



IQWiG Reports – Commission No. A19-77

**Ibrutinib  
(chronic lymphocytic  
leukaemia) –**

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

**Extract**

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<sup>1</sup> Translation of Sections 2.1 to 2.6 of the dossier assessment *Ibrutinib (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 2.0; Status: 14 January 2020). 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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<sup>2</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

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### List of abbreviations

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
AEs	adverse events
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
del17p	17p deletion
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ-5D	European Quality of Life – 5 Dimensions
FCR	fludarabine in combination with cyclophosphamide and rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IGHV	Immunoglobulin Heavy Chain Variable Region
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	independent review committee
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
PFS	progression-free survival
PRAC	Pharmacovigilance Risk Assessment Committee
RAI	radioactive iodine
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small-cell lymphocytic lymphoma
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPC	Summary of product characteristics
TP53	tumour protein 53
VAS	visual analogue scale

## 2 Benefit assessment

### 2.1 Executive summary of the benefit assessment

#### Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug 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 2 September 2019.

#### Research question

The aim of this report was to assess the added benefit of ibrutinib in combination with obinutuzumab (hereinafter referred to as ibrutinib + obinutuzumab) in comparison with the appropriate comparator therapy (ACT) in adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

The G-BA differentiated between 3 different treatment situations and specified a different ACT for each of them. This resulted in 3 research questions for the present benefit assessment. The research questions are presented in Table 2.

Table 2: Research questions of the benefit assessment of ibrutinib + obinutuzumab

Research question	Subindication <sup>a</sup>	ACT <sup>b</sup>
1	Adult patients with previously untreated CLL for whom treatment with fludarabine in combination with cyclophosphamide and rituximab (FCR) is an option	Fludarabine in combination with cyclophosphamide and rituximab
2	Adult patients with previously untreated CLL for whom FCR therapy is not an option	Bendamustine in combination with rituximab or ofatumumab <i>or</i> <b>chlorambucil in combination with rituximab or obinutuzumab</b> or ofatumumab
3	Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib
<p>a. For the present therapeutic indication, the company assumed that the patients were in need of treatment. Moreover, it was assumed that allogeneic stem cell transplantation was not indicated at the time point of treatment.</p> <p>b. 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 <b>bold</b>.</p> <p>17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein 53</p>		

In the present benefit assessment, the following terms were used for the populations of the different research questions:

- Research question 1: patients for whom treatment with fludarabine in combination with cyclophosphamide and rituximab (FCR therapy) is an option
- Research question 2: patients for whom FCR therapy is not an option
- Research question 3: patients with 17p deletion (del17p) and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason

For research questions 1 and 3, the company followed the ACT specified by the G-BA.

For research question 2, the company deviated from the ACT specified by the G-BA insofar as it excluded combination therapies with ofatumumab, because the approval of ofatumumab had been withdrawn. The company chose the combination therapy of chlorambucil + obinutuzumab as ACT from the remaining options. The approach of the company was adequate.

The assessment was made by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

### **Results for research question 1: Patients for whom FCR therapy is an option**

The company presented no data for the assessment of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT (FCR) in patients for whom FCR therapy is an option. This resulted in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

### **Results for research question 2: Patients for whom FCR therapy is not an option**

#### *Study pool and study characteristics*

The iLLUMINATE study was included in the present assessment

The iLLUMINATE study is an open-label, randomized, active-controlled multicentre study on the direct comparison of ibrutinib + obinutuzumab with chlorambucil + obinutuzumab.

The study iLLUMINATE included adults with untreated CLL/small-cell lymphocytic lymphoma (SLL) requiring treatment in accordance with the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria (2008), who had lymph node enlargement measurable by computer tomography (CT). Moreover, patients had to be either  $\geq 65$  years of age or – if younger – they had to have a certain degree of comorbidities (Cumulative Illness Rating Scale [CIRS]  $> 6$ ) or a kidney dysfunction or del17p or tumour protein 53 (TP53) mutation.

The iLLUMINATE study included patients irrespective of whether an FCR therapy was suitable for them or not. The company presented analyses for the relevant subpopulation of

those patients for whom FCR therapy was unsuitable. These were 73 adults in the ibrutinib + obinutuzumab arm and 72 adults in the chlorambucil + obinutuzumab arm.

Ibrutinib was administered once daily in oral doses of 420 mg in the intervention arm until progression of the disease or until the occurrence of unacceptable intolerances. In both study arms, obinutuzumab was administered in intravenous doses of 1000 mg for six 28-day cycles each. In the comparator arm, chlorambucil was administered over 6 cycles, whereby the dosage depended on the body weight. Treatment was performed under consideration of the Summary of Product Characteristics (SPC) on all 3 drugs both in the intervention arm and in the comparator arm of the iLLUMINATE study without relevant deviations from the SPCs.

Primary outcome of the iLLUMINATE study was progression-free survival (PFS). Outcomes on morbidity and adverse events (AEs) were recorded under patient-relevant secondary outcomes. Outcomes on health-related quality of life were not recorded in the study.

The study is ongoing. Analyses on 2 data cut-offs are available. The first data cut-off was prespecified and took place on 26 March 2018. The second data cut-off was performed on 26 February 2019 and was not prespecified. Within the framework of the Extension of indication variation assessment report – Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur’s preliminary assessment report of 18 February 2019, the European Medicines Agency (EMA) requested another data cut-off. Due to the proximity in time, it is assumed that the second data cut-off is the data cut-off subsequently requested by the EMA. The second data cut-off was used for the present benefit assessment due to the higher informational content.

### ***Risk of bias***

The risk of bias across outcomes was rated as low for the study.

The risk of bias was rated as low for the results of the outcome “overall survival”; for all other outcomes it was rated as high.

### ***Mortality***

#### ***Overall survival***

In the present benefit assessment, the results of time from randomization to death for any reason were used for the outcome “overall survival”. The result showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

### ***Morbidity***

#### *Health status (European Quality of Life – 5 Dimensions [EQ-5D] visual analogue scale [VAS])*

The outcome “health status” was recorded using the EQ-5D VAS, operationalized as change at the date of analysis (progression or end of the study) in comparison with baseline. There was a statistically significant difference to the disadvantage of ibrutinib + obinutuzumab. However, the 95% CI of the standardized mean difference (Hedges’ g) was not fully outside the irrelevance range of  $-0.2$  to  $0.2$ . It can therefore not be inferred that the observed effect is relevant. This resulted in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

### ***Health-related quality of life***

Data on health-related quality of life were not recorded in the iLLUMINATE study.

### ***Side effects***

#### *Serious adverse events (SAEs)*

A statistically significant difference in favour of ibrutinib + obinutuzumab was shown for the outcome “SAEs”. Moreover, there was proof of an effect modification by the characteristic “sex”. For women, there was a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. For men, there was no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

#### *Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade $\geq 3$ )*

A statistically significant difference in favour of ibrutinib + obinutuzumab was shown for the outcome “severe AEs (CTCAE grade  $\geq 3$ )”. Moreover, there are effect modifications by the characteristics “sex” and “age” for this outcome. The result on the characteristic “sex” was used for the derivation of the added benefit. There was a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for women. For men, there was no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

#### *Discontinuation due to AEs*

In the iLLUMINATE study, an event was recorded as discontinuation due to AEs when the administration of  $\geq 1$  of the combination partners in the intervention arm (ibrutinib + obinutuzumab) or in the comparator arm (chlorambucil + obinutuzumab) was discontinued due to AEs. Treatment with the respective other combination partner was continued as planned.

There was no statistically significant difference between the treatment groups for the outcome “discontinuation due to AEs”. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

*Specific adverse events*

- infusion-related reaction and nausea

For each of the outcomes “infusion-related reaction” and “nausea”, there was a statistically significant difference in favour of ibrutinib + obinutuzumab. This resulted in a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for each of these outcomes.

- Severe bleeding events

For the outcome “severe bleeding events”, the hazard ratio (HR) cannot be estimated, since no events occurred in the comparator arm. However, only 1 event occurred in the intervention arm. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

- Cardiac disorders

A statistically significant difference to the disadvantage of ibrutinib + obinutuzumab was shown for the outcome “cardiac disorders”. This resulted in a hint of greater harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

- Infections and infestations

No statistically significant difference between the treatment groups was shown for the outcome “infections and infestations”. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

- Severe neutropenia (CTCAE grade  $\geq 3$ )

A statistically significant difference in favour of ibrutinib + obinutuzumab was shown for the outcome “severe neutropenia (CTCAE grade  $\geq 3$ )”. Moreover, there are effect modifications by the characteristics “sex” and “CIRS status” for this outcome. The result on the characteristic “sex” was used for the derivation of the added benefit. For women, there was a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. For men, there was no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven for men.

- Skin and subcutaneous tissue disorders

There was a statistically significant difference to the disadvantage of ibrutinib + obinutuzumab for the outcome “skin and subcutaneous tissue disorders”; however, for this outcome of the category non-serious/non-severe side effects, this difference was no more than marginal. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

### **Results for research question 3: patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason**

The company presented a comparison of individual arms from different studies for patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason. For ibrutinib + obinutuzumab, the company conducted a descriptive comparison of the results from its own study iLLUMINATE; for the ACT “ibrutinib”, it conducted a descriptive comparison of the results on the outcomes “overall survival”, “PFS” and “overall response” from the publications of Burger 2019, Woyach 2018 and Ahn 2018.

When comparing individual arms from different studies, the uncertainty of results is high and conclusions on the added benefit are usually only possible if very large effects are present. The differences in the results presented by the company were too small to show a dramatic effect and could thus be based on systematic bias alone.

Only analyses on the outcomes “overall survival”, “PFS” and “overall response” were available for the comparison of individual arms from different studies. Results for a comparison are not available for further patient-relevant outcomes on “symptoms”, “health-related quality of life” and “side effects”. Balancing of benefit and harm was therefore not possible on the basis of the comparison presented by the company.

The comparison of individual arms from different studies presented by the company was unsuitable to derive an added benefit of ibrutinib + obinutuzumab in comparison with the ACT “ibrutinib”. The company thus presented no suitable data for the assessment of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT “ibrutinib” for patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason. This resulted in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

### **Probability and extent of added benefit, patient groups with therapeutically important added benefit<sup>3</sup>**

Based on the results presented, probability and extent of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT are assessed as follows:

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<sup>3</sup> On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). 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, added benefit not proven, or less benefit). For further details see [1,2].

***Research question 1: patients for whom FCR therapy is an option***

The company presented no data for the assessment of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT in patients for whom FCR therapy is an option. An added benefit of ibrutinib + obinutuzumab is thus not proven for this research question.

***Research question 2: patients for whom FCR therapy is not an option***

Overall, there are several positive effects and one negative effect in the outcome categories on side effects, each with the probability “hint”, however, with different extents.

The positive effects in the outcome category “serious/severe side effects” are only shown for the subgroup of women. Therefore, balancing of positive and negative effects will be separated by sex hereinafter.

*Women*

For women, there is a hint of lesser harm each, for the outcome “SAEs” with the extent “considerable” and for the outcome “severe AEs (CTCAE grade  $\geq 3$ )” with the extent “major”. Further positive effects were shown in the outcome category “non-serious/non-severe side effects”, each with the extent: “considerable”.

The positive effects were offset by a negative effect in the form of a hint of greater harm with the extent “considerable” in the outcome category “non-serious/non-severe side effects”. Overall, the positive effects outweighed the negative effects in women. However, all positive and negative effects are exclusively shown in the outcome category “serious/severe side effects” or “non-serious/non-severe side effects”. Data for the assessment of the added benefit of ibrutinib are only available for 2 further outcomes (“overall survival” and “health status” [EQ-5D VAS]). Although the results for these 2 outcomes are not significant or relevant, they tend to be to the disadvantage of ibrutinib + obinutuzumab. Outcomes on patient-relevant symptoms or health-related quality of life were not recorded in iLLUMINATE study.

In summary, for the above-mentioned reasons, there is a hint of a minor added benefit of ibrutinib + obinutuzumab over chlorambucil + obinutuzumab for women with previously untreated CLL who are not eligible for FCR therapy.

*Men*

For men, there were neither positive nor negative effects in the outcome category: “serious/severe side effects”. In the outcome category “non-serious/non-severe side effects”, the effects corresponded to those described for women. The positive and negative effects in this category largely cancelled each other out. As with women, it is also considered for men that, apart from “side effects”, data are only available for 2 other outcomes, which tend to be to the disadvantage of ibrutinib + obinutuzumab.

Overall, an added benefit of ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab is not proven for men for whom FCR therapy is not an option.

***Research question 3: patients with dell17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason***

Since the company presented no suitable data for the assessment of the added benefit of ibrutinib + obinutuzumab in patients with dell17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason, an added benefit of ibrutinib + obinutuzumab is not proven for this population.

Table 3 presents a summary of the probability and extent of the added benefit of ibrutinib + obinutuzumab.

Table 3: Ibrutinib + obinutuzumab – Probability and extent of added benefit

Subindication <sup>a</sup>	ACT <sup>b</sup>	Probability and extent of added benefit
1: Adult patients with previously untreated CLL for whom treatment with fludarabine in combination with cyclophosphamide and rituximab (FCR) is an option	Fludarabine in combination with cyclophosphamide and rituximab	Added benefit not proven
2: Adult patients with previously untreated CLL for whom FCR therapy is not an option	Bendamustine in combination with rituximab or ofatumumab <i>or</i> <b>chlorambucil in combination with rituximab or obinutuzumab</b> or ofatumumab	<ul style="list-style-type: none"> <li>▪ Women: hint of minor added benefit</li> <li>▪ Men: added benefit not proven</li> </ul>
3: Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib	Added benefit not proven
<p>a: For the present therapeutic indication, the company assumed that the patients were in need of treatment. Moreover, it was assumed that allogeneic stem cell transplantation was not indicated at the time point of treatment.</p> <p>b. 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 <b>bold</b>.</p> <p>17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein 53</p>		

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

## 2.2 Research question

The aim of this report was to assess the added benefit of ibrutinib in combination with obinutuzumab (hereinafter referred to as ibrutinib + obinutuzumab) in comparison with the ACT in adult patients with previously untreated CLL.

The G-BA differentiated between 3 different treatment situations and specified a different ACT for each of them. This resulted in 3 research questions for the present benefit assessment. The research questions are presented in Table 4.

Table 4: Research questions of the benefit assessment of ibrutinib + obinutuzumab

Research question	Subindication <sup>a</sup>	ACT <sup>b</sup>
1	Adult patients with previously untreated CLL for whom treatment with fludarabine in combination with cyclophosphamide and rituximab (FCR) is an option	Fludarabine in combination with cyclophosphamide and rituximab
2	Adult patients with previously untreated CLL for whom FCR therapy is not an option	Bendamustine in combination with rituximab or ofatumumab <i>or</i> <b>chlorambucil in combination with rituximab or obinutuzumab</b> or ofatumumab
3	Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib
<p>a. For the present therapeutic indication, the company assumed that the patients were in need of treatment. Moreover, it was assumed that allogeneic stem cell transplantation was not indicated at the time point of treatment.</p> <p>b. 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 <b>bold</b>.</p> <p>17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein 53</p>		

In the present benefit assessment, the following terms were used for the populations of the different research questions:

- Research question 1: patients for whom FCR therapy is an option
- Research question 2: patients for whom FCR therapy is not an option
- Research question 3: patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason

For research questions 1 and 3, the company followed the ACT specified by the G-BA.

For research question 2, the company deviates from the ACT specified by the G-BA insofar as it excluded combination therapies with ofatumumab, because the approval of ofatumumab was withdrawn [3] (see also Section 2.7.1 of the full dossier assessment). The company chose the combination therapy of chlorambucil + obinutuzumab as ACT from the remaining options. The approach of the company was adequate.

The assessment was made by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs were used for the derivation of the added benefit.

## **2.3 Research question 1: patients for whom FCR therapy 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 + obinutuzumab (status: 18 July 2019)
- bibliographical literature search on ibrutinib + obinutuzumab (last search on 23 July 2019)
- search in trial registries for studies on ibrutinib + obinutuzumab (last search on 18 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 10 September 2019)

The check identified no relevant RCT for a direct or indirect comparison. The company also identified no suitable studies.

### **2.3.2 Results on added benefit**

The company presented no data for the assessment of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT (FCR) in patients for whom FCR therapy is an option (see also Section 4.2.1 of Module 4 A). This resulted in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

### **2.3.3 Probability and extent of added benefit**

The company presented no data for the assessment of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT in patients for whom FCR therapy is an option. An added benefit of ibrutinib + obinutuzumab is thus not proven for this research question.

This concurs with the company's assessment.

### 2.3.4 List of included studies

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

## 2.4 Research question 2: patients for whom FCR therapy 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 list on ibrutinib + obinutuzumab (status: 18 July 2019)
- bibliographical literature search on ibrutinib + obinutuzumab (last search on 23 July 2019)
- search in trial registries for studies on ibrutinib + obinutuzumab (last search on 18 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 10 September 2019)

The check identified no additional relevant study.

#### 2.4.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study <sup>a</sup> (yes/no)	Third-party study (yes/no)
PCYC-1130-CA (iLLUMINATE <sup>b</sup> )	Yes	Yes	No
a. Study sponsored by the company. b. In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of ibrutinib includes the iLLUMINATE study. This concurs with the company's study pool.

Section 2.4.4 contains a reference list for the study included.

#### 2.4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes <sup>a</sup>
iLLUMINATE	RCT, open-label, parallel	<p>Adults with untreated CLL/SLL<sup>b</sup> requiring treatment, who had lymph node enlargement measurable by computer tomography (CT)<sup>c</sup></p> <ul style="list-style-type: none"> <li>▪ ≥ 65 years, or &lt; 65 years with one of the following criteria:                             <ul style="list-style-type: none"> <li>▫ CIRS &gt; 6,</li> <li>▫ estimated creatinine clearance &lt; 70 mL/min<sup>d</sup></li> <li>▫ del17p (FISH)/TP53 mutation (PCR or NGS)</li> </ul> </li> <li>▪ ECOG PS 0–2</li> </ul>	<p>Ibrutinib + obinutuzumab (N = 113)</p> <p>Chlorambucil + obinutuzumab (N = 116)</p> <p>relevant subpopulation thereof (patients for whom FCR therapy is not an option):</p> <p>ibrutinib + obinutuzumab (n = 73)</p> <p>chlorambucil + obinutuzumab (n = 72)</p>	<p>Screening: 30 days</p> <p>treatment:</p> <ul style="list-style-type: none"> <li>▪ study medication for 6 28-day cycles or until progression or unacceptable toxicity</li> <li>▪ from 7th cycle: continued treatment until progression or occurrence of unacceptable toxicity</li> </ul> <p>▫ intervention arm: ibrutinib monotherapy</p> <p>▫ comparator arm: switch to monotherapy with ibrutinib<sup>e</sup> should only be considered after progression</p> <p>observation<sup>f</sup>: outcome-specific, at most until end of study</p>	<p>89 centres in Australia, Austria, Belgium, Canada, Czech Republic, France, Israel, Italy, New Zealand, Poland, Russia, Spain, Sweden, Turkey, United Kingdom, USA</p> <p>10/2014–ongoing</p> <p>first data cut-off: 26 March 2018</p> <p>second data cut-off: 26 February 2019</p>	<p>Primary: progression-free survival</p> <p>secondary: overall survival, morbidity, AEs</p>

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab (continued)

- a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
- b. Diagnosis and need for treatment according to the IWCLL criteria (2008) [4].
- c.  $\geq 1$  lymph node with a diameter  $> 1.5$  cm at a previously non-irradiated site (an irradiated lesion could only be considered if there was a documented progression of the lesion since the termination of the last radiotherapy).
- d. According to Cockcroft-Gault equation.
- e. Patients with confirmed disease progression (IRC) in the comparator arm could receive follow-up therapy with ibrutinib (monotherapy). The sponsor specified the suitability for treatment based on defined criteria.
- f. Outcome-specific information is provided in Table 8.

AE: adverse event; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; CT: computed tomography; del17p: deletion of 17p; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FCR: treatment with fludarabine in combination with cyclophosphamide and rituximab; FISH: fluorescence in situ hybridization; IRC: independent review committee; IWCLL: International Workshop on Chronic Lymphocytic Leukemia; n: relevant subpopulation; N: number of randomized (included) patients; NGS: Next Generation Sequencing; PCR: polymerase chain reaction; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; TP53: tumour protein p53; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab

Study	Intervention	Comparison
iLLUMINATE	<p>Ibrutinib, 420 mg, orally, with approx. 240 mL water, once daily (at the same time of the day)<sup>a</sup></p> <p>+</p> <p>Obinutuzumab, 1000 mg IV, over 6 cycles<sup>c</sup>            cycle<sup>c</sup> 1: 100 mg on day 1, 900 mg on day 2, 1000 mg each on day 8 and day 15            cycles<sup>c</sup> 2 to 6: 1000 mg each on day 1</p> <p><b>Dose adjustment/treatment interruptions</b></p> <p>Ibrutinib:</p> <ul style="list-style-type: none"> <li>▪ treatment interruptions and dose reductions in case of AEs with CTCAE grade <math>\geq 3</math>, surgical interventions or development of liver dysfunctions with subsequent dose adjustment after resumption of the therapy<sup>d</sup></li> </ul> <p>Obinutuzumab: according to protocol</p> <ul style="list-style-type: none"> <li>▪ treatment interruptions for a maximum of 28 days in case of uncontrollable toxicity due to treatment with obinutuzumab</li> <li>▪ treatment discontinuation in case of suspected multifocal leukoencephalopathy (PML)</li> </ul> <p>If one therapy component was discontinued, the other was continued as planned.</p>	<p>Chlorambucil, 0.5 mg per kg of body weight, orally<sup>b</sup> over 6 cycles<sup>c</sup> each on day 1 and day 15</p> <p>+</p> <p>Chlorambucil:</p> <ul style="list-style-type: none"> <li>▪ treatment interruptions for a maximum of 28 consecutive days in case of AEs with CTCAE grade <math>\geq 3</math> with subsequent dose adjustments after resumption of the therapy<sup>d</sup></li> </ul>
	<p><b>Pretreatment not allowed:</b></p> <ul style="list-style-type: none"> <li>▪ any pretreatment with systemic anticancer treatment against CLL/SLL</li> </ul> <p><b>premedication and concomitant treatment</b></p> <ul style="list-style-type: none"> <li>▪ obinutuzumab: mandatory prophylaxis of infusion reactions: analgesics, antipyretics, antihistamines, corticosteroids</li> <li>▪ TLS prophylaxis in patients with high tumour loads: mandatory fluid intake; allopurinol or equivalent</li> <li>▪ patients with neutropenia: strong recommendation for antimicrobial, antiviral and antimycotic prophylaxis</li> </ul> <p><b>further permitted concomitant treatment:</b></p> <ul style="list-style-type: none"> <li>▪ neutrophilic growth factors (e. g. filgrastim, pegfilgrastim)</li> <li>▪ P-glycoprotein substrates with narrow therapeutic index (e.g. digoxin)</li> <li>▪ localized hormonal or bone-preserving treatment and local radiotherapy for other indications</li> <li>▪ erythropoietin<sup>e</sup>, thrombocyte growth factors<sup>e</sup>, sargramostim<sup>e</sup></li> </ul> <p><b>non-permitted concomitant treatment:</b></p> <ul style="list-style-type: none"> <li>▪ corticosteroids &gt; 20 mg/day prednisone-equivalent for &gt; 14 consecutive days</li> <li>▪ moderate to strong CYP3A4 inhibitors/strong CYP3A4 inducers</li> <li>▪ under treatment with ibrutinib: warfarin, vitamin K antagonists<sup>f</sup>, chemotherapy, tumour immunotherapy, radiotherapy</li> </ul>	

(continued)

Table 7: Characteristics of the intervention – RCT, direct comparison: ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab (continued)

<p>a. Ibrutinib was administered until progression of the disease or until the occurrence of unacceptable intolerances.</p> <p>b. If it was difficult to take the total dose at once, the dose could be divided into 2 to 3 doses over 8 hours in one day.</p> <p>c. A treatment cycle comprised 28 days.</p> <p>d. In case of interruption due to AEs, dose adjustment or treatment resumption depended on how often the AE had previously occurred.</p> <p>e. Not allowed only in the first 6 months of therapy.</p> <p>f. Other anticoagulants and drugs that inhibit the platelet function should be administered with caution.</p> <p>AE: adverse event; CLL: chronic lymphocytic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events CYP3A4: cytochrome P450 3A4; IV: intravenous; BW: body weight; p.o.: per os (oral); PML: progressive multifocal leukoencephalopathy; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; TLS: tumour lysis syndrome; vs.: versus</p>
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The included iLLUMINATE study is an open-label, randomized, active-controlled multicentre study on the direct comparison of ibrutinib + obinutuzumab with chlorambucil + obinutuzumab. The study is ongoing.

The study iLLUMINATE included adults with previously untreated CLL/SLL requiring treatment in accordance with the IWCLL criteria (2008), who had lymph node enlargement measurable by CT. Moreover, patients had to be either  $\geq 65$  years of age or – if younger – they had to meet at least one of the following criteria:

- Presence of comorbidities (CIRS > 6)
- Presence of a kidney dysfunction (creatinine clearance < 70 mL/min, estimated using the Cockcroft-Gault equation)
- Presence of del17p or TP53 mutation.

A total of 113 adults were randomized to the intervention arm ibrutinib + obinutuzumab, and 116 adults were randomized to the comparator arm chlorambucil + obinutuzumab. Randomization was stratified by Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0–1 vs. 2) as well as by cytogenetic characteristics (del17p vs. 11 del11q without del17p vs. others [neither del17p nor del11q]). Only a subpopulation of the iLLUMINATE study is relevant for the present benefit assessment (further explanations are found below).

Ibrutinib was administered once daily in oral doses of 420 mg in the intervention arm until progression of the disease or until the occurrence of unacceptable intolerances. In the iLLUMINATE study, treatment with ibrutinib was in compliance with the SPC [5,6].

In both study arms, obinutuzumab was administered in IV doses of 1000 mg for 6 28-day cycles each. The SPC on obinutuzumab contains no information on the application of obinutuzumab in combination with ibrutinib [7]. In both arms of the iLLUMINATE study (ibrutinib +

obinutuzumab and chlorambucil + obinutuzumab), treatment with obinutuzumab was performed in accordance with the SPC [5-7] under consideration of the SPCs on ibrutinib.

In the comparator arm, chlorambucil was administered over 6 cycles, whereby the dosage depended on the body weight. According to the SPC, chlorambucil is approved as monotherapy for the treatment of CLL; information on the application as combination therapy with obinutuzumab are not comprised [8]. However, the combination therapy of chlorambucil + obinutuzumab is comprised in the SPC on obinutuzumab; the dosage of chlorambucil in the combination therapy is also indicated [7]. Considering this information, treatment with chlorambucil was performed without relevant deviations from the SPC in the iLLUMINATE study [7,8].

After discontinuation of the study medication (e.g. due to disease progression), subsequent therapies could be applied. Patients in the comparator arm of the study could receive ibrutinib monotherapy in compliance with the approval after progression of the disease and fulfilment of certain criteria. Information on the subsequent therapies received after discontinuation of the study medication are not available for the relevant subpopulation (see below). In the total population, 4 (3.5%) of 113 patients included in the invention arm (ibrutinib + obinutuzumab) received a subsequent therapy. In the comparator arm (chlorambucil + obinutuzumab), these were 51 (44.0%) of 116 included patients the majority of whom received ibrutinib monotherapy as subsequent therapy. The subsequent therapies in the total population of the iLLUMINATE study are presented in Appendix C of the full dossier assessment.

Primary outcome of the iLLUMINATE study was PFS. Outcomes on morbidity and AEs were recorded under patient-relevant secondary outcomes (see Section 2.4.2.1). Outcomes on health-related quality of life were not recorded in the study.

### ***Analysis and data cut-offs***

There were 2 data cut-offs for the iLLUMINATE study:

- First data cut-off of 26 March 2018: prespecified primary analysis, after reaching 98 PFS events (94 events were planned)
- Second data cut-off of 26 February 2019: not prespecified. Since the EMA requested another data cut-off within the framework of the Extension of indication variation assessment report – PRAC Rapporteur’s preliminary assessment report of 18 February 2019, it is assumed that - due to the proximity in time - the second data cut-off is the data cut-off subsequently requested by the EMA.

The second data cut-off was used for the present benefit assessment due to the higher informational content.

### Treatment duration and follow-up observation

Treatment with the intervention “ibrutinib + obinutuzumab” and with the comparator therapy “chlorambucil + obinutuzumab” was performed for 6 cycles each or until progression of the disease (assessed on the basis of the IWCLL criteria of 2008 [4]), death, occurrence of unacceptable intolerances, withdrawal of the informed consent or pregnancy. If one therapy component was discontinued, treatment with the respective combination partner was continued as planned. After the maximum of 6 cycles with ibrutinib + obinutuzumab, treatment with ibrutinib (as monotherapy) was continued in the intervention arm until progression of the disease, occurrence of unacceptable intolerances or at most until the end of the study. In the comparator arm, patients with disease progression confirmed by an independent review committee (IRC) who met the specified criteria could also receive further treatment with ibrutinib (as monotherapy) within the framework of a subsequent therapy.

Table 8 shows the planned follow-up observation period of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab

Study outcome category outcome	Planned follow-up observation
iLLUMINATE	
Mortality overall survival	▪ until death, withdrawal of consent, lost to follow-up, end of study
Morbidity health status (EQ-5D VAS)	▪ until progression of the disease
Health-related quality of life	▪ not investigated in the study
Side effects All outcomes in the category “side effects”	▪ until 30 days after the last dose of the study medication
EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

The observation periods for the outcome categories “side effects” and “morbidity” were systematically shortened, because they were only recorded for the time period of treatment with the study medication (plus 30 days) or until progression. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for “survival”. The effects of the systematically shortened observation periods for the present benefit assessment are addressed in Section 2.7.4.2. of the full dossier assessment.

### **Subpopulation relevant for the research question**

The iLLUMINATE study included patients irrespective of whether they were candidates for an FCR therapy or not. However, only those patients who were no candidates for an FCR therapy were relevant for the present research question.

In its dossier, the company presented analyses on 2 subpopulations for whom, from its point of view, FCR therapy was not an option. It used one of them as relevant subpopulation. It used the other one (referred to as “conservative selection” in the company’s dossier) for a sensitivity analysis (see Section 2.7.4.3.1 of the full dossier assessment and Section 4.2.5.2.3 of Module 4 A).

The subpopulation for sensitivity analyses formed by the company is not included in the present benefit assessment (see Section 2.7.4.3.1 of the full dossier assessment). The company’s approach to form the subpopulation it defined as relevant will be addressed hereinafter.

### ***Approach of the company to form the relevant subpopulation***

The company used the following approach for the formation of the subpopulation relevant for research question 2 from the total population of the iLLUMINATE study.

The company used several criteria (age, kidney function, thrombocytopenia, anaemia, autoimmune cytopenia, general condition, comorbidities, 17p and TP53 mutation status), which might cause an unsuitability for FCR therapy. When forming this subpopulation, the company considered these criteria as follows:

- Sufficient criteria (if one criterion is met, FCR therapy is no longer an option, e.g. the patients are included in the relevant subpopulation)
  - Absence of del17p and/or TP53 mutation
  - Presence of a kidney dysfunction (creatinine clearance < 70 mL/min, estimated using the Cockcroft-Gault equation)
  - Presence of an autoimmune cytopenia
- Combination criteria (if at least 2 criteria are met, FCR therapy is no longer an option, e.g. the patients are included in the relevant subpopulation)
  - Age > 65 years
  - General condition: ECOG PS  $\geq$  2
  - Comorbidities: CIRS > 6
  - Anaemia and/or reduced platelet count

The company stated that a subpopulation of patients who were candidates for FCR therapy (research question 1) could not be presented for the iLLUMINATE study. The reason for this was that even after identification of all patients for whom FCR therapy was definitely not an

option, it was still unclear whether or not FCR therapy was an option for the remaining population.

According to the company, neither FCR therapy nor any other chemoimmunotherapy would be an option for patients with, for instance, del17p and/or TP53 mutation. These patients would thus have to be assigned to the subpopulation addressed in research question 3 (see Section 2.5).

***Assessment of the approach of the company to form the relevant subpopulation***

In Section 4.2.5.2.3 of Module 4 A of the dossier, the company provides a comprehensible description of the specific criteria on the basis of which it had formed the subpopulation relevant for research question 2. In doing so, it justified the choice of the possibly applied operationalization (e.g. creatinine clearance < 70 mL/min) for each criterion.

There is no consistent scientific consensus regarding the criteria for the suitability of FCR therapy in patients with CLL. In its approach, the company considered criteria that are mentioned, for instance, in guidelines or in the justifications on ibrutinib in connection with the decision on a suitable treatment [9-11]. The criteria used by the company are thus considered suitable for an adequate representation of the subpopulation relevant for research question 2.

The subpopulation formed by the company was included in the present benefit assessment as sufficient approximation to the subpopulation relevant for research question 2.

**Characteristics of the relevant subpopulation**

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

Table 9: Characteristics of the study population – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Study characteristics category	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab
<b>iLLUMINATE</b>	N <sup>a</sup> = 73	N <sup>a</sup> = 72
Age [years], median [min; max]	71 [47; 87]	74 [48; 86]
Sex [F/M], %	40/60	31/69
Family origin, n (%)		
white	72 (99)	69 (96)
other <sup>b</sup>	1 (1) <sup>c</sup>	3 (4) <sup>c</sup>
Histology, n (%)		
CLL	70 (96)	68 (94)
SLL	3 (4)	4 (6)
Stage of RAI, n (%)		
0/I/II	31 (42)	32 (44)
III/IV	42 (58)	40 (56)
ECOG PS, n (%)		
0/1	69 (95)	66 (92)
2	4 (5)	6 (8)
Disease duration: time between first diagnosis and randomization [months], median [min; max]	32.4 [ND]	45.6 [ND]
Bulky disease <sup>d</sup> , n (%)		
≥ 10 cm	2 (3)	1 (1)
≥ 5 cm	21 (29)	27 (38)
Cytopenia <sup>e</sup> , n (%)	44 (60)	41 (57)
Chromosome anomaly, n (%)		
del17p or TP53 mutation	0 (0)	0 (0)
del11q	11 (15)	17 (24)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND
<p>a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.</p> <p>b. Composed of Asian, black/African American, Hawaiian/Pacific origin.</p> <p>c. Institute's calculation.</p> <p>d. The presence of ≥ 1 lymph node with a diameter of ≥ 5 cm is defined as bulky disease.</p> <p>e. Either haemoglobin ≤ 110 g/l or platelet count ≤ 100 x 10<sup>9</sup>/l or neutrophil count ≤ 1.5 x 10<sup>9</sup>/l</p> <p>CLL: chronic lymphocytic leukaemia; del17p: deletion on chromosome 17; del11q: deletion on chromosome 11; ECOG-PS: Eastern Cooperative Oncology Performance Status; F: female; FCR: fludarabine in combination with cyclophosphamide and rituximab; M: male; max: maximum; min.: minimum; ND: no data; n: number of patients in the category; N: number of randomized (or included) patients; RAI: radioactive iodine; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; TP53: tumour protein p53; vs.: versus</p>		

The patient characteristics of the relevant subpopulation of patients not eligible for FCR therapy were sufficiently comparable between the intervention arm ibrutinib + obinutuzumab and the comparator arm chlorambucil + obinutuzumab. The median age of the included patients was 71 to 74 years, and two thirds of them were male. In addition, almost all patients were of white family origin and had an ECOG PS of 0 or 1. Slightly more than half of the patients were in an advanced stage of the disease (RAI [radioactive iodine] stage III/IV). There were slight imbalances in the patient characteristics “disease duration”, “lymph node diameter” and “11q deletion”.

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

<b>Study</b>	<b>Ibrutinib + obinutuzumab</b>	<b>Chlorambucil + obinutuzumab</b>
<b>duration of the study phase</b>		
<b>outcome category</b>		
<b>iLLUMINATE</b>	N = 73	N = 72
Treatment duration [months]		
median [min; max]	40.4 [ND]	5.1 [ND]
Observation period [months]		
Overall survival		
Median [min; max]	40.6 [ND]	40.8 [ND]
Morbidity (EQ-5D VAS)		
Median [min; max]	40.1 [ND]	21.0 [ND]
Side effects		
Median [min; max]	40.5 [ND]	6.1 [ND]
FCR: Fludarabine in combination with cyclophosphamide and rituximab; EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min.: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus		

The median treatment duration for the relevant subpopulation was about 8 times longer in the intervention arm than in the comparator arm. This is due to the fact that in the intervention arm ibrutinib + obinutuzumab, further treatment with ibrutinib (monotherapy) was planned to be continued until the onset of disease progression, the occurrence of unacceptable intolerances, or at most until the end of the study, whereas patients in the control arm with chlorambucil + obinutuzumab could be treated for a maximum of 6 cycles (see Table 6).

The median observation period for the outcome “overall survival” was comparable between the two study arms, while for the outcome “health status (EQ-5D VAS)” it was about twice as long in the intervention arm as in the comparator arm. The difference in the median follow-up observation duration was even greater for AEs, where the median follow-up duration was about

6 to 7 times longer in the intervention arm than in the comparator arm. These large differences in the median follow-up observation period for the outcome “health status” were due to the fact that follow-up observation was continued until disease progression (or until the end of the study), which occurred earlier in the comparator arm than in the intervention arm. For AEs, the reason was that follow-up for AEs was planned only until 30 days after the last dose of the study medication (see Table 8), whereby the study medication in the intervention arm could be administered until the onset of disease progression, while in the comparator arm, the study medication could be administered for a maximum of 6 cycles of 28 days each.

**Risk of bias across outcomes (study level)**

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
iLLUMINATE	yes	yes	no	no	yes	yes	low

FCR: fludarabine in combination with cyclophosphamide and rituximab; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the study. This concurs with the company’s assessment.

Limitations resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.4.2.

**2.4.2 Results on added benefit**

**2.4.2.1 Outcomes included**

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - health status (EQ-5D VAS)

- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade  $\geq 3$ )
  - discontinuation due to AEs
  - infusion-related reaction (PT, AEs)
  - severe bleeding events (modified Medical Dictionary for Regulatory Activities [MedDRA] Standardized MedDRA Query [SMQ])
  - cardiac disorders (System Organ Class [SOC], AEs)
  - infections and infestations (SOC, AEs)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of the outcomes – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Study	Outcomes													
	Overall survival	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs (CTCAE grade $\geq 3$ )	Discontinuation due to AEs	Infusion-related reaction (PT, AEs)	Severe bleeding events (modified SMQ <sup>a</sup> )	Cardiac disorders (SOC, AEs)	Infections and infestations (SOC, AEs)	Severe neutropenia (PT, CTCAE grade $\geq 3$ )	Nausea (PT, AEs)	Skin and subcutaneous tissue disorders (SOC, AEs)	
iLLUMINATE	Yes	Yes	No <sup>b</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	

a. Modified SMQ "haemorrhage terms": comprises all serious bleeding or bleeding with CTCAE grade  $\geq 3$  as well as bleeding of the central nervous system of any severity; events that are based on laboratory values are not included.

b. Outcomes of this outcome category were not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life5 Dimensions; FCR: Fludarabine in combination with cyclophosphamide and rituximab; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

### 2.4.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Study	Study level	Outcomes												
		Overall survival	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs (CTCAE grade $\geq 3$ )	Discontinuation due to AEs	Infusion-related reaction (PT, AEs)	Severe bleeding events (modified SMQ <sup>a</sup> )	Cardiac disorders (SOC, AEs)	Infections and infestations (SOC, AEs)	Severe neutropenia (PT, CTCAE grade $\geq 3$ )	Nausea (PT, AEs)	Skin and subcutaneous tissue disorders (SOC, AEs)
iLLUMINATE	L	L	H <sup>b, c</sup>	– <sup>d</sup>	H <sup>e</sup>	H <sup>e</sup>	H <sup>b</sup>	H <sup>b, e</sup>	H <sup>e</sup>	H <sup>b, e</sup>	H <sup>b, e</sup>	H <sup>e</sup>	H <sup>b, e</sup>	H <sup>b, e</sup>
<p>a. Modified SMQ "haemorrhage terms": comprises all serious bleeding or bleeding with CTCAE grade <math>\geq 3</math> as well as bleeding of the central nervous system of any severity; events that are based on laboratory values are not included.</p> <p>b. Lack of blinding in subjective recording of outcomes.</p> <p>c. Increasingly high proportion of missing values that varies between the treatment arms</p> <p>d. No data on health-related quality of life were recorded.</p> <p>e. Clearly different observation period between the treatment arms</p> <p>AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life5 Dimensions; FCR: Fludarabine in combination with cyclophosphamide and rituximab; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus</p>														

The risk of bias for the results of the outcome “overall survival” was rated as low. This concurs with the company’s assessment.

Due to the increasingly high proportions of missing values, which differ between the treatment arms, and the open-label study design in the subjective recording of outcomes, the risk of bias for the results of the outcome “health status” (EQ-5D VAS) was rated as high. This concurs with the company’s assessment.

The risk of bias of the results on each of the outcomes “SAEs”, “severe AEs (CTCAE grade  $\geq 3$ )”, “infusion-related reaction”, “severe bleeding”, “cardiac disorders”, “infections and infestations”, “severe neutropenia (CTCAE grade  $\geq 3$ )”, “nausea” as well as “skin and subcutaneous tissue disorders” was rated as high. For all mentioned outcomes, the reason for this

is the clearly different observation period between the study arms. In the results on the outcomes “infusion-related reaction”, “cardiac disorders”, “infections and infestations”, “nausea” as well as “skin and subcutaneous tissue disorders”, the lack of blinding in the subjective recording of outcomes additionally contributes to the high risk of bias.

This deviates from the assessment of the company, which derived a low risk of bias for SAEs as well as for severe AEs (CTCAE grade  $\geq 3$ ), while it does not assess the risk of bias for specific AEs.

The risk of bias of the results on the outcome “discontinuation due to AEs” is rated as high due to the lack of blinding in the subjective recording of outcomes. This deviates from the assessment of the company, which derived a low risk of bias for discontinuation due to AEs.

Further information on the risk of bias are found in Section 2.7.4.2. of the full dossier assessment.

### **2.4.2.3 Results**

Table 14 and Table 15 summarize the results on the comparison of ibrutinib + obinutuzumab with chlorambucil + obinutuzumab in patients with previously untreated CLL who are no candidates for an FCR therapy. Where necessary, calculations by the Institute are provided in addition to the data.

Results on common AEs are presented in Appendix B of the full dossier assessment. Kaplan-Meier curves on the presented event time analyses can be found in Appendix A of the full dossier assessment. For the second data cut-off, Kaplan-Meier curves are not available for all specific AEs for the relevant subpopulation.

Table 14: Results (mortality, side effects) – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Study outcome category	Ibrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab HR [95% CI]; p-value <sup>a</sup>
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	
<b>iLLUMINATE</b>					
<b>Mortality</b>					
Overall survival	73	NA 15 (20.5)	72	NA 12 (16.7)	1.21 [0.55; 2.68]; 0.638
<b>Health-related quality of life</b>					
“Health-related quality of life” was not investigated in the study.					
<b>Side effects</b>					
AEs (supplementary information)	73	0.26 [0.13; 0.39] 72 (98.6)	71	0.03 [NC] 69 (97.2)	–
SAEs	73	18.79 [11.24; NC] 42 (57.5)	71	10.61 [NC] 27 (38.0)	0.52 [0.28; 0.97]; 0.040
Severe AEs (CTCAE grade ≥ 3)	73	6.24 [3.22; 7.59] 58 (79.5)	71	2.79 [0.95; 4.04] 55 (77.5)	0.48 [0.31; 0.73]; < 0.001
Discontinuation due to AEs (≥ 1 drug)	73	NA 19 (26.0)	71	NA 10 (14.1)	0.51 [0.17; 1.50]; 0.220
Infusion-related reaction (PT, AEs)	73	NA 18 (24.7)	71	1.02 [0.03; NC] 37 (52.1)	0.43 [0.24; 0.76]; 0.004
Severe bleeding events (modified SMQ <sup>b</sup> )	73	NA 1 (1.4)	71	NA 0 (0)	NC
Cardiac disorders (SOC, AEs)	73	NA [22.64; NC] 30 (41.1)	71	NA 4 (5.6)	5.13 [1.75; 15.06]; 0.003
Severe cardiac disorders (SOC, CTCAE grade ≥ 3)	73	NA 10 (13.7)	71	NA 0 (0)	NC; < 0.124 <sup>c</sup>
Infections and infestations (SOC, AEs)	73	7.46 [4.07; 12.58] 53 (72.6)	71	27.40 [5.19; 27.40] 28 (39.4)	1.19 [0.72; 1.98]; 0.498
Severe neutropenia (PT, CTCAE grade ≥ 3)	73	NA [14.85; NC] 27 (37.0)	71	5.65 [4.04; NC] 35 (49.3)	0.44 [0.25; 0.76]; 0.003

(continued)

Table 14: Results (mortality, side effects) – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy) (continued)

Study outcome category outcome	Ibrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab HR [95% CI]; p-value <sup>a</sup>
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	
Nausea (PT, AEs)	73	NA [NC] 9 (12.3)	71	NA [NC] 18 (25.4)	0.25 [0.10; 0.64]; 0.004
Skin and subcutaneous tissue disorders (SOC, AEs)	73	12.94 [5.52; NC] 38 (52.1)	71	NA [NC] 15 (21.1)	2.00 [1.07; 3.76]; 0.031

a. Cox proportional hazards model stratified by ECOG PS and cytogenetics.  
b. Modified SMQ "haemorrhage terms": comprises all serious or severe (CTCAE grade  $\geq 3$ ) bleeding as well as bleeding of the central nervous system of any severity; events that are based on laboratory values are not included.  
c. P-value: log-rank test.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Performance Status; FCR: Fludarabine in combination with cyclophosphamide and rituximab; HR: Hazard Ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved, NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; vs.: versus

Table 15: Results (morbidity) – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Study outcome category outcome	Ibrutinib + obinutuzumab			Chlorambucil + obinutuzumab			Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab MD [95% CI]; p-value <sup>c</sup>
	N <sup>a</sup>	Values at baseline mean (SD)	Change at the date of analysis <sup>b</sup> mean <sup>c</sup> (SE)	N <sup>a</sup>	Values at baseline mean (SD)	Change at the date of analysis <sup>b</sup> mean <sup>c</sup> (SE)	
<b>iLLUMINATE</b>							
<b>Morbidity</b>							
Health status (EQ-5D VAS) <sup>d</sup>	70	75.78 (14.76)	1.89 (1.29)	65	70.33 (18.00)	5.62 (1.37)	-3.73 [-7.43; -0.03]; 0.048 Hedges' g: -0.34 [-0.68; 0.00]
<p>a. Number of patients considered in the analysis for the calculation of the effect estimation (i.e. those for whom values at baseline and at least one post-baseline value were available); the values at baseline may be based on other patient numbers.</p> <p>b. End of observation period at progression of the disease or at the end of the study.</p> <p>c. MMRM with treatment, visit and baseline value as fixed effects, patient as random effect.</p> <p>d. A positive change in the course of the study indicates improvement, a positive mean difference indicates an advantage of the test intervention.</p> <p>CI: confidence interval; EQ-5D: European Quality of Life5 Dimensions; FCR: Fludarabine in combination with cyclophosphamide and rituximab; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus</p>							

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcome “overall survival”, and at most hints for all other outcomes due to the high risk of bias.

## Mortality

### *Overall survival*

In the present benefit assessment, the results of time from randomization to death for any reason were used for the outcome “overall survival”. The result showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

This concurs with the company’s assessment.

## **Morbidity**

### ***Health status (EQ-5D VAS)***

The outcome “health status” was recorded using the EQ-5D VAS, operationalized as change at the date of analysis (disease progression or end of the study) in comparison with baseline. There was a statistically significant difference to the disadvantage of ibrutinib + obinutuzumab. However, the 95% CI of the standardized mean difference (Hedges’ *g*) was not fully outside the irrelevance range of –0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. This resulted in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

This concurs with the company’s assessment.

### **Health-related quality of life**

No data on health-related quality of life were recorded in the iLLUMINATE study.

### **Side effects**

The company derived an indication of added benefit for the entire outcome category “side effects” based on the results on the outcomes SAEs and severe AEs (CTCAE grade  $\geq 3$ ). It makes no conclusion on the individual outcomes. The company did not use the outcomes on specific AEs for the derivation of an added benefit. For this reason, a description of the extent to which the statement on the added benefit made here differs from the assessment of the company is omitted for the following outcomes.

#### ***SAEs***

A statistically significant difference in favour of ibrutinib + obinutuzumab was shown for the outcome “SAEs”. Moreover, there was an effect modification by the characteristic “sex” for this outcome (see Section 2.4.2.4). For women, there was a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. For men, there was no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

#### ***Severe AEs (CTCAE grade $\geq 3$ )***

A statistically significant difference in favour of ibrutinib + obinutuzumab was shown for the outcome “severe AEs (CTCAE grade  $\geq 3$ )”. Moreover, there are effect modifications by the characteristics “sex” and “age” for this outcome. The result on the characteristic “sex” was used for the derivation of the added benefit (see Section 2.4.2.4). For women, there was a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. For men, there was no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

### ***Discontinuation due to AEs***

In the iLLUMINATE study, an event was recorded as discontinuation due to AEs when the administration of  $\geq 1$  of the combination partners in the intervention arm (ibrutinib + obinutuzumab) or in the comparator arm (chlorambucil + obinutuzumab) was discontinued due to AEs. Treatment with the respective other combination partner was continued as planned.

There was no statistically significant difference between the treatment groups for the outcome “discontinuation due to AEs”. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

### ***Specific adverse events***

#### *Infusion-related reaction and nausea*

For each of the outcomes “infusion-related reaction” and “nausea”, there was a statistically significant difference in favour of ibrutinib + obinutuzumab. This resulted in a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

#### *Severe bleeding events*

The outcome “severe bleeding” is a modified MedDRA SMQ (version 17.0). The modified SMQ comprises all serious bleeding events or bleeding with CTCAE grade  $\geq 3$  as well as bleeding of the central nervous system of any severity; events that are based on laboratory values are not included.

For the outcome “severe bleeding events”, the HR cannot be estimated, since no events occurred in the comparator arm. However, only 1 event occurred in the intervention arm. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

#### *Cardiac disorders*

A statistically significant difference to the disadvantage of ibrutinib + obinutuzumab was shown for the outcome “cardiac disorders”. This resulted in a hint of greater harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

#### *Infections and infestations*

No statistically significant difference between the treatment groups was shown for the outcome “infections and infestations”. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

#### *Severe neutropenia (CTCAE grade $\geq 3$ )*

A statistically significant difference in favour of ibrutinib + obinutuzumab was shown for the outcome “severe neutropenia (CTCAE grade  $\geq 3$ )”. Moreover, there are effect modifications

by the characteristics “sex” and “CIRS status” for this outcome. The result on the characteristic “sex” was used for the derivation of the added benefit (see Section 2.4.2.4). For women, there was a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. For men, there was no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven for men.

#### *Skin and subcutaneous tissue disorders*

There was a statistically significant difference to the disadvantage of ibrutinib + obinutuzumab for the outcome “skin and subcutaneous tissue disorders”; however, for this outcome of the category non-serious/non-severe side effects, this difference was no more than marginal. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; greater or lesser harm is therefore not proven.

#### **2.4.2.4 Subgroups and other effect modifiers**

The following potential effect modifiers were considered for the present assessment:

- sex (female/male)
- age (< 65 years/≥ 65 years)
- family origin (white/non-white)
- RAI stage (0–II / III–IV)
- ECOG PS (0/ 1–2)
- CIRS (≤ 6/>6)
- immunoglobulin Heavy Chain Variable Region (IGHV) (non-mutated/mutated)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the results of the subgroup analyses on the comparison of ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab.

Table 16: Subgroups (side effects) – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Study outcome characteristic Subgroup	Ibrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab	
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]	p-value
<b>iLLUMINATE</b>						
<b>SAEs</b>						
Sex						
Female	29	27.6 [15.0; NC] 14 (48.3)	22	NA [3.7; NC] 10 (45.5)	0.24 [0.07; 0.87]	0.029
Male	44	13.6 [6.9; 42.3] 28 (63.6)	49	10.6 [NC] 17 (34.7)	0.69 [0.32; 1.47]	0.335
total					Interaction <sup>a</sup> :	0.031
<b>Severe AEs (CTCAE grade ≥ 3)</b>						
Sex						
Female	29	7.59 [1.9; 24.5] 23 (79.3)	22	1.41 [0.13; 3.71] 20 (90.9)	0.18 [0.07; 0.44]	< 0.001
Male	44	3.99 [2.0; 7.4] 35 (79.5)	49	2.79 [1.0; 4.6] 35 (71.4)	0.65 [0.38; 1.10]	0.108
Total					Interaction <sup>a</sup> :	0.027
Age						
< 65 years	14	4.16 [1.5; 14.7] 12 (85.7)	11	5.09 [0.1; NC] 6 (54.5)	1.23 [0.41; 3.64]	0.715
≥ 65 years	59	6.44 [2.79; 8.67] 46 (78.0)	60	1.48 [0.33; 3.68] 49 (81.7)	0.40 [0.25; 0.64]	< 0.001
Total					Interaction <sup>a</sup> :	0.0498
<b>Severe neutropenia (CTCAE grade ≥ 3)</b>						
Sex						
Female	29	NA 7 (24.1)	22	4.63 [3.68; NC] 13 (59.1)	0.09 [0.02; 0.42]	0.002
Male	44	NA [5.59; NC] 20 (45.5)	49	NA [4.21; NC] 22 (44.9)	0.66 [0.34; 1.28]	0.219
Total					interaction <sup>a</sup> :	0.018
<b>CIRS</b>						
≤ 6	42	NA 12 (28.6)	45	4.63 [3.12; NC] 24 (53.3)	0.25 [0.11; 0.56]	< 0.001
> 6	29	NA [3.70; NC] 14 (48.3)	25	NA [3.71; NC] 10 (40)	0.77 [0.31; 1.91]	0.577
Total					interaction <sup>a</sup> :	0.031

(continued)

Table 16: Subgroups (side effects) – RCT, direct comparison: ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy) (continued)

<p>a. Cox proportional hazards model, stratified by ECOG PS and cytogenetics with interaction term for treatment × subgroup.</p> <p>AE: adverse event; CI: confidence interval; CIRS: Cumulative Illness Rating Scale; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Performance Status; FCR: fludarabine in combination with cyclophosphamide and rituximab; HR: Hazard Ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus</p>
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### SAEs

There was an effect modification by the characteristic “sex” for the outcome “SAEs”. For women, a statistically significant difference in favour of ibrutinib + obinutuzumab was shown. This resulted in a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for women.

For men, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. Greater or lesser harm is therefore not proven for men.

### Severe AEs (CTCAE grade $\geq 3$ )

Effect modifications by the characteristics “sex”, and “age” were shown for the outcome “severe AEs (CTCAE grade  $\geq 3$ )”.

Severe AEs (CTCAE grade  $\geq 3$ ) is an outcome similar to SAEs. The results of the subgroup analyses show that the characteristic “sex” is the primary characteristic in both outcomes. Due to the consistency between the results of the subgroup analyses for both outcomes, only the characteristic “sex” is hereinafter considered for the derivation of the added benefit for the outcome “severe AEs (CTCAE grade  $\geq 3$ )”.

For women, a statistically significant difference in favour of ibrutinib + obinutuzumab was shown. This resulted in a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for women.

For men, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. Greater or lesser harm is therefore not proven for men.

### Severe neutropenia (CTCAE grade $\geq 3$ )

Effect modifications by the characteristics “sex”, and “CIRS status” were shown for the outcome “severe neutropenia (CTCAE grade  $\geq 3$ )”.

The outcome “severe neutropenia (CTCAE grade  $\geq 3$ )” is a subset of the outcome “severe AEs (CTCAE grade  $\geq 3$ )”. The results of the subgroup analyses show that the characteristic “sex” is the primary characteristic in the three outcomes for which an effect modification is shown. Due to the consistency between the results of the subgroup analyses for these outcomes, only the characteristic “sex” is considered also for the derivation of the added benefit for the outcome “severe neutropenia (CTCAE grade  $\geq 3$ )”.

For women, a statistically significant difference in favour of ibrutinib + obinutuzumab was shown. This resulted in a hint of lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for women.

For men, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. Greater or lesser harm is therefore not proven for men.

The company did not use the results on the subgroup analyses for any of the outcomes for the derivation of an added benefit.

### **2.4.3 Probability and extent of added benefit**

Probability and extent of the added benefit per subpopulation are presented below at outcome level. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

#### **2.4.3.1 Assessment of the added benefit at outcome level**

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2 (see Table 17).

#### **Determination of the outcome category for the outcomes on side effects**

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

#### ***Determination of the outcome category for specific adverse events***

The events occurred in connection with the specific AEs “infusion-related reaction”, “cardiac disorders”, “nausea” and “skin and subcutaneous tissue disorders” are for the most part non-serious. The outcomes were therefore assigned to the outcome category “non-serious/non-severe side effects”.

The outcome “severe neutropenia” was operationalized as CTCAE grade  $\geq 3$ . Therefore, only severe events (CTCAE grade  $\geq 3$ ) were analysed for this outcome; the outcome was thus assigned to the outcome category serious/severe side effects.

The company did not assign the mentioned outcomes to an outcome category.

Table 17: Extent of added benefit at outcome level: ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Outcome category outcome effect modifier subgroup	Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab quantile of time to event (months) or proportion of events (%) or mean (change at the date of analysis <sup>a</sup> ) effect estimation [95% CI]; p-value probability <sup>b</sup>	Derivation of extent <sup>c</sup>
<b>Mortality</b>		
Overall survival	Median: NA vs. NA HR: 1.21 [0.55; 2.68] p = 0.638	Lesser benefit/added benefit not proven
<b>Morbidity</b>		
Health status (EQ-5D VAS)	Mean: 1.89 vs. 5.62 MD: -3.73 [-7.43; -0.03] p = 0.048 Hedges' g: -0.34 [-0.68; 0.00] <sup>d</sup>	Lesser benefit/added benefit not proven
<b>Health-related quality of life</b>		
Outcomes of this outcome category were not investigated in the study included.		
<b>Side effects</b>		
SAEs		
Sex		
Female	Median: 27.6 vs. NA HR: 0.24 [0.07; 0.87] p = 0.029 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Male	Median: 13.6 vs. 10.6 HR: 0.69 [0.32; 1.47] p = 0.335	Greater/lesser harm not proven
Severe adverse events (CTCAE grade $\geq 3$ )		
Sex		
Female	Median: 7.59 vs. 1.41 HR: 0.18 [0.07; 0.44] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ ; risk $\geq 5\%$ lesser harm, extent: "major"
Male	Median: 3.99 vs. 2.79 HR: 0.65 [0.38; 1.10] p = 0.108	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 0.51 [0.17; 1.50] p = 0.220	Greater/lesser harm not proven

(continued)

Table 17: Extent of added benefit at outcome level: ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy) (continued)

<b>Outcome category outcome effect modifier subgroup</b>	<b>Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab quantile of time to event (months) or proportion of events (%) or mean (changes at the date of analysis<sup>a</sup>) effect estimation [95% CI]; p-value probability<sup>b</sup></b>	<b>Derivation of extent<sup>c</sup></b>
Infusion-related reaction (PT, AEs)	Median: NA vs. 1.02 HR: 0.43 [0.24; 0.76] p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe side effects CI <sub>u</sub> < 0.80 lesser harm, extent: "considerable"
Severe bleeding events (modified SMQ)	Median: NA vs. NA HR: NC	Greater/lesser harm not proven
Cardiac disorders (SOC, AEs)	Median: NA vs. NA HR: 5.13 [1.75; 15.06] HR <sup>e</sup> : 0.19 [0.07; 0.57] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects CI <sub>u</sub> < 0.80 greater harm, extent: "considerable"
Infections and infestations (SOC, AEs)	Median: 7.46 vs. 27.40 HR: 1.19 [0.72; 1.98] p = 0.498	Greater/lesser harm not proven
Severe neutropenia (PT, CTCAE grade ≥ 3)		
Sex		
Female	Median: NA vs. 4.63 HR: 0.09 [0.02; 0.42] p = 0.002 probability: "hint"	Outcome category: serious/severe side effects CI <sub>u</sub> < 0.75; risk ≥ 5% lesser harm, extent: "major"
Male	Median: NA vs. NA HR: 0.66 [0.34; 1.28] p = 0.219	Greater/lesser harm not proven
Nausea (PT, AEs)	Median: NA vs. NA HR: 0.25 [0.10; 0.64] p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe side effects CI <sub>u</sub> < 0.80 lesser harm, extent: "considerable"
Skin and subcutaneous tissue disorders (SOC, AEs)	Median: 12.94 vs. NA HR: 2.00 [1.07; 3.76] HR <sup>e</sup> : 0.50 [0.27; 0.93] p = 0.031	Outcome category: non-serious/non-severe side effects 0.90 ≤ CI <sub>u</sub> < 1.00 greater/lesser harm not proven <sup>f</sup>

(continued)

Table 17: Extent of added benefit at outcome level: ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy) (continued)

<p>a. End of observation period at progression of the disease or at the end of the study.</p> <p>b. Probability provided if there is a statistically significant and relevant effect.</p> <p>c. Estimations of effect size are made depending on the outcome category with different limits based on the <math>CI_u</math>.</p> <p>d. If the CI of Hedges' <math>g</math> is fully outside the irrelevance range <math>[-0.2; 0.2]</math>, this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.</p> <p>e. Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.</p> <p>f. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.</p> <p>AE: adverse event; CI: confidence interval; <math>CI_u</math>: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life5 Dimensions; FCR: fludarabine in combination with cyclophosphamide and rituximab; HR: hazard ratio; MD: mean difference; NA: not achieved; NC: not calculable; PT: Preferred Term; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus</p>
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### 2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab (patients who are no candidates for FCR therapy)

Positive effects	Negative effects
<p>Serious/severe side effects</p> <ul style="list-style-type: none"> <li>▪ SAEs <ul style="list-style-type: none"> <li>▫ sex (female) hint of lesser harm – extent “considerable”</li> </ul> </li> <li>▪ Severe AEs (CTCAE grade <math>\geq 3</math>) <ul style="list-style-type: none"> <li>▫ sex (female) hint of lesser harm – extent: “major”, including:</li> <li>▫ severe neutropenia (CTCAE grade <math>\geq 3</math>): <ul style="list-style-type: none"> <li>- sex (female) hint of lesser harm – extent: “major”</li> </ul> </li> </ul> </li> </ul>	<p>–</p>
<p>Non-serious/non-severe side effects</p> <ul style="list-style-type: none"> <li>▪ infusion-related reaction: hint of lesser harm - extent “considerable”</li> <li>▪ nausea: hint of lesser harm – extent: “considerable”</li> </ul>	<p>Non-serious/non-severe side effects</p> <ul style="list-style-type: none"> <li>▪ cardiac disorders: hint of greater harm – extent: “considerable”</li> </ul>
<p>“Symptoms” and “health-related quality of life” were not investigated in the study.</p>	
<p>AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FCR: fludarabine in combination with cyclophosphamide and rituximab; SAE: serious adverse event</p>	

Overall, there are several positive effects and one negative effect in the outcome categories on side effects, each with the probability “hint”, however, with different extent.

The positive effects in the outcome category “serious/severe side effects” are only shown for the subgroup of women. Therefore, balancing of positive and negative effects will be separated by sex hereinafter.

### **Women**

For women, there is a hint of lesser harm each, for the outcome “SAEs” with the extent “considerable” and for the outcome “severe AEs (CTCAE grade  $\geq 3$ )” with the extent “major”. Further positive effects were shown in the outcome category “non-serious/non-severe side effects”, each with the extent: “considerable”.

The positive effects were offset by a negative effect in the form of a hint of greater harm with the extent “considerable” in the outcome category “non-serious/non-severe side effects”. Overall, the positive effects outweighed the negative effects in women. However, all positive and negative effects are exclusively shown in the outcome category “serious/non-severe side effects” or “non-serious/non-severe side effects”. Data for the assessment of the added benefit of ibrutinib are only available for 2 further outcomes (“overall survival” and “health status” [EQ-5D VAS]). Although the results for these 2 outcomes are not significant or relevant, they tend to be to the disadvantage of ibrutinib + obinutuzumab. Outcomes on patient-relevant symptoms or health-related quality of life were not recorded in iLLUMINATE study.

In summary, for the above-mentioned reasons, there is a hint of a minor added benefit of ibrutinib + obinutuzumab over chlorambucil + obinutuzumab for women with previously untreated CLL who are not eligible for FCR therapy.

### **Men**

For men, there were neither positive nor negative effects in the outcome category “serious/severe side effects”. In the outcome category “non-serious/non-severe side effects”, the effects corresponded to those described for women. The positive and negative effects in this category largely cancelled each other out. As with women, it is also considered for men that, apart from “side effects”, data are only available for 2 other outcomes, which tend to be to the disadvantage of ibrutinib + obinutuzumab.

Overall, an added benefit of ibrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab is not proven for men for whom FCR therapy is not an option.

This assessment deviates from that of the company, which did not consider subgroup results and derived a hint of considerable added benefit for the total subpopulation.

#### 2.4.4 List of included studies

##### **iLLUMINATE**

Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; 20(1): 43-56.

Pharmacyclics. A multi-center study of ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in patients with treatment naïve CLL or SLL: study details [online]. In: *ClinicalTrials.gov*. 15.05.2019 [Accessed: 16.10.2019]. URL: <https://ClinicalTrials.gov/show/NCT02264574>.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma [online]. In: *EU Clinical Trials Register*. [Accessed: 16.10.2019]. URL: [https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\\_number:2014-002069-31](https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-002069-31).

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma: clinical trial results [online]. In: *EU Clinical Trials Register*. 12.04.2019 [Accessed: 16.10.2019]. URL: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-002069-31/results>.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma: study PCYC-1130-CA; clinical study report [unpublished]. 2018.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma: study PCYC-1130-CA; protocol [unpublished]. 2018.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma: study PCYC-1130-CA; statistical analysis plan [unpublished]. 2018.

Pharmacyclics. A randomized, multicenter, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma: study PCYC-1130-CA; Zusatzanalysen [unpublished]. 2019.

Pharmacyclics LLC. A multi-center study of ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in patients with treatment naïve CLL or SLL: study results [online]. In: ClinicalTrials.gov. 15.05.2019 [Accessed: 16.10.2019]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT02264574>.

## **2.5 Research question 3: patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason**

### **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 + obinutuzumab (status: 18 July 2019)
- bibliographical literature search on ibrutinib + obinutuzumab (last search on 23 July 2019)
- search in trial registries for studies on ibrutinib + obinutuzumab (last search on 18 July 2019)
- bibliographical literature search on ACTs (last search on 23 July 2019)
- search in trial registries for studies on ACTs (last search on 18 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 10 September 2019)

The check of the completeness of the study pool identified no relevant studies for a direct or indirect comparison for the assessment of the added benefit of ibrutinib + obinutuzumab.

For research question 3, the company also identified no studies for a direct or indirect comparison for the assessment of the added benefit of ibrutinib + obinutuzumab. Therefore, it presents a descriptive comparison of individual arms from different studies, which it does, however, not use itself to derive an added benefit of ibrutinib + obinutuzumab in comparison with the ACT ibrutinib.

The comparison of individual arms from different studies presented by the company was unsuitable to derive an added benefit of ibrutinib + obinutuzumab in comparison with the ACT “ibrutinib”. Hereinafter, at first the studies presented by the company are described.

Subsequently, the reasons for the lack of suitability of the comparison of individual arms from different studies for the present benefit assessment are explained.

### **Study pool of the company**

In the dossier, the company presented a descriptive comparison of individual arms from different studies. It identified the study iLLUMINATE from his own study list for the intervention ibrutinib + obinutuzumab. For the comparator therapy ibrutinib, it identified 3 studies via bibliographic literature search and a search in study registries for which results have been published (Burger 2019, Woyach 2018 and Ahn 2018 [12-14]) and which it considered relevant for a comparison of individual arms from different studies and which it included .

#### ***iLLUMINATE***

The included iLLUMINATE study is an ongoing 2-arm multicentre RCT with open-label study design. The study compares the intervention ibrutinib + obinutuzumab with chlorambucil + obinutuzumab. A detailed description of the study can be found in Section 2.4.1.2.

In the iLLUMINATE study, the company identified a subpopulation of 18 patients with del17p and/or TP53 mutation relevant for research question 3 (see Section 4.2.1 of Module 4 A).

#### ***Burger 2019***

The publication of Burger 2019 [14] describes an open-label, randomized phase II study on adults with CLL/SLL that compared ibrutinib monotherapy with the combination therapy ibrutinib + rituximab.

It included pretreated patients who were rated as requiring treatment in accordance with the IWCLL criteria (2008) [4]. Moreover, treatment-naïve patients with del17p or TP53 mutation could be included in the study. In the study arm that was relevant for the comparison of individual arms from different studies, patients received 420 mg ibrutinib per day (orally) until progression of the disease or until the onset of intolerances.

In the study published by Burger in 2019, outcomes on “overall response” and “AEs” were recorded in addition to the primary outcome “PFS”. The median follow-up observation period was 35.8 months in patients with ibrutinib monotherapy.

27 patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for other reasons can be identified from the publication Burger 2019. 15 of these 27 patients received treatment with ibrutinib. The company included these 15 patients in the comparison of individual arms from different studies.

In the publication of Burger 2019, results are only reported for the outcome “overall response” for the subpopulation relevant for research question 3.

### ***Woyach 2018***

The phase III study described by Woyach 2018 [14] is a 3-arm multicentre RCT with open-label study design [15].

It included a total of 547 adults ( $\geq 65$  years) with untreated CLL for whom treatment in accordance with the IWCLL criteria (2008) [4] was indicated.

The study compared the 3 therapies bendamustine + rituximab, ibrutinib as well as ibrutinib + rituximab. In the study arm that was relevant for the comparison of individual arms from different studies, 182 patients received 420 mg ibrutinib per day, until progression of the disease or until the onset of unacceptable intolerances.

PFS was the primary outcome of the study, further patient-relevant outcomes were, for instance, “overall survival” and “AEs”. The patients were observed over periods from 6 months to 10 years [15], the median follow-up observation period was 38 months. The median treatment duration in the ibrutinib arm was 32 months at the time point of the data cut-off.

9 patients with del17p who were treated with ibrutinib could be identified from the publication Woyach 2018. 15 patients treated with ibrutinib were found to have TP53 mutation. The publication does not particularly describe the extent of the intersection between patients with del17p and TP53 mutation. Moreover, the publication contains no analyses for a joint subpopulation of patients with del17p and/or TP53 mutation.

For the subpopulation relevant for research question 3, the publication of Woyach 2018 contains an analysis on PFS in patients with del17p (N=9), which the company used for the comparison of individual arms from different studies.

### ***Ahn 2018***

A single-arm phase II study with open-label study design was described in the publication of Ahn 2018 [12].

A total of 86 patients were enrolled in the study. One of the inclusion criteria was the presence of CLL/SLL requiring treatment [4] in combination with 17p deletion, TP53 mutation or an age  $\geq 65$  years. All patients included in the study were jointly analysed as single-arm study. Moreover, separate analyses were conducted for the 51 patients with TP53 mutation (and possibly 17p deletion) included in the study, and for the 35 patients without TP53 mutation aged  $\geq 65$  years. 4 weeks had to have passed since any received pretreatment.

Ibrutinib was administered at a dosage of 420 mg once daily until progression of the disease or the onset of unacceptable intolerances.

Primary outcome was the overall response after 6 months (assessed according to the IWCLL criteria (2008) [4]), with other outcomes including “overall survival”, “PFS” and “AEs”. The median follow-up observation period was 4.8 years.

35 patients from those patients with TP53 mutation included in the study were treatment-naive. These were used by the company for the comparison of individual arms from different studies.

In Ahn's 2018 publication, no effect estimations are reported for the subpopulation relevant for research question 3, but Kaplan-Meier curves are available for the outcomes "PFS" and "overall survival" for the relevant subpopulation.

### **Approach of the company**

For a comparison of individual arms from different studies on research question 3, the company conducted a descriptive comparison of the results from its own study iLLUMINATE for ibrutinib + obinutuzumab; for the ACT "ibrutinib" it conducted a descriptive comparison of the results on the outcomes "overall survival", "PFS" and "overall response" from the publications of Burger 2019, Woyach 2018 and Ahn 2018 [12-14]1. Due to a lack of a dramatic effect and to the heterogeneous study design of the studies considered and the associated high uncertainty, the company did not use the comparisons of individual arms from different studies to derive the added benefit and considered an added benefit as not proven.

### **Assessment of the comparison of individual arms from different studies presented by the company**

The assessment of the company on the relevance of its comparison of individual arms from different studies is adequate.

### ***Lack of suitability for the derivation of an added benefit***

When comparing individual arms from different studies, the uncertainty of results is high and conclusions on the added benefit are usually only possible if very large effects are present. The differences in the results presented by the company are not large enough for any of the outcomes to prevent them from being explained by systematic bias alone.

Analyses on the outcomes "overall survival", "PFS" and "overall response" are available for the comparison of individual arms from different studies. Results for a comparison are not available for further patient-relevant outcomes on "symptoms", "health-related quality of life" and "side effects". Balancing of benefit and harm was therefore not possible on the basis of the comparison presented by the company.

For these reasons, the comparison of individual arms from different studies presented by the company for research question 3 is unsuitable for an assessment of the added benefit of ibrutinib and is therefore not included in the present benefit assessment and is not considered further.

### **2.5.2 Results on added benefit**

The company presented no suitable data for the assessment of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT "ibrutinib" for patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason. This resulted

in no hint of an added benefit of ibrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

### **2.5.3 Probability and extent of added benefit**

Since the company presented no appropriate data for the assessment of the added benefit of ibrutinib + obinutuzumab versus the ACT ibrutinib in patients with del17p and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason, an added benefit of ibrutinib + obinutuzumab is not proven for this population.

This concurs with the company's assessment.

### **2.5.4 List of included studies**

Not applicable as the company did not present any relevant data for the benefit assessment.

## **2.6 Probability and extent of added benefit – summary**

The result of the assessment of the added benefit of ibrutinib + obinutuzumab in comparison with the ACT is summarized in Table 19.

Table 19: Ibrutinib + obinutuzumab – Probability and extent of added benefit

Subindication <sup>a</sup>	ACT <sup>b</sup>	Probability and extent of added benefit
1: Adult patients with previously untreated CLL for whom treatment with fludarabine in combination with cyclophosphamide and rituximab (FCR) is an option	Fludarabine in combination with cyclophosphamide and rituximab	Added benefit not proven
2: Adult patients with previously untreated CLL for whom FCR therapy is not an option	Bendamustine in combination with rituximab or ofatumumab <i>or</i> <b>chlorambucil in combination with rituximab</b> or <b>obinutuzumab</b> or ofatumumab	<ul style="list-style-type: none"> <li>▪ Women: hint of minor added benefit</li> <li>▪ men: added benefit not proven</li> </ul>
3: Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib	Added benefit not proven
<p>a. For the present therapeutic indication, the company assumed that the patients were in need of treatment. Moreover, it was assumed that allogeneic stem cell transplantation was not indicated at the time point of treatment.</p> <p>b. 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 <b>bold</b>.</p> <p>17p: short arm of chromosome 17; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein 53</p>		

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

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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*The full report (German version) is published under*

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