IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ibrutinib (chronic lymphocytic leukaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ibrutinib (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 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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[2] 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
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BSC	best supportive care
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FCR	combination therapy of fludarabine with cyclophosphamide and rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IGHV	immunoglobulin heavy-chain variable
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small lymphocytic lymphoma
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

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 24 June 2016.

Research question

The aim of this report was to assess the added benefit of ibrutinib in comparison with the appropriate comparator therapy (ACT) specified by the G-BA for adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Table 2: Research questions of the benefit assessment of ibrutinib

Research question	Subindication[a]	ACT[b]
Patients with previously untreated CLL for whom chemo-immunotherapy is an option		
1a	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR
1b	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Chemo-immunotherapy specified by the physician, under consideration of the approval status
Patients with previously untreated CLL for whom chemo-immunotherapy is not an option		
2	Adult patients with previously untreated CLL for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation	BSC[c]

a: It is assumed for the present therapeutic indication that stem cell transplantation is not indicated at the time point of treatment.
b: Presentation of the respective ACT specified by the G-BA.
c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee

The company followed the ACTs specified by the G-BA for the respective research questions.

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

Results

Research question 1a: adult patients with previously untreated CLL for whom combination therapy of fludarabine with cyclophosphamide and rituximab (FCR) is an option

In its dossier, the company presented no data for the assessment of the added benefit of ibrutinib in adult patients with previously untreated CLL for whom FCR treatment is an option.

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

Research question 1b: adult patients with previously untreated CLL for whom treatment with FCR is not an option

For research question 1b, the company presented 3 indirect comparisons between ibrutinib and a chemo-immunotherapy, i.e. the combination therapies obinutuzumab + chlorambucil, rituximab + chlorambucil and ofatumumab + chlorambucil. The indirect comparisons were conducted using the common comparator chlorambucil and the same study on ibrutinib (RESONATE-2) in each case. The CLL11 study was used for each of the indirect comparisons with obinutuzumab + chlorambucil and rituximab + chlorambucil. The COMPLEMENT 1 study was used for the indirect comparison with ofatumumab + chlorambucil.

All 3 indirect comparisons presented by the company were unsuitable for the assessment of the added benefit of ibrutinib versus the ACT specified by the G-BA for several reasons. The reasons for this are as follows:

- Indirect comparisons of the studies RESONATE-2 and CLL11: The 2 studies RESONATE-2 and CLL11 showed low similarity regarding the dosage of the common comparator. Differences in the study design of the 2 studies led to an underdosing of the common comparator chlorambucil in the CLL11 study in comparison with the RESONATE-2 study. Furthermore, the chlorambucil dosing regimen used in the monotherapy and in the combination therapies of the CLL11 study did not comply with the requirements of the Summary of Product Characteristics (SPC). In addition, the study populations differed regarding age structure, mutation status and comorbidities of the patients. These are factors that may influence prognosis, treatment and course of a CLL disease. Finally, it can be assumed for both studies that they also included patients who did not concur with the target population relevant for this research question. The consideration of the results of the indirect comparison and of the individual studies CLL11 and RESONATE-2 supports the conclusion that the 2 studies were not sufficiently similar. In addition, the results were not robust for the outcome “overall survival”; the company’s analysis on side effects was incomplete.
- Indirect comparison of the studies RESONATE-2 and COMPLEMENT 1: The 2 studies RESONATE-2 and COMPLEMENT 1 showed low similarity and differed regarding

critical, potentially effect-modifying patient characteristics as well as the dosage of the common comparator chlorambucil. As a result of the different dosing regimens of the studies, the patients in the COMPLEMENT 1 study were receiving a high chlorambucil dose from the start of treatment in comparison with the RESONATE-2 study. In addition, the dosing regimen of chlorambucil used in the COMPLEMENT 1 study deviated from the dosage recommended in the SPC. Furthermore, it can be assumed for both studies that they also included patients who did not concur with the target population relevant for this research question.

- It can also not be assumed for all 3 indirect comparisons that they fulfilled the G-BA criterion "choice of the chemo-immunotherapy as specified by the physician". The RESONATE-2 study compared ibrutinib with chlorambucil, from which it can be inferred that chemo-immunotherapy was no treatment as specified by the physician for these patients. Since all indirect comparisons were conducted with the same ibrutinib study, but different chemo-immunotherapies were used for the comparison, it can also not be inferred for any of the 3 indirect comparisons that the chemo-immunotherapy for the patients was chosen individually as specified by the physician. Finally, the randomized allocation to 2 different chemo-immunotherapies in the CLL11 study also contradicts this G-BA criterion.

Overall, there was no hint of an added benefit of ibrutinib in comparison with the ACT for research question 1b. An added benefit is therefore not proven.

Research question 2: adult patients with previously untreated CLL for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation

The company presented one study of direct comparison for research question 2. This was the randomized controlled trial (RCT) RESONATE-2. The study presented by the company was unsuitable for the assessment of the added benefit of ibrutinib versus the ACT in the present research question.

The RESONATE-2 study included patients who were not eligible for FCR treatment. However, it cannot be derived from this that these patients would not have been eligible for an alternative chemo-immunotherapy. Hence it can be assumed that the RESONATE-2 study included patients who would have been eligible for an alternative chemo-immunotherapy and therefore did not concur with the relevant target population. Furthermore, all patients in the comparator arm received chlorambucil. The ACT specified by the G-BA (BSC) in the sense of a best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life was therefore not implemented.

Overall, there was no hint of an added benefit of ibrutinib in comparison with the ACT for research question 2. An added benefit is therefore not proven.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug ibrutinib compared with the ACT is assessed as follows:

Table 3: Ibrutinib – extent and probability of added benefit

Research question	Subindication[a]	ACT[b]	Extent and probability of added benefit
Patients with previously untreated CLL for whom chemo-immunotherapy is an option			
1a	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR	Added benefit not proven
1b	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Chemo-immunotherapy specified by the physician, under consideration of the approval status	Added benefit not proven
Patients with previously untreated CLL for whom chemo-immunotherapy is not an option			
2	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation	BSC[c]	Added benefit not proven

a: It is assumed for the present therapeutic indication that stem cell transplantation is not indicated at the time point of treatment.
b: Presentation of the respective ACT specified by the G-BA.
c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report was to assess the added benefit of ibrutinib in comparison with the ACT specified by the G-BA for adult patients with previously untreated CLL.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of ibrutinib

Research question	Subindication[a]	ACT[b]
Patients with previously untreated CLL for whom chemo-immunotherapy is an option		
1a	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR
1b	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Chemo-immunotherapy specified by the physician, under consideration of the approval status
Patients with previously untreated CLL for whom chemo-immunotherapy is not an option		
2	Adult patients with previously untreated CLL for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation	BSC[c]

a: It is assumed for the present therapeutic indication that stem cell transplantation is not indicated at the time point of treatment.
b: Presentation of the respective ACT specified by the G-BA.
c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee

The company followed the ACTs specified by the G-BA for the respective research questions. It should be noted that the patient populations 1a, 1b and 2 presented in the present benefit assessment were designated populations 1, 2 and 3 in the company's dossier.

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 2 of the 3 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**[a]	**Data presented by the company**
1a	Adult patients with previously untreated CLL for whom treatment with FCR is an option	No data
1b	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	▪ Indirect comparisons based on the studies RESONATE-2 and CLL11 ▫ ibrutinib vs. obinutuzumab + chlorambucil ▫ ibrutinib vs. rituximab + chlorambucil ▪ Indirect comparison based on the studies RESONATE-2 and COMPLEMENT 1 ▫ ibrutinib vs. ofatumumab + chlorambucil
2	Adult patients with previously untreated CLL for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation	Study of direct comparison (RESONATE-2) ibrutinib vs. chlorambucil

a: It is assumed for the present therapeutic indication that stem cell transplantation is not indicated at the time point of treatment.

CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab

2.3 Research question 1a: adult patients with previously untreated CLL for whom treatment with FCR is an option

2.3.1 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: 6 May 2016)
- bibliographical literature search on ibrutinib (last search on 9 May 2016)
- search in trial registries for studies on ibrutinib (last search on 2 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 7 July 2016)

Concurring with the company, the check of the completeness of the study pool produced no relevant RCTs on the direct comparison of ibrutinib versus the ACT or on an indirect comparison based on RCTs.

2.3.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of ibrutinib in adult patients with previously untreated CLL for whom FCR treatment is an option. This resulted in no hint of an added benefit of ibrutinib in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

The company presented no data for the assessment of the added benefit of ibrutinib in adult patients with previously untreated CLL for whom FCR treatment is an option. Hence an added benefit of ibrutinib is not proven for these patients.

2.3.4 List of included studies

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

2.4 Research question 1b: adult patients with previously untreated CLL for whom treatment with FCR is not an option

2.4.1 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 lists on ibrutinib (status: 6 May 2016 and 9 May 2016)
- bibliographical literature search on ibrutinib (last search on 9 May 2016)
- search in trial registries for studies on ibrutinib (last search on 2 May 2016)
- bibliographical literature search on the ACT (last search on 9 May 2016)
- search in trial registries for studies on the ACT (last search on 3 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 7 July 2016)
- search in trial registries for studies on the ACT (last search on 7 July 2016)

Concurring with the company, no relevant RCT on the direct comparison of ibrutinib versus the ACT was identified from the check of the completeness of the study pool.

The company identified several studies for an indirect comparison based on RCTs. For the indirect comparisons presented by the company (see Sections 2.4.1.1 and 2.4.1.2), no additional relevant studies were identified from the check of the completeness of the study pool.

For research question 1b, the company presented 3 indirect comparisons between ibrutinib and a chemo-immunotherapy, i.e. the chemo-immunotherapies obinutuzumab + chlorambucil, rituximab + chlorambucil and ofatumumab + chlorambucil. The indirect comparisons were conducted using the common comparator chlorambucil and the same study on ibrutinib (RESONATE-2) in each case. The CLL11 study, which compared both chemo-immunotherapies with chlorambucil in a 3-arm design, was used for the indirect comparisons with obinutuzumab + chlorambucil and rituximab + chlorambucil. The COMPLEMENT 1 study was used for the indirect comparison with ofatumumab + chlorambucil. The following figures (Figure 1 and Figure 2) show an overview of the indirect comparisons presented by the company.

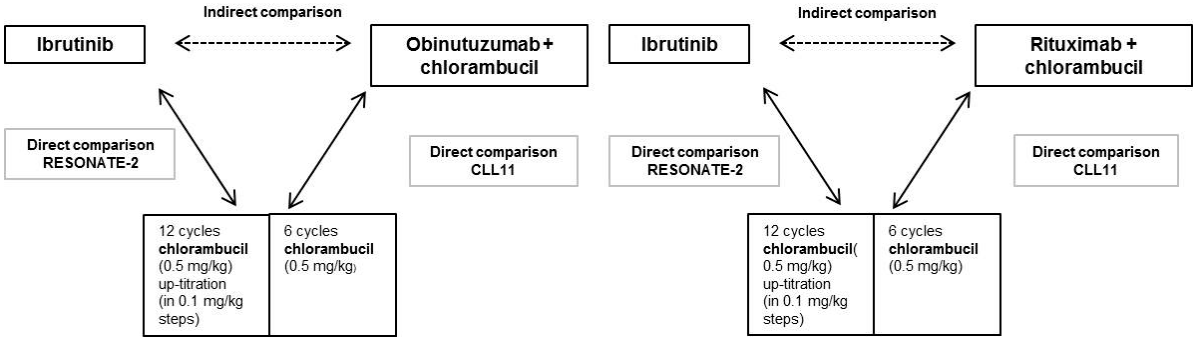

Figure 1: Study pool of the company for the indirect comparison between ibrutinib versus obinutuzumab + chlorambucil and versus rituximab + chlorambucil using the common comparator chlorambucil

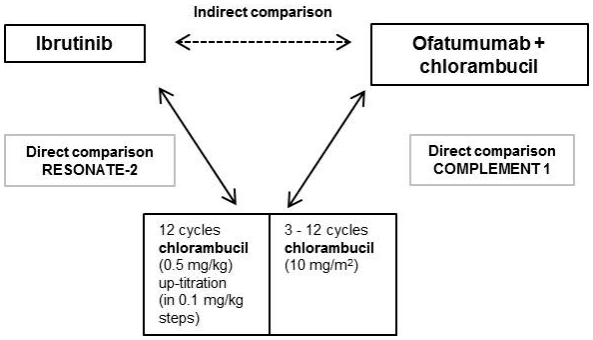

Figure 2: Study pool of the company for the indirect comparison between ibrutinib versus ofatumumab + chlorambucil using the common comparator chlorambucil

All 3 indirect comparisons presented by the company were unsuitable for the assessment of the added benefit of ibrutinib versus the ACT specified by the G-BA for several reasons. The reasons for this are as follows:

- Indirect comparisons of the studies RESONATE-2 and CLL11: The 2 studies RESONATE-2 and CLL11 showed low similarity regarding the dosage of the common comparator. Differences in the study design of the 2 studies led to an underdosing of the common comparator chlorambucil in the CLL11 study in comparison with the RESONATE-2 study. Furthermore, the chlorambucil dosing regimen used in the monotherapy and in the combination therapies of the CLL11 study did not comply with the requirements of the SPC. In addition, the study populations differed regarding age structure, mutation status and comorbidities of the patients. These are factors that may influence prognosis, treatment and course of a CLL disease. Finally, it can be assumed for both studies that they also included patients who did not concur with the target population relevant for this research question. The consideration of the results of the indirect comparison and of the individual studies CLL11 and RESONATE-2 supports the conclusion that the 2 studies were not sufficiently similar. In addition, the results were not

robust for the outcome “overall survival”; the company’s analysis on side effects was incomplete.

- Indirect comparison of the studies RESONATE-2 and COMPLEMENT 1: The 2 studies RESONATE-2 and COMPLEMENT 1 showed low similarity and differed regarding critical, potentially effect-modifying patient characteristics as well as the dosage of the common comparator chlorambucil. As a result of the different dosing regimens of the studies, the patients in the COMPLEMENT 1 study were receiving a high chlorambucil dose from the start of treatment in comparison with the RESONATE-2 study. In addition, the dosing regimen of chlorambucil used in the COMPLEMENT -1 study deviated from the dosage recommended in the SPC. Furthermore, it can be assumed for both studies that they also included patients who did not concur with the target population relevant for this research question.
- It can also not be assumed for all 3 indirect comparisons that they fulfilled the G-BA criterion “choice of the chemo-immunotherapy as specified by the physician”. The RESONATE-2 study compared ibrutinib with chlorambucil, from which it can be inferred that chemo-immunotherapy was no treatment as specified by the physician for these patients. Since all indirect comparisons were conducted with the same ibrutinib study, but different chemo-immunotherapies were used for the comparison, it can also not be inferred for any of the 3 indirect comparisons that the chemo-immunotherapy for the patients was chosen individually as specified by the physician. Finally, the randomized allocation to 2 different chemo-immunotherapies in the CLL11 study also contradicts this G-BA criterion.

The reasons mentioned are described in detail below.

2.4.1.1 Indirect comparisons of the studies RESONATE-2 and CLL11 using the common comparator chlorambucil

The company presented the following indirect comparisons using the common comparator chlorambucil:

- ibrutinib versus obinutuzumab + chlorambucil
- ibrutinib versus rituximab + chlorambucil

Study design of the RESONATE-2 study

The RESONATE-2 study was a randomized, active controlled, multicentre study on the comparison of ibrutinib with chlorambucil (common comparator of the indirect comparison). Neither study participants nor investigators were blinded in the open-label study. The study included adult (≥ 65 years) patients with previously untreated CLL or small lymphocytic lymphoma (SLL) requiring therapy.

269 patients were randomized in a ratio of 1:1, stratified by physical status (Eastern Cooperative Oncology Group Performance Status [ECOG PS 0–2]), Rai disease stage 3 or 4, and geographical region.

Treatment with ibrutinib was administered until disease progression or occurrence of unacceptable side effects. Treatment with chlorambucil was administered on days 1 and 15 of a 28-day cycle for a maximum of 12 cycles if no disease progression or unacceptable side effects occurred.

The RESONATE-2 study consisted of 2 parts. Randomization, treatment, and observation until disease progression was conducted in study PCYC-1115-CA. On occurrence of disease progression or termination of the PCYC-1115-CA study, patients could enter the extension study PCYC-1116-CA. Only a small proportion of patients in the PCYC-1115-CA study did not participate in the PCYC-1116-CA study. Further information on the RESONATE-2 study can be found in Appendix A (Table 10 and Table 11) of the full dossier assessment.

Study design of the CLL11 study

The CLL11 study was a randomized, active controlled, multicentre, 3-arm study on the comparison of the chemo-immunotherapies obinutuzumab + chlorambucil and rituximab + chlorambucil with chlorambucil monotherapy (common comparator of the indirect comparison). The study included adult (≥ 18 years) patients with previously untreated CLL requiring therapy.

The patients were randomly allocated to the study arms in 2 steps. In the first step, random allocation to the treatment arms was stratified according to region and Binet disease stage in a ratio of 2:2:1 (obinutuzumab + chlorambucil:rituximab + chlorambucil:chlorambucil). After 175 events of the primary outcome "progression-free survival (PFS)" and after observation of 250 participants for at least 1 year, further randomization only for the 2 treatment arms (obinutuzumab + chlorambucil:rituximab + chlorambucil) in a ratio of 1:1 took place in the second step.

For the combination therapies and the chlorambucil monotherapy, treatment was administered over a maximum of 6 cycles of 28 days each. Treatment with chlorambucil in all treatment arms was administered on days 1 and 15 of each cycle. Treatment with obinutuzumab was administered on days 1, 8 and 15 of the first cycle and on day 1 for the following cycles. Treatment of rituximab was administered on the first day of each cycle.

In case of disease progression, the patients in the chlorambucil monotherapy arm could switch to the obinutuzumab + chlorambucil arm. Of the 118 participants in the chlorambucil arm of the CLL11 study, 30 (25%) patients received subsequent therapy with obinutuzumab + chlorambucil [3].

It is unclear whether the combination therapy of chlorambucil with rituximab or obinutuzumab is approved for the present therapeutic indication. The respective SPCs do not describe the dosing regimens of the combination therapies used in the CLL11 study [4,5]. On request, the responsible regulatory authorities (Federal Institute for Drugs and Medical Devices [BfArM] and Paul Ehrlich Institute) issued contradictory statements in a joint comment [6].

A detailed description of the CLL11 study can be found in Appendix A (Table 10 and Table 11) of the full dossier assessment.

Inclusion of patients for whom FCR treatment is unsuitable (RESONATE-2 and CLL11)

The RESONATE-2 study was to include patients for whom FCR treatment is not an option. To ensure this in the study, the RESONATE-2 required at least one of the following comorbidities for patients between 65 and 70 years of age: reduced renal function (creatinine clearance < 70 mL/min), reduced haemoglobin levels (< 10 g/dL) and platelet count (< 100 000 per µL), autoimmune cytopenia or ECOG PS of 1 or 2. Patients over 70 years of age (corresponding to about 70% of the total population) were included in the study also without proven comorbidities.

Hence for the majority of the patients in the RESONATE-2 study, eligibility for FCR treatment was only determined on the basis of age. According to current guidelines, this alone is no sufficient criterion for the choice of treatment [7,8].

The CLL11 study was not explicitly targeted to include patients for whom FCR treatment is not an option. Patients with a Cumulative Illness Rating Scale (CIRS) score of > 6 and/or reduced renal function (calculated creatinine clearance < 70 mL/min) were included. Patients with cytopenia were also included in the study if this was not caused by the underlying condition.

In summary, it can be assumed for both studies that they also included patients who did not concur with the target population because they were eligible for FCR treatment. In addition, different criteria for the decision against FCR treatment were applied, which raises doubts about the similarity of the study populations (see below).

Check of the similarity of the studies RESONATE-2 and CLL11

The studies RESONATE-2 and CLL11 were not sufficiently similar both regarding the included patient populations and regarding the common comparator used. This is explained in detail below.

Dosage of the common comparator chlorambucil

The 2 studies RESONATE-2 and CLL11 differed both in the duration of chlorambucil treatment and in the dosing regimen of chlorambucil. This resulted in a major difference in the total dose of chlorambucil.

The patients in the RESONATE-2 study received chlorambucil at a dose of 0.5 mg/kg body weight on days 1 and 7 of a 28-day cycle. Treatment was administered in a total of 12 cycles. Within the 12 cycles, stepwise up-titration to a total of 0.8 mg/kg body weight was possible if the treatment was well tolerated. This resulted in a cumulative dose of 6 mg/kg body weight up to about 9 mg/kg body weight (in case of maximum up-titration). Apart from an increased starting dose (the SPC recommends 0.4 mg/kg), the dosing regimen used in the RESONATE-2 study complied with the information provided in the SPC on chlorambucil [9].

The patients in the CLL11 study, in contrast, received chlorambucil at a constant dose of 0.5 mg/kg body weight. Up-titration, as recommended in the SPC, was not mandated. Furthermore, treatment was limited to 6 cycles (see Table 11 in Appendix A of the full dossier assessment). In the CLL11 study, this resulted in a cumulative dose of 381 mg (over 6 cycles) and hence in a dose that was about 40% to 60% lower than in the RESONATE-2 study.

The patients in the CLL11 studies were therefore underdosed in comparison with the patients in the RESONATE-2 study regarding their chlorambucil treatment. The company noted that the different chlorambucil dosing regimens might cause bias to the disadvantage of ibrutinib in the results of the indirect comparison. This assessment was not followed because the direction of the bias differed for the different patient-relevant outcomes. Whereas the risk of bias for the outcomes on benefit (e.g. all-cause mortality) was to the disadvantage of ibrutinib, the risk of bias for the outcomes on harm were in favour of ibrutinib (see also the explanations on the interpretability of the indirect comparison summarized below).

Patient characteristics

Both studies RESONATE-2 and CLL11 investigated adult patients with previously untreated CLL. The CLL11 study included patients paged 18 years and older, whereas the RESONATE-2 study included patients aged 65 years and older. This resulted in differences in the age structure of both studies. About 20% of the patients in the CLL11 study were younger than 65 years (Table 12 in Appendix A of the full dossier assessment). In CLL patients, higher age is associated with higher severity grades of the disease [10].

Both studies recorded accompanying diseases with the CIRS score. The patients in the CLL11 study had notably higher values. This suggests that the patients in the CLL11 study had more and/or more severe comorbidities than the patients in the RESONATE-2 study (see Table 13 in Appendix A of the full dossier assessment).

Regarding prognostic genetic markers, the RESONATE-2 study showed a more favourable constellation than the CLL11 study. The proportion of patients with unmutated

immunoglobulin heavy-chain variable (IGHV) was higher in the CLL11 study than in the RESONATE-2 study (62% versus 44%). Furthermore, about 8% of the patients in the CLL11 study had 17p deletion, whereas patients with this deletion were excluded from the RESONATE-2 study (see Table 12 in Appendix A of the full dossier assessment). Both genetic modifications are associated with worse prognosis [11].

SLL was diagnosed in about 7% of the patients in the RESONATE-2 study. The CLL11 study provided no information regarding the histological diagnosis of the patients. It could be inferred from the inclusion and exclusion criteria that patients with SLL were not included in the CLL11 study. Although CLL and SLL are different manifestations of the same underlying disease, the histological difference (CLL versus SLL) resulted in an indication of an effect modification for the characteristic "overall survival" in the RESONATE-2 study. Patients with SLL did not benefit from ibrutinib treatment.

In summary, the patient populations in both studies differed regarding various patient characteristics (age, mutations, comorbidities), which may influence prognosis, course of disease and treatment effect [12-17]. Regarding the subgroup characteristics "age" (< 70 years versus ≥ 70 years), histological finding (CLL versus SLL), Rai disease stage (0 to II versus III to IV), the RESONATE-2 study showed at least indications of effect modifications for patient-relevant outcomes. No subgroup results on patient-relevant outcomes were available for the CLL11 study. The presence of effect modifications in the RESONATE-2 suggests that the differences in patient characteristics had a potential influence on the treatment effect.

Summarizing assessment of the interpretability of the results of the indirect comparison

The 2 studies RESONATE-2 and CLL11 differed regarding dosage and treatment duration of the common comparator chlorambucil. In addition, the studies differed in several patient characteristics that may influence prognosis, treatment and course of disease. In summary, the studies included in the indirect comparison were not sufficiently similar. Hereinafter, it is described on the basis of the results of the indirect comparison that, in addition, the effects of the indirect comparison were not so clear as to allow the derivation of an added benefit of ibrutinib despite lacking similarity of the studies.

The results of the indirect comparison are presented in Appendix C (Table 14) of the full dossier assessment.

The company presented data on patient-relevant outcomes in the indirect comparison only on 2 outcome categories (mortality and side effects). There were no results on patient-relevant outcomes of the categories "morbidity" and "health-related quality of life".

Overall survival

For the outcome "overall survival", the company conducted 6 indirect comparisons with different data cut-offs of both studies. Below, the observation period included in the analyses

is provided in brackets; only time periods and not average observation periods were available for the CLL11 study:

1) Ibrutinib (18 months) versus rituximab + chlorambucil (10 to 37 months)
2) Ibrutinib (28 months) versus rituximab + chlorambucil (10 to 37 months)
3) Ibrutinib (28 months) versus rituximab + chlorambucil (21 to 48 months)
4) Ibrutinib (18 months) versus obinutuzumab + chlorambucil (10 to 37 months)
5) Ibrutinib (28 months) versus obinutuzumab + chlorambucil (10 to 37 months)
6) Ibrutinib (28 months) versus obinutuzumab + chlorambucil (21 to 48 months)

A statistically significant result was only shown for the first of these 6 indirect comparisons (ibrutinib versus rituximab + chlorambucil, first data cut-off; hazard ratio [HR] [95% confidence interval (CI)]: 0.25 [0.06; 0.97]); see also Appendix C (Table 14) of the full dossier assessment.

The company named the treatment switching in both studies as an explaining factor for the presence of a statistically significant result in only one of the comparisons. It argued that potential bias to the disadvantage of ibrutinib resulted from the treatment switching from the control to the intervention arm of the CLL11 study and from the missing information on whether the data of the CLL11 study were adjusted regarding the treatment switching.

This rationale was not followed. In the present case, the different results are not necessarily explained with treatment switching within the studies.

For the assessment of a treatment strategy with the intervention to be assessed versus control treatment, treatment switching in both treatment groups to approved and adequate alternative treatments is to be considered part of the respective treatment strategy and does not per se result in an increased risk of bias.

This was the situation in the RESONATE-2 study (first-line treatment with ibrutinib versus chlorambucil). On disease progression, patients in both treatment arms could switch to the respective other treatment arm or to a different antineoplastic treatment at the investigator's discretion. Both ibrutinib and chlorambucil are approved second-line treatments for CLL. Consequently, it is assumed that the results of the later data cut-off of this study do not per se have a greater risk of bias in comparison with the earlier data cut-off. On the contrary, the second data cut-off contains more information than the first data cut-off due to the longer observation period and is therefore primarily relevant.

In the 3-arm CLL11 study (rituximab + chlorambucil, obinutuzumab + chlorambucil, chlorambucil), however, targeted treatment switching can be assumed. According to the study protocol of this study, patients with disease progression in the chlorambucil arm were to switch primarily to the obinutuzumab + chlorambucil arm. At the data cut-off 10 to

37 months, 25% had already undergone this treatment switching. It cannot be excluded that such restrictive treatment switching prevents or delays an alternative, more effective second-line treatment, which would result in an overestimation of the treatment effect. Overall, extent and direction of this potential bias cannot be determined neither in qualitative nor in quantitative terms.

This assessment was supported by the consideration of the individual analyses on overall survival (Table 14 in Appendix C of the full dossier assessment). For the CLL11 study, only minor differences were shown between the individual analyses of both data cut-offs despite targeted treatment switching. In the RESONATE-2 study, in contrast, no bias from targeted treatment switching can be expected. However, notable differences between the individual analyses of both data cut-offs were shown here (Table 14 in Appendix C of the full dossier assessment). Only the first data cut-off showed a statistically significant difference in favour of ibrutinib. The corresponding Kaplan-Meier curves showed no marked difference (see Figure 3 and Figure 4 in Appendix B of the full dossier assessment). Only the censorings occurred notably later in the second data cut-off than in the first data cut-off due to the longer observation periods, which produced additional information for the second data cut-off.

In summary, the results on overall survival at the different data cut-offs were not consistent. The most informative analyses showed no statistically significant difference between the treatment groups. Due to the differences in the patient populations and the study design, the results overall have a high risk of bias. Extent and direction of the potential bias in the indirect comparison, which contains additional uncertainty, cannot be determined in qualitative or quantitative terms. Overall, the results on overall survival were not robust and could therefore not be conclusively interpreted with certainty.

Adverse Events

The company's analyses on AEs were incomplete and selective. Only results for the first data cut-offs of both studies were available. The company presented no data for the later data cut-offs. In addition, the company did not analyse serious adverse events (SAEs) without providing further justification.

The low chlorambucil dosage of the patients in the CLL11 study already mentioned possibly resulted in a marked underestimation of the side effects of ibrutinib in the indirect comparison. The comparison of the rates of specific adverse events (AEs) in the chlorambucil arm of both studies supported this assumption (see Table 16 in Appendix D of the full dossier assessment). For example, the proportion of patients with the AE "anaemia" was twice as high in the RESONATE-2 study (21%) as in the CLL11 study (10%). Hence for the intervention therapies of the CLL11 study, rituximab and obinutuzumab, there were higher AE rates in relation to chlorambucil than for ibrutinib in relation to chlorambucil in the RESONATE-2 study. In the indirect comparison, this resulted in an underestimation of the side effects of ibrutinib versus the combination therapies rituximab + chlorambucil and obinutuzumab + chlorambucil.

Regarding the overall rate of SAEs, the situation was reversed: The proportion of patients with SAEs in the chlorambucil arm of the CLL11 study was notably higher than in the chlorambucil arm of the RESONATE-2 study (38% versus 25%, see Table 15 in Appendix C of the full dossier assessment). This was potentially caused by more common and/or more severe comorbidities of the patients in the CLL11 study (measured with the CIRS score at the start of the study). It was unclear whether different observation periods of the 2 chlorambucil arms or different methods of recording also contributed to this clear difference because no information was available on these aspects. The fact that the SAE rates under chlorambucil were notably higher in the CLL11 study than in the RESONATE-2 study, although chlorambucil was notably lower in the CLL11 study, is further evidence for the low similarity of the 2 studies and therefore for the missing interpretability of the indirect comparison.

2.4.1.2 Indirect comparison based on the studies RESONATE-2 and COMPLEMENT 1 using the common comparator chlorambucil

The third indirect comparison with the common comparator chlorambucil presented by the company was:

- ibrutinib vs. ofatumumab + chlorambucil

The company used the RESONATE-2 study (ibrutinib versus chlorambucil) and the COMPLEMENT 1 study (ofatumumab + chlorambucil versus chlorambucil) for this indirect comparison. A description of the RESONATE-2 study can be found in Section 2.4.1.1 and in Table 10 and Table 11 in Appendix A of the full dossier assessment.

Study design of the COMPLEMENT 1 study

The COMPLEMENT 1 study was a randomized, active controlled, open-label, multicentre study on the comparison of the combination therapy ofatumumab + chlorambucil (ACT) versus chlorambucil monotherapy (common comparator). The study included adult (≥ 18 years) patients with previously untreated CLL requiring therapy. A protocol extension limited study inclusion to patients who were not eligible for fludarabine-based treatment (see below for more details).

The 447 study participants were randomly allocated in a ratio of 1:1 to the 2 treatment arms ofatumumab + chlorambucil and chlorambucil, stratified according to age, Binet disease stage and physical status (ECOG PS).

Treatment was administered over at least 3 to at most 12 cycles. Ofatumumab was given on days 1 and 8 of the first cycle and on day 1 of the subsequent cycles. Treatment with chlorambucil was administered continuously on days 1 and 7 of each cycle. Further information can be found in Appendix A (Table 10 and Table 11) of the full dossier assessment.

Treatment switching from the chlorambucil arm to the ofatumumab + chlorambucil arm was not mandated. On disease progression, the patients were treated with another neoplastic second-line treatment at the investigator's discretion.

Inclusion of patients for whom FCR treatment is unsuitable (RESONATE-2 and COMPLEMENT 1)

In the COMPLEMENT 1 study, a protocol extension limited study inclusion to patients for whom fludarabine-based treatment is not an option. The criteria for this were that the patients were at least 65 years of age, had more than 2 comorbidities, or had reduced renal function (calculated creatinine clearance < 70 mL/min). The protocol was extended with these criteria 8 months after the start of the study. Up to this time point, 35% of the study population had already been enrolled. These patients were assessed retrospectively as to whether fludarabine-based treatment would have been an option for them. Retrospective assessment was not possible for 8% of the patients enrolled [18]. Furthermore, 24% of the patients were considered unsuitable for fludarabine-based treatment irrespective of comorbidities or age. For instance, 4% of the patients were not eligible for treatment because of financial difficulties, and another 9% because fludarabine was not available. Hence it was uncertain for a noteworthy part of the study population that the patients were unsuitable for fludarabine-based treatment.

As described in Section 2.4.1.1, for the majority of the patients in the RESONATE-2 study, suitability for FCR treatment was determined solely based on age so that probably also patients were included who were suitable for FCR treatment.

In summary, the studies had different criteria for the decision for or against fludarabine-based treatment. In addition, it can be assumed for both studies that patients for whom fludarabine-based treatment was an option were also included. Hence a noteworthy proportion of both patient populations did not concur with the target population.

Check of the similarity of the studies RESONATE-2 and COMPLEMENT 1

The studies RESONATE-2 and COMPLEMENT 1 were not sufficiently similar both regarding the included patient populations and regarding the common comparator used. This is explained in detail below.

Patient characteristics

Both studies included adult patients with previously untreated CLL. The COMPLEMENT 1 study included patients aged 18 years or older. The RESONATE-2 study, in contrast, included patients aged 65 years or older. This resulted in differences in the age structure between the 2 studies. 31% of the patients in the COMPLEMENT 1 study were younger than 65 years.

In CLL patients, higher age is associated with higher severity grades of the disease [10]. Corresponding to the patient population with a higher average age in the RESONATE-2

study, more patients with higher disease stages (Binet B and C or Rai IV) and restricted renal function were included in this study than in the COMPLEMENT 1 study.

Regarding genetic prognostic markers, the RESONATE-2 study showed a more favourable constellation than the COMPLEMENT 1 study. 6% of the patients in the COMPLEMENT 1 study had 17p deletion, whereas patients with this deletion were excluded from the RESONATE-2 study. In addition, notably more patients in the COMPLEMENT 1 study showed unmutated IGHV. Both genetic modifications are associated with worse prognosis [11]. Only the proportion of patients with 11q deletion was marginally lower in the COMPLEMENT 1 study than in the RESONATE-2 study (see Table 12 in Appendix A of the full dossier assessment). However, the prognostic value of 11q deletion is questionable in patients older than 55 years [19].

As mentioned above, about 7% of the patients in the RESONATE-2 study were diagnosed with SLL. Patients with this diagnosis were excluded from the COMPLEMENT 1 study.

The patients in the COMPLEMENT 1 study had notably higher CIRS scores. The proportion of patients with a CIRS core > 6 was more than twice as high as in the RESONATE-2 study (about 32% versus 79%; see Table 13 in Appendix A of the full dossier assessment). This suggests that the patients in the COMPLEMENT 1 study had comparably more and/or more severe comorbidities. In summary, the patient populations in both studies differed regarding various patient characteristics (age, mutations, severity grade, comorbidities), which may influence prognosis, course of disease and treatment effect [12-17]. It cannot be assessed in how far these factors in studies influence the treatment effect in the respective studies, also because relevant subgroup analyses on the COMPLEMENT 1 study were not available.

Dosage of the common comparator chlorambucil

The chlorambucil dosing regimen differed notably between the 2 studies RESONATE-2 and COMPLEMENT 1. In addition, chlorambucil was not used in compliance with the recommendations of the SPC in the COMPLEMENT 1 study [9].

Section 2.4.1.1 contains information on the chlorambucil dosing regimen in the RESONATE-2 study.

The patients in the COMPLEMENT 1 study received 10 mg/m^2 body surface area on days 1 to 7 of a 28-day cycle for a minimum of 3 to a maximum of 12 cycles. Hence, in comparison with the RESONATE-2 study, the patients in the COMPLEMENT 1 study were receiving higher chlorambucil doses from the start. This dosing regimen is not mandated by the SPC [9]. For a patient with a height of 170 cm, a body weight of 70 kg and a body surface area of 1.8 m^2 (calculated with the Du Bois formula), this resulted in a constant dose of 129 mg in each cycle in the COMPLEMENT 1 study [20]. In the RESONATE-2 study, the dose was initially 70 mg and could be at most 112 mg (after up-titration).

In summary, the 2 studies RESONATE-2 and COMPLEMENT 1 showed low similarity regarding several patient characteristics. Moreover, the chlorambucil treatment in the COMPLEMENT 1 study did not comply with the recommendations in the SPC, and the dosing regimens between the 2 studies RESONATE-2 and COMPLEMENT 1 were not sufficiently similar. The indirect comparison of the studies COMPLEMENT 1 and RESONATE-2 was therefore unsuitable for the present benefit assessment.

2.4.2 Results on added benefit (research question 1b)

In its dossier, the company presented no suitable data for the assessment of the added benefit of ibrutinib in adult patients with previously untreated CLL for whom FCR treatment is not an option. This resulted in no hint of an added benefit of ibrutinib in comparison with the ACT (chemo-immunotherapy specified by the physician, under consideration of the approval status). An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of ibrutinib in adult patients with previously untreated CLL for whom FCR treatment is not an option. Hence an added benefit of ibrutinib is not proven for these patients.

2.4.4 List of included studies

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

2.5 Research question 2: adult patients with previously untreated CLL for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation

2.5.1 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: 6 May 2016)
- bibliographical literature search on ibrutinib (last search on 9 May 2016)
- search in trial registries for studies on ibrutinib (last search on 2 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 7 July 2016)

Deviating from the company, no relevant RCT on the direct comparison of ibrutinib versus the ACT (BSC) was identified from the check of the completeness of the study pool.

2.5.2 Results on added benefit

In its dossier, the company presented no suitable data for research question 2 for the assessment of the added benefit of ibrutinib in adult patients with previously untreated CLL for whom FCR treatment is not an option and who have no 17p deletion or TP53 mutation. The reasons are presented in Section 2.7.2.2 of the full dossier assessment. This resulted in no hint of an added benefit of ibrutinib in comparison with the ACT (BSC). An added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of ibrutinib in adult patients with previously untreated CLL for whom chemo-immunotherapy is not an option. Hence an added benefit of ibrutinib is not proven for these patients.

2.5.4 List of included studies

Not applicable as the company presented no suitable data for this research question.

2.6 Extent and probability of added benefit

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

Table 6: Ibrutinib – extent and probability of added benefit

Research question	Subindication[a]	ACT[b]	Extent and probability of added benefit
Patients with previously untreated CLL for whom chemo-immunotherapy is an option			
1a	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR	Added benefit not proven
1b	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Chemo-immunotherapy specified by the physician, under consideration of the approval status	Added benefit not proven
Patients with previously untreated CLL for whom chemo-immunotherapy is not an option			
2	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation	BSC[c]	Added benefit not proven

a: It is assumed for the present therapeutic indication that stem cell transplantation is not indicated at the time point of treatment.
b: Presentation of the respective ACT specified by the G-BA.
c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee

An added benefit of ibrutinib is not proven for any of the research questions. For research questions 1a and 2, the company presented no or no suitable data in its dossier. The data presented for research question 1b allowed no valid indirect comparison and therefore no conclusive interpretation of the results.

This deviates from the company's approach, which derived a hint of considerable added benefit for adult patients with previously untreated CLL for whom FCR treatment is not an option (research question 1b). The company derived an indication of considerable added benefit for adult patients with previously untreated CLL for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation (research question 2).

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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