes "appetite loss" and "diarrhoea") and in health-related quality of life (disadvantage for the outcomes "role functioning" and "emotional perception") as well as potentially greater harm (SAEs/severe AEs CTCAE grade ≥ 3) of ibrutinib in comparison with the ACT BSC. Greater harm can outweigh an advantage in mortality. Hence an added benefit of ibrutinib is not proven for patients with relapsed or refractory CLL for whom chemotherapy is not indicated.

This deviates from the company's assessment, which claimed at least an indication of a major added benefit on the basis of the data presented by the company.

The G-BA decides on the added benefit.

I 2.4.4 List of studies of the company (research question 1b)

PCYC-1112-CA

Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014; 371(3): 213-223.

Janssen-Cilag. A randomized, multicenter, open-label, phase 3 study of the Bruton´s Tyrosine Kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: study PCYC-1112-CA; Nachberechnungen [unpublished]. 2015.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [online]. In: EU Clinical Trials Register [Accessed: 19.02.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000694-23.

Pharmacyclics. A phase 3 study of ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia: full text view [online]. In: ClinicalTrials.gov. 11.09.2015 [Accessed: 19.02.2016]. URL: https://ClinicalTrials.gov/show/NCT01578707.

Pharmacyclics. A phase 3 study of ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia: study results [online]. In: ClinicalTrials.gov. 11.09.2015 [Accessed: 19.02.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01578707.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton´s Tyrosine Kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: study PCYC-1112-CA; clinical study report; appendix I: protocol and amendments [unpublished]. 2012.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton´s Tyrosine Kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: study PCYC-1112-CA; protocol [unpublished]. 2012.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton´s Tyrosine Kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: study PCYC-1112-CA; clinical study report; appendix 9: statistical methods and supplemental reports [unpublished]. 2013.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: study PCYC-1112-CA; clinical study report [unpublished]. 2014.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton´s Tyrosine Kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: study PCYC-1112-CA; Nachberechnungen: Shift Table of Disease-related Symptoms [unpublished]. 2014.

Pharmacyclics. A phase 3 study of ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia (RESONATE): full text view [online]. In: ClinicalTrials.gov. 11.09.2015 [Accessed: 04.11.2015]. URL: https://clinicaltrials.gov/ct2/show/NCT01578707.

I 2.5 Research question 2: first-line treatment of the CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy

I 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 ibrutinib (status: 12 November 2015)
- bibliographical literature search on ibrutinib (last search on 12 November 2015)
- search in trial registries for studies on ibrutinib (last search on 2 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 12 February 2016)

The check of the completeness of the study pool produced no relevant RCTs on the comparison of ibrutinib versus the ACT. This deviates from the company's approach, which included study PCYC-1112-CA for research question 2. Information on the study design can be found in Section I 2.4.1.2. The company presented the results for the subpopulation of patients with 17p deletion.

The study was not relevant for research question 2 (first-line treatment) of the present benefit assessment. This resulted particularly from the fact that patients with at least one prior systemic therapy were included in the study. Correspondingly, the dosage in the comparator arm (ofatumumab + BSC) after the first infusion was considerably higher (week 2 to 8 and then in monthly intervals, 2000 mg for each infusion) than recommended in the SPC for treatment-naive patients (1000 mg for each infusion on day 8 of the first cycle, and on day 1 of the subsequent cycles; 28-day cycles).

With reference to the Committee for Medicinal Products for Human Use (CHMP) report on ibrutinib published by the European Medicines Agency (EMA) the company noted that the results for the subpopulation of patients with 17p deletion could be transferred to the target population of research question 2. 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 and the different dosages). This is not proven in the EMA document mentioned nor does the company present such proof.

Moreover, the interpretation of the result of the study carries the same problems as research question 1b. The comparator therapy (ofatumumab + BSC) used in the study did not concur with the ACT specified by the G-BA (idelalisib or BSC). Apart from the outcome "overall survival", it could not be estimated for the further outcomes of the categories "morbidity",

"health-related quality of life" and "side effects" in how far the data were influenced by the additional administration of ofatumumab in the comparator arm. Further information on this can be found in Section I 2.4.2.3.

Overall, the PCYC-1112-CA study was therefore not relevant for the benefit assessment in the framework of research question 2.

I 2.5.2 Results on added benefit (research question 2)

The company presented no relevant data for the assessment of the added benefit of ibrutinib for research question 2. This resulted in no hint of an added benefit of ibrutinib in comparison with the ACT; an added benefit is therefore not proven.

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

The company presented no suitable data for the assessment of the added benefit of ibrutinib in the first-line treatment of the CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Hence an added benefit of ibrutinib is not proven for these patients.

Based on the data presented by the company, the company derived an indication of considerable or major (discrepant information in Module 4 A) added benefit.

The G-BA decides on the added benefit.

I 2.5.4 List of included studies (research question 2)

Not applicable as no studies for research question 2 were included in the benefit assessment.

I 2.6 Extent and probability of added benefit – summary

Table 11 presents a summary of the extent and probability of the added benefit of ibrutinib.

Table 11: Ibrutinib – extent and probability of added benefit

Research question		ACT[a]	Extent and probability of added benefit
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	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	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	Idelalisib or **best supportive care**[b]	Added benefit not proven
2	First-line treatment of the CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy	Idelalisib[c] or **best supportive care**[b]	Added benefit not proven

a: Presentation of the appropriate comparator therapy 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.
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.
c: The approval of idelalisib was changed in the course of the benefit assessment. Following this change, idelalisib in first-line treatment is now only approved for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment [1]. This had no consequences for the present benefit assessment, however, because the company had not chosen idelalisib as comparator therapy.
CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

An added benefit of ibrutinib is not proven for any of the 3 research questions: The company presented no suitable data in its dossier for the research questions 1a and 2 of the benefit assessment in the therapeutic indication CLL. No balancing of positive and negative effects versus the ACT was possible on the basis of the study presented by the company for research question 1b.

This assessment deviates from that of the company. The company saw an indication of considerable added benefit for research question 1a, and an indication of a major added benefit for each of the research questions 1b and 2.

The G-BA decides on the added benefit.

References for English extract

Please see full assessment for full reference list.

1. Gilead. Zydelig Filmtabletten: Fachinformation [online]. 03.2016. URL: http://www.fachinfo.de.

2. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.03.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

3. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodologica approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

4. Hallek M, Kay NE, Osterborg A, Chanan-Khan AA, Mahler M, Salman M et al. The HELIOS trial protocol: a phase III study of ibrutinib in combination with bendamustine and rituximab in relapsed/refractory chronic lymphocytic leukemia. Future Oncol 2015; 11(1): 51-59.

5. Wendtner CM, Dreger P, Gregor M, Greil R, Knauf WU, Pritzukleit R et al. Chronische Lymphatische Leukämie (CLL) [online]. In: Onkopedia Leitlinien. 11.2014 [Accessed: 02.02.2016]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@view/html/index.html.

6. National Comprehensive Cancer Network. Non-Hodgin's lymphomas: version 4.2014 [online]. In: NCCN Guidelines. 22.08.2014 [Accessed: 04.04.2016]. URL: http://www.nccn.org.

7. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(Suppl 5): v78-v84.

8. Beinlich P (BfArM). AW: Nachfrage zum Zulassungsstatus von Ibrutinib (Imbruciva). E-Mail an Haag S (IQWiG). 15.03.2016.

9. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014; 371(3): 213-223.

10. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691.

11. Osterborg A, Udvardy M, Zaritskey A, Andersson PO, Grosicki S, Mazur G et al. Phase III, randomized study of ofatumumab versus physicians' choice of therapy and standard versus extended-length ofatumumab in patients with bulky fludarabine-refractory chronic lymphocytic leukemia. Leuk Lymphoma 19.01.2016 [Epub ahead of print].

12. Novartis Pharma. Arzerra 100 mg Konzentrat zur Herstellung einer Infusionslösung, Arzerra 1.000 mg Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 05.2015 [Accessed: 05.04.2016]. URL: http://www.fachinfo.de.

13. Gilead Sciences. A phase 3, randomized, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with ofatumumab for previously treated chronic lymphocytic leukemia [online]. In: EU Clinical Trials Register. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-001236-65.

Ibrutinib

Assessment module II

Relapsed or refractory mantle cell lymphoma

Medical and scientific advice:

- Andreas Hüttmann, Department of Haematology, Essen University Hospital, Germany

IQWiG thanks the medical and scientific advisor for his 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: ibrutinib, lymphoma – mantle-cell, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCL	mantle cell lymphoma
MID	minimally important difference
MMRM	mixed-effects model repeated measures
PFS	progression-free survival
R-FCM	rituximab, fludarabine, cyclophosphamide and mitoxantrone
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
sMIPI	simplified MCL International Prognostic Index
SPC	Summary of Product Characteristics
VAS	visual analogue scale

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 ibrutinib. 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 1 February 2016.

The drug ibrutinib is approved for several therapeutic indications. The present assessment module II contains the assessment of the therapeutic indication relapsed or refractory mantle cell lymphoma (MCL).

Research question

The aim of this report was to assess the added benefit of ibrutinib compared with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory MCL.

Table 1 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 1: Research question of the benefit assessment of ibrutinib

Research question	Subindication	Appropriate comparator therapy[a]
1	Adult patients with relapsed or refractory mantle cell lymphoma[b]	▪ Individually optimized treatment specified by the physician, principally under consideration of the respective approval status ▪ Outside the approval: under consideration of Appendix VI, Part A, No VI of the Pharmaceutical Directive (off-label use): fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type[c] and resistance to CHOP (with or without rituximab)

a: Presentation of the appropriate comparator therapy specified by the G-BA.
b: It is assumed for the present therapeutic indication that the patients are not eligible for allogeneic or autologous stem cell transplantation at the time point of treatment.
c: CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia.
CHOP: cyclophosphamide/doxorubicin/vincristine/predniso(lo)ne; FCM-R: fludarabine, cyclophosphamide, mitoxantrone and rituximab; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma

The ACT specified by the G-BA was used for the present assessment. The assessment was conducted based on patient-relevant outcomes and on the data of one randomized controlled trial (RCT) provided by the company in the dossier.

Results

Study pool

The study pool for the benefit assessment of ibrutinib in comparison with the ACT consisted of the RCT PCI-32765MCL3001 (hereinafter referred to as "MCL3001"). In the MCL3001 study, ibrutinib was compared with temsirolimus. Temsirolimus is one of several options for the implementation of individually optimized treatment. Due to its design and the patient population included, the MCL3001 study was suitable to derive conclusions on the added benefit of ibrutinib for patients for whom temsirolimus constitutes the individually optimized treatment. Conclusions on the added benefit of ibrutinib for patients for whom temsirolimus is no or a secondary treatment option could not be derived on the basis of this study. Due to the data presented, the benefit assessment is divided into the 2 following subquestions:

- research question 1a: adult patients with relapsed or refractory MCL for whom temsirolimus constitutes the individually optimized treatment
- research question 1b: adult patients with relapsed or refractory MCL for whom temsirolimus is no or a secondary treatment option

Data were only available for research question 1a (study MCL3001).

Research question 1a: patients for whom temsirolimus constitutes the individually optimized treatment option

Study characteristics

The MCL3001 study was an RCT on the comparison of ibrutinib with temsirolimus, in which adult patients with relapsed or refractory MCL were included who had received at least one rituximab-containing chemotherapy. Patients had to be in good general condition (corresponding to an Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1). Patients with an ECOG PS of 2 or higher were not to be included. A total of 280 patients were randomly assigned (139 patients to the ibrutinib group, and 141 patients to the temsirolimus group). The use of ibrutinib and temsirolimus in the study was in compliance with the information provided in the Summary of Product Characteristics (SPC). Other MCL treatments were prohibited for all patients.

Relevant population

The subpopulation of the MCL3001 study with ≥ 3 prior therapies was considered primarily relevant for research question 1a (ibrutinib n = 54, temsirolimus n = 56) because temsirolimus is an option mainly for later lines of treatment. Hence for this subpopulation it can be assumed with greater certainty that temsirolimus constitutes the individually optimized treatment than for patients with < 3 prior therapies. However, temsirolimus can also partly constitute an individually optimized treatment option for patients with < 3 prior therapies in the MCL3001 study. In the present benefit assessment, only the subpopulation with ≥ 3 prior therapies was considered in case of indications of effect modifications between the

subpopulations with < 3 and ≥ 3 prior therapies; in other cases the total population was considered.

Risk of bias

The risk of bias at study level for study MCL3001 was rated as low.

Usable results were available for the outcomes "overall survival", "health status" (recorded with the visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D]) and for the outcomes on adverse events (AEs).

The risk of bias for the outcome "overall survival" was rated as high because of the high proportion of patients who switched treatment in both treatment groups. The risk of bias for the outcome on health status was rated as high due to the lack of blinding and important differences regarding missing values at the start of the study. The risk of bias of the results on side effects (serious adverse events [SAEs], discontinuation due to AEs and severe AEs Common Terminology Criteria for Adverse Events [CTCAE] grade 3/4) was rated as high due to important differences in the observation period between the treatment groups. Moreover, the lack of blinding resulted in a high risk of bias for the outcome "discontinuation due to AEs".

No usable data were available for the outcome "health-related quality of life" (recorded with the Functional Assessment of Cancer Therapy-Lymphoma [FACT-Lym]). This resulted from the important differences in observation period and the incomplete and selective reporting of results for responder analyses.

Results

- Mortality

No statistically significant difference between the treatment groups was shown for the total population for the outcome "overall survival". Hence there was no hint of an added benefit of ibrutinib in comparison with temsirolimus for this outcome; an added benefit is therefore not proven.

- Morbidity – health status

Statistically significant results in favour of ibrutinib were available for the total population for the outcome "health status", measured with the EQ-5D VAS for the mean change and for the time to deterioration. The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result on the mean change. The 95% confidence interval (CI) of the SMD was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. These results on the outcome "health status" had a high risk of bias. Hence there was a hint of an added benefit of ibrutinib in comparison with temsirolimus for this outcome.

- Health-related quality of life

No usable data were available for the outcome "health-related quality of life" measured with the FACT-Lym questionnaire. Hence there was no hint of an added benefit of ibrutinib in comparison with temsirolimus for this outcome; an added benefit is therefore not proven.

- Side effects
  - Serious adverse events

There was a statistically significant result in favour of ibrutinib for the total population for the outcome "SAEs". This had a high risk of bias. Since due to the different observation periods the direction of the bias could be estimated (to the disadvantage of ibrutinib), and since this was accompanied by a statistically significant and also clear effect in favour of ibrutinib, a high certainty of results was assumed. Hence there was an indication of lesser harm from ibrutinib in comparison with temsirolimus for the outcome "SAEs".

  - Discontinuation due to adverse events

For the outcome "discontinuation due to AEs", there was an indication of effect modification for the number of prior therapies (< 3 versus ≥ 3). Hence for this outcome, the subpopulation with ≥ 3 prior therapies was used for the benefit assessment.

There was a statistically significant result in favour of ibrutinib for the outcome "discontinuation due to AEs". This outcome was allocated to the outcome category of non-serious/non-severe side effects. Only marginal effect size was shown for the outcome "discontinuation due to AEs". Hence for this outcome, there was no hint of greater or lesser harm from ibrutinib in comparison with temsirolimus; greater or lesser harm for this outcome is therefore not proven.

  - Severe adverse events (CTCAE grade 3/4)

There was a statistically significant result in favour of ibrutinib for the total population for the outcome "severe AEs (CTCAE grade 3/4)". Analogous to the outcome "SAEs", a high certainty of results was assumed despite the high risk of bias. Hence there was an indication of lesser harm from ibrutinib in comparison with temsirolimus for the outcome "severe AEs".

Research question 1b: patients for whom temsirolimus is no or a secondary treatment option

The company presented no data in its dossier for the assessment of the added benefit of ibrutinib in patients with relapsed or refractory MCL for whom temsirolimus is no or a secondary treatment option. This resulted in no hint of an added benefit of ibrutinib in comparison with the ACT; an added benefit is therefore not proven.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug ibrutinib compared with the ACT for the therapeutic indication of relapsed or refractory MCL is assessed as follows:

Research question 1a: patients for whom temsirolimus constitutes the individually optimized treatment option

For patients for whom temsirolimus constitutes the individually optimized treatment, on the side of positive effects, there is a hint of considerable added benefit for the outcome "health status", and for each of the outcomes "SAEs" and "severe AEs (CTCAE grade 3/4)", an indication of lesser harm with the extent "major". This was not offset by negative effects.

In summary, there is an indication of a major added benefit of ibrutinib versus the ACT for these patients.

Research question 1b: patients for whom temsirolimus is no or a secondary treatment option

Since the company presented no data for the assessment of the added benefit of ibrutinib in patients with relapsed or refractory MCL for whom temsirolimus is no or a secondary treatment option, an added benefit of ibrutinib is not proven for these patients.

Summary

Table 2 presents a summary of the extent and probability of the added benefit of ibrutinib in the therapeutic indication relapsed or refractory MCL.

Table 2: Ibrutinib – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with relapsed or refractory mantle cell lymphoma[b]	▪ Individually optimized treatment specified by the physician, principally under consideration of the respective approval status ▪ Outside the approval: under consideration of Appendix VI, Part A, No VI of the Pharmaceutical Directive (off-label use): fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type[c] and resistance to CHOP (with or without rituximab)	
a) for whom temsirolimus constitutes the individually optimized treatment option		Indication of major added benefit
b) for whom temsirolimus is no or a secondary treatment option		Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: It is assumed for the present therapeutic indication that the patients are not eligible for allogeneic or autologous stem cell transplantation at the time point of treatment.
c: CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia.
ACT: appropriate comparator therapy; CHOP: cyclophosphamide/doxorubicin/vincristine/predniso(lo)ne; FCM-R: fludarabine, cyclophosphamide, mitoxantrone and rituximab; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. 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 ibrutinib compared with the ACT in adult patients with relapsed or refractory MCL.

Table 3 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 3: Research question of the benefit assessment of ibrutinib

Research question	Subindication	Appropriate comparator therapy[a]
1	Adult patients with relapsed or refractory mantle cell lymphoma[b]	▪ Individually optimized treatment specified by the physician, principally under consideration of the respective approval status ▪ Outside the approval: under consideration of Appendix VI, Part A, No VI of the Pharmaceutical Directive (off-label use): fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type[c] and resistance to CHOP (with or without rituximab)

a: Presentation of the appropriate comparator therapy specified by the G-BA.
b: It is assumed for the present therapeutic indication that the patients are not eligible for allogeneic or autologous stem cell transplantation at the time point of treatment.
c: CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia.
CHOP: cyclophosphamide/doxorubicin/vincristine/predniso(lo)ne; FCM-R: fludarabine, cyclophosphamide, mitoxantrone and rituximab; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma

The ACT specified by the G-BA was used for the present assessment. This deviates from the company's approach, which initially followed the ACT specified by the G-BA, but then limited this to the treatment options temsirolimus and the combination of rituximab with fludarabine, cyclophosphamide and mitoxantrone (R-FCM).

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

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 ibrutinib (status: 12 November 2015)
- bibliographical literature search on ibrutinib (status: 12 November 2015)
- search in trial registries for studies on ibrutinib (status: 2 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 12 February 2016)

No additional relevant study was identified from the check.

II 2.3.1 Studies included

The study listed in the following tables was included in the benefit assessment.

Table 4: Study pool – RCT, direct comparison: ibrutinib vs. temsirolimus

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PCI-32765MCL3001[b]	No	Yes	No
a: Study for which the company was sponsor. b: In the following tables, the study is referred to with its abbreviated form "MCL3001". RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of ibrutinib in comparison with the ACT consisted of the RCT PCI-32765MCL3001 (in the present report referred to as "MCL3001") and concurred with the study pool of the company. In the MCL3001 study, ibrutinib was compared with temsirolimus. Temsirolimus is approved for the treatment of patients with MCL [1]. Hence temsirolimus is one of several options for the implementation of the ACT, which is individually optimized treatment. Due to its design and the patient population included, the MCL3001 study was suitable to derive conclusions on the added benefit of ibrutinib for patients for whom temsirolimus constitutes the individually optimized treatment (see also Section II 2.4). Conclusions on the added benefit of ibrutinib for patients for whom temsirolimus is no or a secondary treatment option could not be derived on the basis of this study. Accordingly, the reporting of results and derivation of the added benefit is hereinafter divided into 2 subquestions. These are shown together with the data presented by the company in Table 5.

Table 5: Ibrutinib – subquestions and data presented for the benefit assessment

Research question	Population	Data presented
1a	Adult patients with relapsed or refractory MCL for whom temsirolimus constitutes the individually optimized treatment	RCT (MCL3001)
1b	Adult patients with relapsed or refractory MCL for whom temsirolimus is no or a secondary treatment option	No data
MCL: mantle cell lymphoma; RCT: randomized controlled trial		

Section II 2.4.4 contains a reference list for the study included for research question 1a.

II 2.4 Research question 1a: patients for whom temsirolimus constitutes the individually optimized treatment option

II 2.4.1 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment of ibrutinib in comparison with temsirolimus.

Table 6: Characteristics of the study included – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MCL3001	RCT, open-label, parallel	Adult patients with relapsed or refractory MCL, at least one prior rituximab-containing chemotherapy, ECOG PS ≤ 1, at least one measurable lymph node involvement by Revised Response Criteria for Malignant Lymphoma	Ibrutinib (N = 139) temsirolimus (N = 141) Subpopulation thereof with ≥ 3 prior therapies[b]: ibrutinib (n = 54) temsirolimus (n = 56)	Screening: ≤ 30 days before the first administration of the study medication Treatment: until disease progression or occurrence of unacceptable toxicity[c] Observation: until progression, death or end of study	98 study centres in 21 countries: Brazil, Canada, Columbia, Europe, Mexico, South Korea, Taiwan 12/2012 – ongoing Clinical data cut-off: 4/2015[d]	Primary: PFS Secondary: overall survival, health status, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Based on IWRS.
c: After confirmed disease progression and fulfilment of several specific criteria, patients in the temsirolimus group had the option to cross over to ibrutinib treatment. Furthermore, patients in both groups were allowed to start subsequent therapy for the treatment of their MCL after progression (without consideration of further criteria) and decision of the physician.
d: Planned after about 178 PFS events.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IWRS: interactive web response system; MCL: mantle cell lymphoma; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study	Intervention	Comparison	Prior and concomitant medication
MCL3001	Ibrutinib 560 mg (four 140 mg capsules) daily, orally[a]	Temsirolimus IV for 30 to 60 min[a]: ▪ cycle 1: 175 mg on day 1, 8 and 15 ▪ from cycle 2: 75 mg on day 1, 8 and 15	Pretreatment: ▪ at least one prior rituximab-containing chemotherapy Concomitant medication allowed: ▪ standard medication for supportive treatment (e.g. antiemetics, loperamide) Non-permitted concomitant medication: ▪ any chemotherapy, immunotherapy, investigational treatment and radiotherapy, systemic corticosteroids (> 20 mg/day prednisone equivalent)[b]
a: Dose modifications according to the SPC were allowed in the study. b: Corticosteroids > 10 days were prohibited if not approved by the medical monitor. IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus			

Study design

The MCL3001 study was a randomized, open-label, active-controlled approval study on the comparison of ibrutinib with temsirolimus. The MCL3001 study was a multicentre study conducted in 98 centres in 21 countries, of which about 80% were in Europe.

Adult patients with relapsed or refractory MCL who had received at least one rituximab-containing chemotherapy were included in the study. Patients had to be in good general condition (corresponding to an ECOG PS of 0 or 1). Patients with an ECOG PS of 2 or higher were not to be included.

A total of 280 patients were randomly assigned (139 patients to the ibrutinib group, and 141 patients to the temsirolimus group). Randomization was stratified by the number of prior therapies (1 or 2 versus ≥ 3 prior therapies) and simplified MCL International Prognostic Index (sMIPI; low risk [0 to 3] versus intermediate risk [4 to 5] versus high risk [6 to 11]).

The patients in the ibrutinib group received 560 mg (4 capsules) ibrutinib once daily. The use concurred with the specifications in the SPC [2].

The patients in the temsirolimus group received 175 mg temsirolimus once weekly for 3 weeks, followed by weekly doses of 75 mg, each infused over 30 to 60 minutes. The use concurred with the specifications in the SPC [1].

All patients were allowed to additionally receive supportive drugs for the treatment of disease-related symptoms such as nausea. Other anti-MCL treatments (chemotherapy, immunotherapy, radiotherapy or investigational treatments) were prohibited for all patients.

Treatment with ibrutinib or temsirolimus was to be continued in both study arms until disease progression (measured with the Revised Response Criteria for Malignant Lymphoma [3]) or unacceptable toxicity occurred.

On confirmed progression and fulfilment of further criteria (e.g. defined haematological and biochemical threshold values), patients in the temsirolimus group were allowed to cross over to ibrutinib. The patients in both study arms were allowed to switch to further treatment options after progression and according to the physician's specification. During the study, a total of 31.7% of the patients in the ibrutinib group, and 58.2% in the temsirolimus group switched to subsequent therapy (see Table 26 of the full dossier assessment). Of these patients in the temsirolimus group, 32 (23% of the total population) switched to ibrutinib. It remained unclear how large the proportion of patients was who switched to treatments that are not approved for the present therapeutic indication in Germany. For example, 15.1% of the patients in the ibrutinib group and 25.5% of the patients in the temsirolimus group received rituximab, a large proportion of which apparently not as R-FCM (see Table 26 of the full dossier assessment).

Relevant population for research question 1a

The subpopulation of the MCL3001 study with ≥ 3 prior therapies was considered to be primarily relevant for the benefit assessment for the present research question (patients for whom temsirolimus constitutes the individually optimized treatment). Concurring with the explanations of the company, this is justified by the fact that temsirolimus is an option particularly for later lines of treatment [4,5]. Hence for this subpopulation it can be assumed with greater certainty that temsirolimus constitutes the individually optimized treatment than for patients with < 3 prior therapies. However, temsirolimus can also partly constitute an individually optimized treatment option for patients with < 3 prior therapies in the MCL3001 study. The study documents contained no information on this, however. In the present benefit assessment, only the subpopulation with ≥ 3 prior therapies was considered in case of indications of effect modifications between the subpopulations with < 3 and ≥ 3 prior therapies; in other cases the total population was considered. In addition to the analyses of the total population of the MCL3001 study, the company provided the results of the subpopulation with ≥ 3 prior therapies on all outcomes it presented.

Planned duration of the follow-up and data cut-off

Progression-free survival (PFS) was the primary outcome of the MCL3001 study; overall survival, health status, health-related quality of life and AEs were secondary outcomes.

Table 8 shows the planned duration of follow-up of the patients for the relevant outcomes.

Table 8: Planned duration of follow up – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study **Outcome category** **Outcome**	**Planned follow-up**
MCL3001	
Mortality	
Overall survival	Until end of study
Morbidity	
Health status (EQ-5D VAS)	Until death or end of study
Health-related quality of life (FACT-Lym)	Until progression, death or clinical data cut-off
Side effects	
AEs/SAEs/discontinuation due to AEs/AEs CTCAE grade ≥ 3	Until 30 days after the last treatment or start of subsequent therapy
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus	

The data of all patients on overall survival and on health status were considered in the analysis also after the end of the study medication and possible treatment switch. The outcomes on health-related quality of life and side effects were recorded only until progression or 30 days after the last treatment or start of subsequent therapy.

The MCL3001 study was not yet completed at the time of the benefit assessment. The clinical data cut-off, which was the basis for the present benefit assessment, was planned after about 178 PFS events. After the clinical data cut-off, the study was to be continued until 80% of the randomized patients had died or until 3 years after randomization of the last patient or until the sponsor ended the study.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study **Population** **Characteristics** **Category**	**Ibrutinib**	**Temsirolimus**
MCL3001		
Total population	N[a] = 139	N[a] = 141
Age [years], mean (SD)	67 (8.7)	67 (9.8)
Sex [F/M], %	28/72	23/77
Ethnicity, n (%)		
White	115 (82.7)	129 (91.5)
Asian	16 (11.5)	5 (3.5)
Other	3 (2.2)	4 (2.8)
Unknown/not reported	5 (3.6)	3 (2.1)
Number of prior therapies[b], n (%)		
1-2	85 (61.2)[c]	85 (60.3)[c]
≥ 3	54 (38.8)	56 (39.7)
Treatment indication, n (%)		
Relapsed disease[d]	103 (74.1)	94 (66.7)
Refractory disease[e]	36 (25.9)	47 (33.3)
ECOG PS, n (%)		
0	67 (48.2)	67 (47.5)
1	71 (51.1)	72 (51.1)
2	1 (0.7)	2 (1.4)
Time since diagnosis [months], mean (SD)	50.0 (42.7)	51.2 (33.6)
Stage of MCL, n (%)		
I	3 (2.2)	2 (1.4)
II	7 (5.0)	5 (3.5)
III	17 (12.2)	14 (9.9)
IV	112 (80.6)	120 (85.1)
sMIPI, n (%)		
Low risk (1–3)	44 (31.7)	42 (29.8)
Intermediate risk (4–5)	65 (46.8)	69 (48.9)
High risk (6–11)	30 (21.6)	30 (21.3)
Histology at diagnosis, n (%)		
Blastoid	16 (11.5)	17 (12.1)
Diffuse	56 (40.3)	61 (43.3)
Nodular	38 (27.3)	40 (28.4)
Other	9 (6.5)	5 (3.5)
Unknown	20 (14.4)	18 (12.8)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a) (continued)

Study Population Characteristics Category	Ibrutinib	Temsirolimus
MCL3001		
Total population	N[a] = 139	N[a] = 141
Treatment discontinuation, n (%)	74 (53.2)[f]	124 (87.9)[g]
Study discontinuation, n (%)	66 (47.5)[h]	78 (55.3)[i]
Subpopulation (≥ 3 prior therapies)	n = 54	n = 56
On all characteristics named above	ND	

a: Number of randomized patients.
b: Based on IWRS.
c: Percentage calculated by the Institute.
d: Defined as relapse or disease progression after at least a partial response to the last regimen before study entry.
e: Defined as failure to achieve a partial response to the last regimen before study entry.
f: Including 6 (4.3%) deaths.
g: Including 8 (5.7%) deaths.
h: Including 59 (42.4%) deaths.
i: Including 63 (44.7%) deaths.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IWRS: interactive web response system; M: male; MCL: mantle cell lymphoma; n: number of patients; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; sMIPI: simplified MCL International Prognostic Index; vs: versus

The mean age of the patients in the MCL3001 study was 67 years. About 83% (ibrutinib group) and about 92% (temsirolimus group) of the patients were white, and the majority were men.

The patients' average disease duration at the start of the study was about 50 months (about 4 years). About 40% of the patients had already received more than 2 prior therapies. In accordance with the inclusion criteria, almost all patients had an ECOG PS of 0 or 1; the MCL stage was stated to be IV in most patients.

The proportion of patients who discontinued treatment was about 53% in the ibrutinib group, and about 88% in the temsirolimus group. About half of the patients discontinued the study.

No information on patient characteristics was available for the primarily relevant subpopulation (patients with ≥ 3 prior therapies).

Duration of treatment and follow-up

Table 10 shows the median and mean treatment duration of the patients and the follow-up period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study **Population** **Duration of the study phase** **Outcome category**	**Ibrutinib**	**Temsirolimus**
MCL3001		
Total population	N = 139	N = 141
Treatment duration [months]		
Median [min; max]	14.4 [0.0; 28.2]	3.0 [0.0; 27.0][a]
Mean (SD)	13.3 (8.3)	6.0 (6.8)[a]
Observation period [months]		
Overall survival		
Median [min; max]	20.4 [0.2; 28.2]	19.7 [0.0; 27.7]
Mean (SD)	15.2 (7.6)	12.9 (8.2)
Health status		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Subpopulation (≥ 3 prior therapies)	n = 54	n = 56
On all information on the course of the study mentioned above	ND	

a: Referring to n = 139 because 2 of the patients randomized to the temsirolimus group never received the study medication.

max: maximum; min: minimum; N: number of randomized patients; n: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median and mean treatment durations differed notably between the 2 study arms with the shorter treatment duration under temsirolimus.

Despite the different treatment durations, the observation periods for the outcome “overall survival” were comparable. No information on the observation period for other outcomes was available. However, it could be inferred from the planned follow-up duration for the outcome “health status” (see Table 8) that these – as the one for the outcome “overall survival” – were comparable between both groups. The observation periods for health-related quality of life and side effects probably differed notably, however.

No information on treatment and observation periods was available for the subpopulation with ≥ 3 prior therapies.

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
MCL3001	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for study MCL3001 was rated as low. This concurs with the company's assessment.

Restrictions resulting from the open-label study design and the different treatment durations or different observation periods in the 2 treatment arms are described in Section II 2.4.2.2 for the outcome-specific risk of bias.

II 2.4.2 Results on added benefit

II 2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section II 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - Overall survival
- Morbidity
  - health status measured with the VAS of the EQ-5D questionnaire
- Health-related quality of life
  - measured with the FACT-Lym questionnaire
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade 3/4)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4B) (see Section II 2.7.2.4.3 of the full dossier assessment).

As described above, the total population of the MCL3001 study was used for the benefit assessment if no indications of an effect modification between the subpopulations with < 3 and ≥ 3 prior therapies were present. Possible effect modifications between the corresponding subpopulations were assessed on the basis of the interaction test. In case of a p-value of < 0.2, an outcome-specific consideration of the subpopulation ≥ 3 prior therapies was conducted.

Table 12 shows for which outcomes data were available in the study included, as well as the corresponding results of the interaction test and for the subgroup characteristic of < 3 versus ≥ 3 prior therapies.

Table 12: Matrix of outcomes – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study	**Outcomes**					
	Overall survival	**Health status (EQ-5D VAS)**	**Health-related quality of life (FACT-Lym)[a]**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade 3/4)**
MCL3001						
Usable data	Yes	Yes	No[b]	Yes	Yes	Yes
p-value interaction[c]	0.784	0.698[d]/0.472[e]	–	0.819	0.153	0.431

a: FACT-Lym is comprised of FACT-LymS and FACT-G.
b: No usable data available; for reasons, see Sections II 2.7.2.4.2 and II 2.7.2.4.3 of the full dossier assessment.
c: Interaction p-values for the subgroups: number of prior therapies (< 3 vs. ≥ 3 prior therapies based on IWRS); referring to the analyses used for the benefit assessment.
d: Interaction p-value for the MID 7 (time to deterioration), no information was available for the threshold value 12.
e: Interaction p-value for the MMRM analysis.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-Lym: FACT-Lymphoma; FACT-LymS: FACT-Lym subscale; IWRS: interactive web response system; MID: minimally important difference; MMRM: mixed-effects model repeated measures; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

There were no usable data for the outcome “health-related quality of life”. This resulted from the important differences in observation period and the incomplete and selective reporting of

results for responder analyses (see also Sections II 2.7.2.4.2 and II 2.7.2.4.3 of the full dossier assessment).

The MCL3001 study contained an indication of effect modification by the number of prior therapies for the outcome "discontinuation due to AEs". Hence for the present benefit assessment the subpopulation with ≥ 3 prior therapies was used for this outcome.

II 2.4.2.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes and analyses.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study	Study level	Outcomes					
		Overall survival	Health status (EQ-5D VAS)	Health-related quality of life (FACT-Lym)	SAEs	Discontinuation due to AEs	Severe AEs CTCAE grade 3/4)
MCL3001	L	H[a]	H[b]	-[c]	H[d]	H[d, e]	H[d]

a: High proportion of patients who switched treatment (31.7% [ibrutinib group] vs. 58.2% [temsirolimus group]).
b: Lack of blinding and important difference regarding missing values at the start of the study between the treatment groups (6.5% [ibrutinib] vs. 14.9% [temsirolimus]). The high proportion of patients who switched treatment (31.7% vs. 58.2%) may also have caused bias in the MMRM analyses.
c: No usable data available; for reasons, see Sections II 2.7.2.4.2 and II 2.7.2.4.3 of the full dossier assessment).
d: Important differences in observation period between the treatment groups (median treatment duration 14.4 [ibrutinib] vs. 3.0 [temsirolimus] months plus at most 30 days of follow-up).
e: Lack of blinding.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; H: high; L: low; MMRM: mixed-effects model repeated measures; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "overall survival" was rated as high because of the high proportion of patients who switched treatment in both treatment groups. This deviates from the company's assessment, which rated the risk of bias as low.

The risk of bias for the outcome on health status (EQ-5D VAS) was rated as high due to the lack of blinding and important differences regarding missing values at the start of the study. The high proportions of patients who switched treatment can also cause bias in the results of

the mean change (mixed-effects model repeated measures [MMRM] analyses). This deviates from the company's assessment, which rated the risk of bias as low.

Since no usable data were available for the outcome "health-related quality of life", the risk of bias for this outcome was not assessed. This deviates from the company's assessment, which rated the risk of bias for the outcome "health-related quality of life" as high.

The risk of bias of the results on side effects (SAEs, discontinuation due to AEs and severe AEs [CTCAE grade 3/4]) was rated as high due to important differences in the observation period between the treatment groups. Moreover, the lack of blinding resulted in a high risk of bias for the outcome "discontinuation due to AEs". This deviates from the company's arguments, which derived an overall high risk of bias for all AE outcomes, but did not name the different observation periods as a reason.

II 2.4.2.3 Results

Table 14 summarizes the results on the comparison of ibrutinib with temsirolimus in patients with relapsed or refractory MCL for whom temsirolimus constitutes the individually optimized treatment. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 14: Results – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a)

Study **Outcome**	**Ibrutinib**			**Temsirolimus**			**Ibrutinib vs. temsirolimus**
Population	**N**	**Median time to event [95% CI]** **patients with event n (%)**		**N**	**Median time to event [95% CI]** **patients with event n (%)**		**HR [95% CI][a]; p-value**
MCL3011							
Mortality							
Overall survival [months]							
Total population	139	NA [18.6; NA] 59 (42.4)		141	21.3 [13.0; NA] 63 (44.7)		0.76 [0.53; 1.09]; p = 0.132
Morbidity							
Health status (EQ-5D VAS)							
Time to worsening							
MID 7 points [weeks]							
Total population	139	48 [ND] 63 (45.3)		141	9.1 [ND] 78 (55.3)		0.47 [0.33; 0.68]; p < 0.001
Threshold value 12 points [weeks]							
Total population	139	NA 40 (28.8)		141	15 [ND] 64 (45.4)		0.38 [0.25; 0.57]; p < 0.001
		Baseline values mean (SD)	**Change at end of study mean[b] (SD)**	**N**	**Baseline values mean (SD)**	**Change at end of study mean[b] (SD)**	**Effect [95% CI]; p-value**
Mean change							
Total population	132	71.7 (16.9)	6.0 (1.0)	125	64.8 (19.4)	-1.8 (1.2)	7.83 [5.10; 10.55]; p < 0.001 Hedges' g: 0.63 [0.38; 0.88]
Health-related quality of life							
FACT-Lym	No usable data[c]						

(continued)

Table 14: Results – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a) (continued)

Study Outcome Population	Ibrutinib N	Ibrutinib Median time to event [95% CI] patients with event n (%)	Temsirolimus N	Temsirolimus Median time to event [95% CI] patients with event n (%)	Ibrutinib vs. temsirolimus HR [95% CI][a]; p-value
MCL3011					
Side effects					
AEs (supplementary information) [weeks]					
Total population	139	1.3 [ND] 138 (99.3)	139	0.9 [ND] 138 (99.3)	-
SAEs [weeks]					
Total population	139	60.7 [ND] 67 (48.2)	139	17.9 [ND] 80 (57.6)	0.53 [0.38; 0.74]; p < 0.001
Discontinuation due to AEs [weeks]					
					Interaction: *p = 0.153*[d]
Subpopulation with ≥ 3 prior therapies	54	NA 10 (18.5)	56	NA 14 (25.0)	0.40 [0.17; 0.92]; p = 0.031
Severe AEs (CTCAE grade 3/4)[e] [weeks]					
Total population	139	48.0 [ND] 71 (51.1)	139	2.9 [ND] 105 (75.5)	0.28 [0.20; 0.39]; p < 0.001

a: Stratified Cox proportional hazards model with the stratification factors used for randomization.
b: MMRM analyses of patients for whom at least one value after the start of the study was available.
c: No usable data available; for reasons, see Sections II 2.7.2.4.2 and II 2.7.2.4.3 of the full dossier assessment.
d: Interaction p-value for < 3 prior therapies vs. ≥ 3 prior therapies (based on IWRS).
e: Survival time analyses on CTCAE grade ≥ 3 were not available.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; HR: hazard ratio; IWRS: interactive web response system; MID: minimally important difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the total population for the outcome "overall survival". Hence there was no hint of an added benefit of ibrutinib in comparison with temsirolimus for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Health status (EQ-5D VAS)

Statistically significant results in favour of ibrutinib were shown for the total population for the outcome "health status", measured with the EQ-5D VAS for the time to deterioration as well as for the mean change.

For the time to deterioration (responder analyses), this statistically significant result was available both for the validated minimally important difference (MID) of 7 and for the threshold value of 12. The interpretation of the results was subject to uncertainty because the threshold value 12 is no validated MID. For the EQ-5D VAS, the threshold values of 7 to 10 represented the range of a validated MID [6]. Further analyses, at least up to the threshold value of 10, were not available. Due to the clear effects in the same direction, a clear effect can also be assumed with sufficient certainty for the MID 10, which was not used (see Section II 2.7.2.4.3 of the full dossier assessment).

The SMD in the form of Hedges' g was considered to check the relevance of the result of the mean change (MMRM analysis). The 95% CI of the SMD was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect.

There was a high risk of bias for the outcome "health status". Hence overall there was a hint of an added benefit of ibrutinib in comparison with temsirolimus for this outcome.

This assessment deviates from that of the company, which derived an indication of an added benefit and the conclusion of which comprised both the EQ-5D VAS and the EQ-5D utility.

Health-related quality of life

No usable data were available for the outcome "health-related quality of life" measured with the FACT-Lym questionnaire. Hence there was no hint of an added benefit of ibrutinib in comparison with temsirolimus for this outcome; an added benefit is therefore not proven.

Side effects

SAEs

There was a statistically significant result in favour of ibrutinib for the total population for the outcome "SAEs". Due to the important difference in observation periods between the treatment groups, the result for this outcome has a high risk of bias. Since due to the different observation periods the direction of the bias could be estimated (to the disadvantage of ibrutinib), and since this was accompanied by a statistically significant and also clear effect in favour of ibrutinib, a high certainty of results was still assumed. Hence there was an indication of lesser harm from ibrutinib in comparison with temsirolimus for the outcome "SAEs".

This assessment deviates from that of the company, which derived no indication of an increased risk of harm from ibrutinib and drew its conclusion for the totality of all AE outcomes.

Discontinuation due to adverse events

For the outcome "discontinuation due to AEs", there was an indication of effect modification for the number of prior therapies (< 3 versus ≥ 3). Hence for this outcome, the subpopulation with ≥ 3 prior therapies was used for the benefit assessment.

There was a statistically significant result in favour of ibrutinib for the outcome "discontinuation due to AEs". This outcome was allocated to the outcome category of non-serious/non-severe side effects. Only marginal effect size was shown for the outcome "discontinuation due to AEs". Hence for this outcome, there was no hint of greater or lesser harm from ibrutinib in comparison with temsirolimus; greater or lesser harm for this outcome is therefore not proven.

This assessment deviates from that of the company, which overall derived no indication of an increased risk of harm from ibrutinib for all AE outcomes it included.

Severe AEs (CTCAE grade 3/4)

There was a statistically significant result in favour of ibrutinib for the total population for the outcome "severe AEs (CTCAE grade 3/4)". Due to the important difference in observation periods between the treatment groups, the result for this outcome has a high risk of bias. Since the direction of the bias could be estimated (to the disadvantage of ibrutinib), and since this was accompanied by a statistically significant and also clear effect in favour of ibrutinib, a high certainty of results was still assumed. Hence there was an indication of lesser harm from ibrutinib in comparison with temsirolimus for the outcome "severe AEs".

This assessment deviates from that of the company, which derived no indication of an increased risk of harm from ibrutinib and drew its conclusion for the total of all AE outcomes.

II 2.4.2.4 Subgroups and other effect modifiers

Due to the clear differences in treatment durations and observation periods between the treatment groups and possible additional interactions between the number of prior therapies and subgroup characteristics, the subgroup analyses of the MCL3001 study were not meaningfully interpretable. They were therefore not considered in this benefit assessment.

II 2.4.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

II 2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section II 2.4.2.3 resulted in a hint of an added benefit of ibrutinib in comparison with temsirolimus for the outcome "health status" and in an indication of lesser harm for each of the outcomes "SAEs" and "severe AEs (CTCAE grade 3/4)". The extent of the respective added benefit under consideration of the outcome category at outcome level was estimated from these results (see Table 15).

The outcome "health status" was allocated to the outcome category of non-serious/non-severe symptoms/late complications because there was no proof of serious change for the patients included in the MCL3001 study. The outcome "discontinuation due to AEs" was allocated to the outcome category of non-serious/non-severe side effects because no information on the proportion of underlying severe events was available for the subpopulation of ≥ 3 prior therapies.

Table 15: Extent of added benefit at outcome level: ibrutinib vs. temsirolimus (research question 1a)

Outcome category **Outcome**	**Ibrutinib vs. temsirolimus** **Median time to event or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 21.3 months HR: 0.76 [0.53; 1.09]; p = 0.132	Lesser benefit/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)	*Time to worsening* *MID 7:* 48 vs. 9.1 weeks HR: 0.47 [0.33; 0.68]; p < 0.001 probability: "hint" *Threshold value 12:* NA vs. 15 weeks HR: 0.38 [0.25; 0.57]; p < 0.001 probability: "hint" Mean change: 6.0 vs. −1.8 MD: 7.83 [5.10; 10.55]; p < 0.001 Hedges' g 0.63 [0.38; 0.88][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Health-related quality of life		
FACT-Lym	No usable data	Lesser benefit/added benefit not proven
Side effects		
SAEs	60.7 vs. 17.9 weeks HR: 0.53 [0.38; 0.74]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 0.40 [0.17; 0.92]; p = 0.031[d]	Outcome category: non-serious/non-severe AEs $0.9 < CI_u < 1$ Lesser benefit/added benefit not proven[e]
Severe AEs (CTCAE grade 3/4)	48.0 vs. 2.9 weeks HR: 0.28 [0.20; 0.39]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Added benefit assumed with upper and lower CI limits < −0.2 or > 0.2.
d: Based on subpopulation with ≥ 3 prior therapies due to an indication of interaction for < 3 vs. ≥ 3 prior therapies (based on IWRS).
e: Lesser benefit or added benefit is not proven because the effect size was only marginal.
AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IWRS: interactive web response system; MD: mean difference; MID: minimally important difference; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

II 2.4.3.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of ibrutinib compared with temsirolimus (research question 1a)

Positive effects	Negative effects
Morbidity (non-serious/non-severe symptoms/late complications) ▪ Health status (EQ-5D VAS): hint of an added benefit – extent: “considerable”	–
Serious/severe side effects ▪ SAEs: indication of lesser harm – extent: “major” ▪ Severe AEs (CTCAE grade 3/4): indication of lesser harm – extent: “major”	–
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus	

For patients for whom temsirolimus constitutes the individually optimized treatment, on the side of positive effects, there is a hint of considerable added benefit for the outcome “health status”, and for each of the outcomes “SAEs” and “severe AEs (CTCAE grade 3/4)”, an indication of lesser harm with the extent “major”. This was not offset by negative effects.

In summary, there is an indication of major added benefit of ibrutinib in comparison with the ACT for patients with relapsed or refractory MCL for whom temsirolimus constitutes the individually optimized treatment.

II 2.4.4 List of included studies

MCL3001

Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rusconi C, Trneny M et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet 2016; 387(10020): 770-778.

Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rusconi C, Trneny M et al. Supplement to: "Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet 2016; 387(10020): 770-778" [online]. [Accessed: 06.04.2016]. URL: http://www.sciencedirect.com/science/article/pii/S0140673615006674.

Janssen Research & Development. Study of ibrutinib (a Bruton's tyrosine kinase inhibitor), versus temsirolimus in patients with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy: full text view [online]. In: ClinicalTrials.gov. 19.01.2016 [Accessed: 19.02.2016]. URL: https://ClinicalTrials.gov/show/NCT01646021.

Janssen Research & Development. A randomized, controlled, open-label, multicenter phase 3 study of the Bruton's tyrosine kinase (Btk) inhibitor, ibrutinib, versus temsirolimus in subjects with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy: study MCL3001; statistical analysis plan [unpublished]. 2015.

Janssen Research & Development. A randomized, controlled, open-label, multicenter phase 3 study of the Bruton's tyrosine kinase (Btk) inhibitor, ibrutinib, versus temsirolimus in subjects with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy: study MCL3001; clinical protocol amendment INT-3 [unpublished]. 2015.

Janssen Research & Development. A randomized, controlled, open-label, multicenter phase 3 study of the Bruton's tyrosine kinase (Btk) Inhibitor, ibrutinib, versus temsirolimus in subjects with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy; study MCL3001; Zusatzanalysen [unpublished]. 2015.

Janssen Research & Development. A randomized, controlled, open-label, multicenter phase 3 study of the Bruton's tyrosine kinase (Btk) inhibitor, ibrutinib, versus temsirolimus in subjects with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy: study MCL3001; clinical study report [unpublished]. 2015.

Janssen-Cilag International. A randomized, controlled, open-label, multicenter phase 3 study of the Bruton's tyrosine kinase (Btk) inhibitor, ibrutinib, versus temsirolimus in subjects with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy [online]. In: EU Clinical Trials Register. [Accessed: 19.02.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000601-74.

II 2.5 Research question 1b: patients for whom temsirolimus is no or a secondary treatment option

II 2.5.1 Results on added benefit

The company presented no data in its dossier for the assessment of the added benefit of ibrutinib in patients with relapsed or refractory MCL for whom temsirolimus is no or a secondary treatment option. This resulted in no hint of an added benefit of ibrutinib in comparison with the ACT; an added benefit is therefore not proven.

II 2.5.2 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of ibrutinib in patients with relapsed or refractory MCL for whom temsirolimus is no or a secondary treatment option, an added benefit of ibrutinib is not proven for these patients.

II 2.5.3 List of included studies

Not applicable as no data were available for this research question.

II 2.6 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of ibrutinib in comparison with the ACT is summarized in Table 17.

Table 17: Ibrutinib – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with relapsed or refractory mantle cell lymphoma[b]	▪ Individually optimized treatment specified by the physician, principally under consideration of the respective approval status ▪ Outside the approval: under consideration of Appendix VI, Part A, No VI of the Pharmaceutical Directive (off-label use): fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type[c] and resistance to CHOP (with or without rituximab)	
a) for whom temsirolimus constitutes the individually optimized treatment option		Indication of major added benefit
b) for whom temsirolimus is no or a secondary treatment option		Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: It is assumed for the present therapeutic indication that the patients are not eligible for allogeneic or autologous stem cell transplantation at the time point of treatment.
c: CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia.
ACT: appropriate comparator therapy; CHOP: cyclophosphamide/doxorubicin/vincristine/predniso(lo)ne; FCM-R: fludarabine, cyclophosphamide, mitoxantrone and rituximab; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma

This deviates from the company's approach, which derived an indication of considerable added benefit for the total target population in the therapeutic indication.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full assessment for full reference list.

1. Pfizer. Torisel 30 mg Konzentrat und Verdünnungsmittel zur Herstellung einer Infusionslösung: Fachinformation [online]. 09.2014. URL: http://www.fachinfo.de/.

2. Janssen. IMBRUVICA 140 mg Hartkapseln: Fachinformation [online]. 06.2015 [Accessed: 15.02.2016]. URL: http://www.fachinfo.de/.

3. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25(5): 579-586.

4. Dreyling M, Herold M, Drach J, Rummel MJ, Buske C. Mantelzell-Lymphom [online]. In: Onkopedia Leitlinien. 03.2012 [Accessed: 07.01.2016]. URL: http://www.dgho-onkopedia.de/de/onkopedia/leitlinien/mantelzell-lymphom.

5. Dreyling M, Geisler C, Hermine O, Kluin-Nelemans HC, Le Gouill S, Rule S et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25(Suppl 3): iii83-iii92.

6. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007; 5: 70.

7. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.03.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

Ibrutinib

Assessment module III

Waldenström macroglobulinaemia

Medical and scientific advice:

- Andreas Hüttmann, Department of Haematology, Essen University Hospital, Germany

IQWiG thanks the medical and scientific advisor for his 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.

IQWiG employees involved in the assessment[1]:

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Keywords: ibrutinib, Waldenstrom macroglobulinemia, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
R-FCM	rituximab, fludarabine, cyclophosphamide and mitoxantrone
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

III 2 Benefit assessment

III 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 ibrutinib. 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 1 February 2016.

The drug ibrutinib is approved for several therapeutic indications. The present assessment module III contains the assessment of the therapeutic indication Waldenström macroglobulinaemia in adult patients.

Research question

The aim of the present report was the assessment of the added benefit of ibrutinib in comparison with individually optimized treatment specified by the physician (principally under consideration of the approval status and under consideration of Appendix VI of the Pharmaceutical Directive [off-label use]) as appropriate comparator therapy (ACT) in adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

Two patient populations, which have to be considered separately, resulted from the approval of ibrutinib. Table 1 shows the resulting research questions for the benefit assessment and the ACT.

Table 1: Ibrutinib – research questions of the benefit assessment

Research question	Subindication	Appropriate comparator therapy[a]
1	Adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy	Individually optimized treatment specified by the physician, principally under consideration of the respective approval status and under consideration of Appendix VI of the Pharmaceutical Directive (off-label use)[b]
2	First-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy	

a: Presentation of the appropriate comparator therapy specified by the G-BA.
b: Appendix VI of the Pharmaceutical Directive states for the off-label use: "Fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type (CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia) and resistance to CHOP (with or without rituximab)".
CHOP: cyclophosphamide/doxorubicin/vincristine/prednisone; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma

The ACT specified by the G-BA was applicable for the present assessment. The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

The company presented data only for one of both research questions. An overview of the data presented by the company is shown in Table 2.

Table 2: Ibrutinib – data presented on the research questions

Research question	Subindication	Data presented by the company
1	Adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy	One-arm study on ibrutinib and data on the outcome "overall survival" for the ACT retrospectively recorded from patient charts
2	First-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy	No data
ACT: appropriate comparator therapy		

Results

Research question 1: pretreated patients

Since randomized controlled trials (RCTs) were lacking, the company presented a historical comparison based on uncontrolled studies on ibrutinib and on the ACT. The company included a one-arm study on ibrutinib (PCYC-1118E, referred to as "1118E" in the present report). For the ACT, it presented data retrospectively recorded from patient charts in Germany.

The historical comparison presented by the company was unsuitable for the present benefit assessment because, on the one hand, it was based on a selective choice of data, and, on the other, the selectively chosen data were not valid. This is particularly due to the following reasons:

- The company conducted no systematic literature search for the ACT, but only presented one source selectively chosen by the company. This was a set of slides on a study of patient charts conducted with an online survey of European treatment centres.
- The company selectively considered only the outcome "overall survival", but not further patient-relevant outcomes such as adverse events, symptoms or health-related quality of life.
- It remained unclear where the data on overall survival presented by the company came from. The set of slides submitted by the company in the dossier did not contain the analyses used by the company. The company presented survival time curves in an additional document, but there were several discrepancies between the data in the set of slides, the additional document, and Module 4 C of the dossier. The methods used for the

analysis on overall survival are not described in any of the documents and were therefore not comprehensible. For example, there was no information on whether adjustments by prognostic factors were conducted, and, if so, which factors were used, whether these were prespecified, etc.

- It remained unclear from the documents presented by the company whether the patients analysed by the company had been treated with the ACT at all.
- From the analysis of patient charts, the company only used data from Germany, although it had been a European-wide analysis. This was not meaningful in the present case because the ibrutinib study 1118E had not been conducted in Germany, but in the USA. If it had been mandatory to limit the data to Germany for reasons of content (e.g. because of different baseline risks, care pathways, etc.), the company's ibrutinib study would also have been unsuitable for the historical comparison and, as a consequence, would have had to be excluded by the company. Based on the data from Germany used by the company, the company postulated a statistically significant difference in favour of ibrutinib for the outcome "overall survival". Considering the European data in total, however, no statistically significant difference was shown. Irrespective of this, the difference used by the company was not of a magnitude that allows the derivation of a conclusion on the added benefit in the framework of a historical comparison.

Hence the company overall presented no usable data for research question 1 (patients with Waldenström macroglobulinaemia who have received at least one prior therapy). Hence there was no hint of an added benefit of ibrutinib in comparison with the ACT; the added benefit of ibrutinib is not proven.

Research question 2: patients in first-line treatment who are unsuitable for chemo-immunotherapy

The company presented no data on the first-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy. Hence there was no hint of an added benefit of ibrutinib in comparison with the ACT; the added benefit of ibrutinib is not proven.

Ongoing RCT

The company noted that it was currently conducting an RCT (PCYC-1127-CA) on the therapeutic indication Waldenström macroglobulinaemia in treatment-naive patients and in pretreated patients on the comparison of ibrutinib plus rituximab with placebo plus rituximab. The end of the study is planned for January 2019.

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

Table 3 presents a summary of the extent and probability of the added benefit of ibrutinib in the therapeutic indication Waldenström macroglobulinaemia in adult patients.

Table 3: Ibrutinib – extent and probability of added benefit

Subindication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy	Individually optimized treatment specified by the physician, principally under consideration of the approval status and under consideration of Appendix VI of the Pharmaceutical Directive (off-label use)[b]	Added benefit not proven
First-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy		Added benefit not proven

a: Presentation of the appropriate comparator therapy specified by the G-BA.

b: Appendix VI of the Pharmaceutical Directive states for the off-label use: "Fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type (CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia) and resistance to CHOP (with or without rituximab)".

CHOP: cyclophosphamide/doxorubicin/vincristine/prednisone; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma

The G-BA decides on the added benefit.

III 2.2 Research question

The aim of the present report was the assessment of the added benefit of ibrutinib in comparison with individually optimized treatment specified by the physician (principally under consideration of the approval status and under consideration of Appendix VI of the Pharmaceutical Directive [off-label use] [1]) as ACT in adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

Two patient populations, which have to be considered separately, resulted from the approval of ibrutinib [2]. Table 4 shows the 2 resulting research questions for the benefit assessment and the ACT.

Table 4: Ibrutinib – research questions of the benefit assessment

Research question	Subindication	Appropriate comparator therapy[a]
1	Adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy	Individually optimized treatment specified by the physician, principally under consideration of the respective approval status and under consideration of Appendix VI of the Pharmaceutical Directive (off-label use)[b]
2	First-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy	
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: Appendix VI of the Pharmaceutical Directive states for the off-label use: "Fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type (CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia) and resistance to CHOP (with or without rituximab)" [1]. CHOP: cyclophosphamide/doxorubicin/vincristine/prednisone; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma		

The ACT specified by the G-BA was applicable for the present assessment. This approach deviates from that of the company, which formally followed the ACT specified by the G-BA, but then limited this with regard to content to the treatment options chlorambucil and the combination of rituximab with fludarabine, cyclophosphamide and mitoxantrone (R-FCM).

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

The company presented data only for one of both research questions. An overview of the data presented by the company is shown in Table 5.

Table 5: Ibrutinib – data presented on the research questions

Research question	Subindication	Data presented by the company
1	Adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy	One-arm study on ibrutinib and data on the outcome "overall survival" for the ACT retrospectively recorded from patient charts
2	First-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy	No data
ACT: appropriate comparator therapy		

III 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 ibrutinib (status: 2 November 2015)
- bibliographical literature search on ibrutinib (status: 11 December 2015)
- search in trial registries for studies on ibrutinib (status: 2 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 12 February 2016)

No studies suitable for deriving an added benefit of ibrutinib in comparison with the ACT for any of both research questions were identified from the steps of information retrieval mentioned. This deviates from the company's approach, which also identified no RCT, but included a one-arm study (PCYC-1118E, referred to as "study 1118E" in the present report) on ibrutinib [3] for the assessment of research question 1.

For the ACT, it presented data retrospectively recorded from patient charts in Germany [4] for the outcome "overall survival". The company conducted no systematic information retrieval of further investigations with the ACT.

III 2.3.1 Research question 1: pretreated patients

The data presented by the company for research question 1 were unsuitable for the present benefit assessment.

Information on ibrutinib (study 1118E)

64 pretreated patients, of whom one patient had received no ibrutinib dose, were included in the one-arm study 1118E presented by the company. The median number of prior therapies received by the patients was 2 (range: 1 to 11). The median age of the patients was 63 (range: 44 to 86) years, the general condition was relatively good (Eastern Cooperative Oncology

Group Performance Status [ECOG PS] 0 or 1). The patients were taking ibrutinib 420 mg orally once daily, thus in compliance with the approval; the maximum treatment duration was 40 4-week cycles. The first analysis was conducted after a median study duration of 14.8 months (data cut-off: 28 February 2014), and a further analysis, including an analysis for the outcome "overall survival", was conducted after a median study duration of 24.4 months (data cut-off: 19 December 2014).

Information on the appropriate comparator therapy

The company included data of patients with 2 or more previous lines of treatment in a historical comparison with ibrutinib. These data were taken from an analysis of data retrospectively recorded from patient charts in Europe. From this analysis, the company only included the data from Germany in its assessment. The data presented by the company for the ACT were inadequate for several reasons because it presented data selectively and the validity of these data was inadequate.

The company's approach was selective particularly for 2 reasons. First, the company conducted no systematic literature search for the ACT, which is necessary to obtain a complete study pool. The company selectively presented data from the source chosen by the company. This was a set of slides on a data analysis on patients with Waldenström macroglobulinaemia and their health care situation commissioned by the company Pharmacyclics [4]. The data were recorded with an online survey of European treatment centres. The company also presented an additional document containing survival time analyses on the outcome "overall survival" [5]. Second, the company only considered the outcome "overall survival", but not all the outcomes designated to be relevant by the company.

Besides the company's selective reporting of results on the ACT, the validity of the data on the outcome "overall survival" presented by the company was also inadequate. Overall, it remained unclear where the data on overall survival came from. There were several discrepancies between the set of slides, the additional document, and Module 4 C, which could not be clarified, e.g. on patient numbers: Whereas the patient number inferred from the set of slides was n = 454, the patient number in the survival time analyses was n = 630. The number of the corresponding patients from Germany was n = 66 and n = 74. Only 40 patients from Germany were stated in Module 4 C of the dossier for the information on type and number of prior therapies, however. In addition, the methods used for the analyses were not clearly comprehensible from the documents provided by the company. It remained unclear, for instance, whether an adjustment by prognostic factors was conducted and, if so, for which. In addition, it was unclear, also because of the discrepant information between the individual documents, which treatments the patients had exactly received and therefore also whether these concurred with the ACT at all. Finally, from the analysis of patient charts, the company only used data from Germany, although it had been a European-wide analysis. This was not meaningful in the present case because the ibrutinib study 1118E had not been conducted in Germany, but in the USA. If it had been mandatory to limit the data to Germany for reasons

of content (e.g. because of different baseline risks, care pathways, etc.), the company's ibrutinib study would also have been unsuitable for the historical comparison and, as a consequence, would have had to be excluded by the company.

Irrespective of the lack of validity, based on the comparator data from Germany used by the company, the company postulated a statistically significant advantage in favour of ibrutinib versus the data retrospectively recorded for the outcome "overall survival" (hazard ratio [HR] [95% confidence interval] 0.25 [0.07; 0.88], p-value = 0.031; n = 74). Considering the data from Europe, no statistically significant difference was shown (HR [95 % confidence interval] 0.39 [0.12; 1.25][2], p-value = 0.115; n = 630). Irrespective of this, the difference was not of a magnitude that allows the derivation of a conclusion on the added benefit in the framework of a historical comparison.

Overall, the company presented no usable data for a historical comparison. Referring to its research question, which included both pretreated patients and patients in first-line treatment for whom chemo-immunotherapy is unsuitable, the company derived a hint of an added benefit of ibrutinib of non-quantifiable extent (at least "considerable").

Conclusion

The company presented no usable data for a historical comparison of ibrutinib with the ACT for adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy. This was mainly due to the selective choice of studies, the selective reporting of results and the lack of validity of the data presented.

III 2.3.2 Research question 2: patients in first-line treatment who are unsuitable for chemo-immunotherapy

The company presented no data on the first-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy.

III 2.3.3 Ongoing RCT

The company noted that it was currently conducting an RCT (PCYC-1127-CA [6]) on the therapeutic indication Waldenström macroglobulinaemia. No results on this ongoing study were yet available. The RCT compared the combination of ibrutinib and rituximab with placebo and rituximab. Ibrutinib alone was investigated in a further study arm – without randomized comparison. According to the inclusion criterion of the study, both pretreated and treatment-naive patients were to be included. The end of the study is planned for January 2019.

[2] Inverse HR: Institute's calculation (for comparability with the HR mentioned before).

III 2.4 Results on added benefit

The company presented no usable data for research question 1 for the assessment of the added benefit of ibrutinib in comparison with the ACT in patients with Waldenström macroglobulinaemia who have received at least one prior therapy.

The company presented no data for research question 2 for the assessment of the added benefit of ibrutinib in comparison with the ACT in first-line treatment in patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy.

Hence for both research questions, there was no hint of an added benefit of ibrutinib in comparison with the ACT. In both cases, an added benefit is therefore not proven.

III 2.5 Extent and probability of added benefit

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

Table 6: Ibrutinib – extent and probability of added benefit

Subindication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy	Individually optimized treatment specified by the physician, principally under consideration of the approval status and under consideration of Appendix VI of the Pharmaceutical Directive (off-label use)[b]	Added benefit not proven
First-line treatment in adult patients with Waldenström macroglobulinaemia who are unsuitable for chemo-immunotherapy		Added benefit not proven
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: Appendix VI of the Pharmaceutical Directive states for the off-label use: “Fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (FCM-R) in suitable patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell type (CD20-positive NHL, including lymphocytic, lymphoplasmacytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell myeloma, marginal zone myeloma, non-multiple myeloma, non-hairy cell leukaemia) and resistance to CHOP (with or without rituximab)” [1]. CHOP: cyclophosphamide/doxorubicin/vincristine/prednisone; G-BA: Federal Joint Committee; NHL: non-Hodgkin lymphoma		

The assessment of the added benefit deviates from that of the company because the company did not distinguish between the patient populations in its research question and, referring to its research question, derived a hint of non-quantifiable added benefit (at least “considerable”) of ibrutinib.

The G-BA decides on the added benefit.

III 2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

References for English extract

Please see full assessment for full reference list.

1. Gemeinsamer Bundesausschuss. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use) [online]. 05.05.2015 [Accessed: 29.03.2016]. URL: https://www.g-ba.de/downloads/83-691-377/AM-RL-VI-Off-label-2015-05-05.pdf.

2. Janssen. Imbruvica 140 mg Hartkapseln: Fachinformation [online]. 07.2015 [Accessed: 26.01.2016]. URL: http://www.fachinfo.de.

3. Dana-Faber Cancer Institute. Ibrutinib (PCI-32765) in Waldenstrom´s Macroglobulinemia: full text view [online]. In: ClinicalTrials.gov. 11.11.2015 [Accessed: 06.01.2016]. URL: https://clinicaltrials.gov/ct2/show/NCT01614821.

4. Pharmacyclics. Waldenstrom's macroglobulinaemia: patient chart study; report [Präsentationsfolien] [unpublished]. 2015.

5. Pharmacyclics. Kaplan-Meier curves for OS [SAS output] [unpublished]. 2015.

6. Pharmacyclics. Ibrutinib with rituximab in adults with Waldenström's Macroglobulinemia: full text view [online]. In: ClinicalTrials.gov. 27.10.2015 [Accessed: 06.01.2016]. URL: https://clinicaltrials.gov/ct2/show/NCT02165397.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-04-ibrutinib-benefit-assessment-according-to-35a-social-code-book-v.7200.html.