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Ibrutinib (chronic lymphocytic leukaemia) –

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

Extract

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Table of contents

Page

List of tables ..... **v**
List of abbreviations ..... **vi**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **9**
2.3 Research question 1: patients for whom treatment with FCR is an option **10**
2.3.1 Information retrieval and study pool 10
2.3.1.1 Information retrieval 10
2.3.1.2 Studies included 10
2.3.1.3 Study characteristics 11
2.3.1.3.1 Study and intervention characteristics 11
2.3.1.3.2 Planned treatment duration and follow-up observation 15
2.3.1.3.3 Data cut-offs 16
2.3.1.3.4 Method of analysis 17
2.3.1.3.5 Characteristics of the population 17
2.3.1.3.6 Treatment duration and observation period as well as subsequent therapies 19
2.3.1.3.7 Risk of bias across outcomes (study level) 21
2.3.1.3.8 Transferability of the study results to the German health care context 21
2.3.2 Results on added benefit 22
2.3.2.1 Outcomes included 22
2.3.2.2 Risk of bias 24
2.3.2.3 Results 26
2.3.2.4 Subgroups and other effect modifiers 33
2.3.3 Probability and extent of added benefit 34
2.3.3.1 Assessment of the added benefit at outcome level 34
2.3.3.2 Overall conclusion on added benefit 38
2.4 Research question 2: patients for whom treatment with FCR is not an option **40**
2.4.1 Information retrieval and study pool 40
2.4.2 Results on added benefit 40
2.4.3 Probability and extent of added benefit 41
2.5 Research question 3: patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons **41**
2.5.1 Information retrieval and study pool 41

2.5.2 Results on added benefit 41
2.5.3 Probability and extent of added benefit 41
2.6 Probability and extent of added benefit – summary 42
References for English extract 42

List of tables[2]

Page

Table 2: Research questions of the benefit assessment of ibrutinib + rituximab 1
Table 3: Ibrutinib + rituximab – probability and extent of added benefit 8
Table 4: Research questions of the benefit assessment of ibrutinib + rituximab 9
Table 5: Study pool – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 10
Table 6: Characteristics of the included study – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 12
Table 7: Characteristics of the interventions – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 13
Table 8: Planned duration of follow-up observation – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 16
Table 9: Characteristics of the study population – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 18
Table 10: Information on the course of the study – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 20
Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 21
Table 12: Matrix of outcomes – ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 23
Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 25
Table 14: Results (mortality, side effects) – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 27
Table 15: Results (morbidity) – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 29
Table 16: Extent of added benefit at outcome level: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) 35
Table 17: Positive and negative effects from the assessment of ibrutinib + rituximab in comparison with FCR (patients for whom FCR therapy is an option) 39
Table 18: Ibrutinib + rituximab – probability and extent of added benefit 42

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
11q deletion	deletion of the long arm of chromosome 11
17p deletion	deletion of the short arm of chromosome 17
ACT	appropriate comparator therapy
AE	adverse event
ANCOVA	analysis of covariance
BSA	body surface area
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-ACRIN	Eastern Cooperative Oncology Group – American College of Radiology Imaging Network
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FCR	fludarabine + cyclophosphamide + rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IGHV	immunoglobulin heavy-chain variable region
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small lymphocytic lymphoma
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
TOI	Trial Outcome Index
TP53 mutation	mutation of the tumour protein p53
WHO	World Health Organization

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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 October 2020.

Research question

The aim of the present report is the assessment of the added benefit of ibrutinib in combination with rituximab (hereinafter referred to as "ibrutinib + rituximab") 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. Table 2 shows the resulting 3 research questions for the present benefit assessment.

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

Research question	Subindication[a]	ACT[b]
1	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR
2	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Bendamustine in combination with rituximab or chlorambucil in combination with rituximab or obinutuzumab
3	Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA.

17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

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

- Research question 1: patients for whom treatment with fludarabine + cyclophosphamide + rituximab (FCR) is an option
- Research question 2: patients for whom treatment with FCR is not an option
- Research question 3: patients with deletion of the short arm of chromosome 17 (17p deletion) and/or mutation of the tumour protein p53 (TP53 mutation) or for whom chemo-immunotherapy is not indicated for other reasons

The company followed the ACT in all 3 research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided 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

Study pool and study characteristics

The study pool for research question 1 consists of the ECOG-E1912 study. This is an open-label, randomized, controlled, multicentre study on the direct comparison of ibrutinib + rituximab with FCR, conducted exclusively in the USA.

The ECOG-E1912 study included adults (between 18 and 70 years of age) with CLL according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (2008) or small lymphocytic lymphoma (SLL) according to the World Health Organization (WHO) criteria, each previously untreated and in need of treatment. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) between 0 and 2 and no 17p deletion.

The company presented analyses for the relevant subpopulation of those patients for whom FCR therapy was an option in accordance with the criteria of the Summaries of Product Characteristics (SPCs) and guidelines. These were 141 of the 354 patients in the ibrutinib + rituximab arm and 65 of the 175 patients in the FCR arm.

In the intervention arm, treatment with ibrutinib + rituximab was given in compliance with the SPC for ibrutinib. Accordingly, ibrutinib was given until disease progression or until the occurrence of unacceptable intolerances. The administration of rituximab in the intervention arm was limited to cycles 2 to 7. In the control arm, treatment was given in cycles 1 to 6, with fludarabine and cyclophosphamide being given as combination partners of rituximab, which is in compliance with the SPC for rituximab. The administration of rituximab deviates slightly from the recommendations of the SPC, as the dose for cycle 1 was not administered as a total dose of 375 mg/m² body surface area (BSA) IV on day 1, but had been divided into 2 subdoses (50 mg/m² BSA IV on day 1 and 325 mg/m² BSA IV on day 2). Study treatment was ended at any time upon the occurrence of at least one of the following discontinuation criteria: disease progression (assessed based on the 2008 iwCLL criteria), death, occurrence of unacceptable toxicity, or withdrawal of consent.

The primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, morbidity, and adverse events (AEs).

The ECOG-E1912 study is still ongoing, and results are available for 2 data cut-offs. The first data cut-off was scheduled for 24 to 27 months after completion of recruitment and was conducted on 17 July 2018. All outcomes were analysed. The prespecified efficacy criterion for PFS was achieved with the first data cut-off. The second data cut-off was performed at the request of the European Medicines Agency; it included only PFS and overall survival and was conducted on 2 August 2019. With the exception of overall survival, the results of the first data cut-off were used to derive the added benefit.

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", and as high for all other outcomes.

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcome "overall survival". Due to the high risk of bias, at most hints, e.g. of an added benefit, can be determined for the other outcomes.

For the specific AEs "lymphocyte count decreased" and "white blood cell count decreased" (each defined as Preferred Term [PT] in accordance with the Medical Dictionary for Regulatory Activities [MedDRA], severe AEs [Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3]), the certainty of results is not reduced despite the high risk of bias because the observed effect is very large.

Mortality

Overall survival

Both the main analysis and the sensitivity analysis showed a statistically significant advantage of ibrutinib + rituximab in comparison with FCR for the outcome "overall survival". This resulted in an indication of an added benefit of ibrutinib + rituximab in comparison with FCR.

Morbidity

Functional Assessment of Cancer Therapy – Leukemia – Trial Outcome Index (FACT-Leu TOI)

No statistically significant difference between the 2 treatment arms was shown for the morbidity outcome "FACT-Leu TOI". Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; an added benefit is therefore not proven.

Health-related quality of life

Deviating from the company's approach, the FACT-Leu TOI was assigned to morbidity and not to health-related quality of life. Thus, no data for health-related quality of life were

available. Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; an added benefit is therefore not proven.

Side effects

When interpreting the results on side effects, it should be noted that the fixed treatment duration and the associated discontinuation of observation in the control arm mean that the hazard ratio only reflects approximately the first 9 months after randomization.

SAEs

No results are available for the outcome "serious adverse events (SAEs)", as the data recording does not allow an analysis of the comparison of the 2 treatment arms. Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Discontinuation due to AEs (≥ 1 component)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the outcome "discontinuation due to AEs (≥ 1 component)". This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Haemorrhage

Major haemorrhage (Standardized MedDRA Query [SMQ] haemorrhage terms [excl laboratory terms], severe AEs [CTCAE grade ≥ 3])

No results are available for the outcome "major haemorrhage" (SMQ haemorrhage terms [excl laboratory terms], severe AEs [CTCAE grade ≥ 3]). Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

Haemorrhage (SMQ haemorrhage terms [excl laboratory terms], AEs)

The company only presented the proportions of patients with event per study arm for the outcome "haemorrhage" (SMQ haemorrhage terms [excl laboratory terms], AEs). The company did not present an effect estimation and a p-value based on an event time analysis. There were therefore no usable results available. Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

Contusion (PT, AEs)

A statistically significant difference to the disadvantage of ibrutinib + rituximab was shown for the specific AEs "contusion" (PT, AEs), which is part of the SMQ haemorrhage terms (excl

laboratory terms). This resulted in a hint of greater harm of ibrutinib + rituximab in comparison with FCR.

Infections and infestations (System Organ Class [SOC], AEs)

No statistically significant difference between the treatment arms was shown for the outcome "infections and infestations" (SOC, AEs). Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

Upper respiratory tract infection (PT, AE)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the specific AEs "upper respiratory tract infection" (PT, AEs). This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])

No statistically significant difference between the treatment arms was shown for the outcome "cardiac disorders" (SOC, severe AEs [CTCAE grade ≥ 3]). Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

The results of all other specific AEs are described below in summary form according to the direction of effect.

Further specific AEs in favour of ibrutinib + rituximab

Cytopenias: lymphocyte count decreased, white blood cell count decreased, febrile neutropenia and platelet count decreased (each PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for each of the following specific AEs: lymphocyte count decreased, white blood cell count decreased, febrile neutropenia, and platelet count decreased (each PT, severe AEs [CTCAE grade ≥ 3]).

This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR for each of the outcomes "febrile neutropenia" and "platelet count decreased" (each PT, severe AEs [CTCAE grade ≥ 3]). For the outcomes "lymphocyte count decreased" and "white blood cell count decreased" (each PT, severe AEs [CTCAE grade ≥ 3]), there was an indication of lesser harm of ibrutinib + rituximab in comparison with FCR due to the size of the respective observed effects.

Hyperglycaemia (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the specific AEs "hyperglycaemia" (PT, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Nausea, constipation, vomiting and decreased appetite (each PT, AE)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the following specific AEs: nausea, constipation, vomiting and decreased appetite (each PT, AEs). In each case, this resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Pollakiuria (PT, AEs)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the outcome "pollakiuria" (PT, AEs). This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Further specific AEs to the disadvantage of ibrutinib + rituximab

Lymphocyte count increased and leucocytosis (each PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of ibrutinib + rituximab was shown for each of the specific AEs "lymphocyte count increased" and "leucocytosis" (each PT, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of greater harm of ibrutinib + rituximab in comparison with FCR.

Results for research question 2: patients for whom treatment with FCR is not an option

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

Results for research question 3: patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

The company presented no data for the assessment of the added benefit of ibrutinib + rituximab in comparison with the ACT for patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons. This resulted in no hint of an added benefit of ibrutinib + rituximab 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[3]

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

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

In the overall assessment, there are positive and negative effects, which, with the exception of the outcomes "overall survival", "lymphocyte count decreased" and "white blood cell count decreased" (each indication) have the probability of a hint.

There was an indication of a major added benefit for the outcome "overall survival". At the level of side effects, there was lesser harm of minor extent for the overall rate of severe AEs (CTCAE grade ≥ 3), and lesser harm of considerable extent for discontinuations due to AEs, each with the probability of a hint.

There were mainly positive and few negative effects within the severe (CTCAE grade ≥ 3) and the non-serious/non-severe side effects.

There were no results for the outcome category of health-related quality of life.

In summary, there is an indication of a major added benefit of ibrutinib + rituximab in comparison with the ACT FCR for patients with previously untreated CLL for whom treatment with FCR is an option.

Research question 2: patients for whom treatment with FCR is not an option

Since the company did not present any data for the assessment of the added benefit of ibrutinib + rituximab in patients for whom treatment with FCR is not an option, an added benefit of ibrutinib + rituximab for this population is not proven.

Research question 3: patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Since the company presented no data for the assessment of the added benefit of ibrutinib + rituximab in patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons, an added benefit of ibrutinib + rituximab is not proven for this population.

[3] 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].

Table 3 shows a summary of the probability and extent of the added benefit of ibrutinib + rituximab.

Table 3: Ibrutinib + rituximab – probability and extent of added benefit

Research question	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR	Indication of major added benefit
2	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Bendamustine in combination with rituximab or chlorambucil in combination with rituximab or obinutuzumab	Added benefit not proven
3	Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	Added benefit not proven

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA.

17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The approach for the derivation of 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 the present report is the assessment of the added benefit of ibrutinib in combination with rituximab (hereinafter referred to as "ibrutinib + rituximab") 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. Table 4 shows the resulting 3 research questions for the present benefit assessment.

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

Research question	Subindication[a]	ACT[b]
1	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR
2	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Bendamustine in combination with rituximab or chlorambucil in combination with rituximab or obinutuzumab
3	Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA.

17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

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

- Research question 1: patients for whom treatment with FCR is an option
- Research question 2: patients for whom treatment with FCR is not an option
- Research question 3: patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

The company followed the specification of the G-BA regarding the ACT in all 3 research questions.

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

2.3 Research question 1: patients for whom treatment with FCR is an option

2.3.1 Information retrieval and study pool

2.3.1.1 Information retrieval

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ibrutinib (status: 3 August 2020)
- bibliographical literature search on ibrutinib (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on ibrutinib (last search on 3 August 2020)
- search on the G-BA website for ibrutinib (last search on 7 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 8 October 2020)

The check did not identify any additional relevant studies.

2.3.1.2 Studies included

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

Table 5: Study pool – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
E1912/ PCYC-1126e-CA (ECOG-E1912[c])	Yes	No[d]	Yes[d]	Yes [3-5]	Yes [6]]	Yes [7]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Hereinafter, the study is referred to with this abbreviated form.
d. The study was conducted by the ECOG-ACRIN group and sponsored by the NCI.

CSR: clinical study report; ECOG-ACRIN: Eastern Cooperative Oncology Group – American College of Radiology Imaging Network; FCR: fludarabine + cyclophosphamide + rituximab; NCI: National Cancer Institute; RCT: randomized controlled trial; vs.: versus

The study pool concurs with that of the company.

2.3.1.3 Study characteristics

2.3.1.3.1 Study and intervention characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ECOG-E1912	RCT, open-label, parallel	Patients with previously untreated CLL/SLL[b] in need of treatment without 17p deletion aged ≥ 18 years to ≤ 70 years and ECOG PS 0-2	Ibrutinib + rituximab (N = 354) FCR (N = 175) Relevant subpopulation thereof[c]: ibrutinib + rituximab (n = 141) FCR (n = 65)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, withdrawal of consent, or death (rituximab in the intervention arm and FCR in the control arm for a maximum of 6 cycles) Observation[d]: up to 10 years from study inclusion	201 centres in the USA 3/2014–ongoing Data cut-offs: 17 July 2018[e] 2 August 2019[f]	Primary: PFS Secondary: overall survival, morbidity, AEs

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. CLL diagnosis in accordance with NCI or iwCLL criteria, or SLL diagnosis in accordance with WHO criteria.
c. Treatment-naive CLL patients for whom treatment with FCR is an option.
d. Outcome-specific information is provided in Table 8.
e. First interim analysis was scheduled for 24-27 months after completion of recruitment (analysis of all outcomes).
f. Analysis for PFS and overall survival requested by the EMA.

17p deletion: deletion of the short arm of chromosome 17; AE: adverse event; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; FCR: fludarabine + cyclophosphamide + rituximab; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; n: relevant subpopulation; N: number of randomized patients; NCI: National Cancer Institute; PFS: progression-free survival; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; vs.: versus; WHO: World Health Organization

Table 7: Characteristics of the interventions – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Study	Intervention	Comparison
ECOG-E1912	Ibrutinib 420 mg, orally, once/day[a] (from day 1) + rituximab Cycle 2: 50 mg/m² BSA IV on day 1, 325 mg/m² BSA IV on day 2 Cycles 3–7: 500 mg/m² BSA IV on day 1	Fludarabine phosphate 25 mg/m² BSA IV on days 1, 2 and 3 (cycles 1–6) + cyclophosphamide 250 mg/m² BSA IV on days 1, 2 and 3 (cycles 1–6) + rituximab Cycle 1: 50 mg/m² BSA IV on day 1, 325 mg/m² IV on day 2 Cycles 2–6: 500 mg/m² BSA IV on day 1
	Each cycle is 28 days.	
	Dose adjustments:	
	▪ ibrutinib: in case of CTCAE grade ≥ 3 AEs, treatment interruption until CTCAE grade ≤ 1 is reached, then resumption at reduced dose (by 140 mg/day each) with the option of re-escalation after 2 cycles; ▪ discontinuation of treatment from the 4th occurrence of an AE associated with ibrutinib, or if > 60 days of interruption due to non-toxicity-related AEs	▪ fludarabine and cyclophosphamide: dose reduction in case of haematological AEs or CTCAE grade ≥ 2 non-haematological AEs (no re-escalation thereafter); ▪ in case of neutropenia: interruption of all treatment components (resumption of fludarabine and cyclophosphamide at a lower dose level); ▪ treatment discontinuation of all components if interrupted > 56 days, after 2nd dose reduction or autoimmune cytopenia
	▪ no dose adjustments for rituximab; if treatment with rituximab was discontinued, administration of the other treatment components could be continued	
	Pretreatment <u>Not allowed:</u> ▪ chemotherapy, BTK inhibitor, monoclonal antibody therapy for treatment of CLL or SLL ▪ corticosteroids for autoimmune complications that have developed since the first diagnosis of CLL ▪ antibiotic therapy within 14 days before the first dose of study medication ▪ warfarin or other vitamin K antagonists within 30 days before study inclusion ▪ live vaccines within 4 weeks before the first dose of study medication ▪ radiotherapy within 4 weeks before study inclusion ▪ major surgery within 28 days or minor surgery within 3 days before the first dose of study medication ▪ systemic immunosuppressive therapy other than corticosteroids within 28 days before the first dose of study medication	

Table 7: Characteristics of the interventions – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Study	Intervention	Comparison
	Concomitant treatment All patients: ▪ premedication before rituximab: ▫ hydrocortisone 100 mg IV (before doses 1 and 2, then in case of uncontrolled AEs) ▫ diphenhydramine 50 mg IV or orally (alternatively antihistamine) and paracetamol 650 mg orally 30 minutes before the rituximab infusion ▪ antiemetics before fludarabine and cyclophosphamide ▪ supportive treatment: ▫ allopurinol 300 mg daily on days 1–14 of cycle 1, or also in cycle 2 in the intervention arm only, thereafter at the discretion of the investigator ▫ prophylactic treatment with - antibiotic sulfamethoxazole/trimethoprim (or alternative), 1 tablet each 3 times per week (Mondays/Wednesdays/Fridays) - aciclovir 400 mg 2 times daily from cycle 1 to week 52 Allowed: ▪ low doses of steroids (< 10 mg prednisone or equivalent) for the treatment of non-haematological conditions (up to 14 days); for autoimmune cytopenias only allowed in the intervention arm ▪ neutrophil growth factors (filgrastim, sargramostim, PEG-filgrastim) for the treatment of febrile neutropenia ▪ erythropoietin Not allowed: ▪ strong CYP3A inhibitors ▪ chemotherapy, anticancer immunotherapy, other study medication or radiotherapy	
a. Treatment from cycle 1 until disease progression, unacceptable toxicity, withdrawal of consent, or death. AE: adverse event; BSA: body surface area; BTK: Bruton tyrosine kinase; CLL: chronic lymphocytic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; CYP3A: cytochrome P450 3A; FCR: fludarabine + cyclophosphamide + rituximab; IV: intravenous; PEG: pegylated; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; vs.: versus		

The ECOG-E1912 study is an open-label, randomized, controlled, multicentre study on the direct comparison of ibrutinib + rituximab with FCR. The ECOG-E1912 study is conducted by the Eastern Cooperative Oncology Group – American College of Radiology Imaging Network (ECOG-ACRIN) study group; all study centres are located in the USA.

The ECOG-E1912 study included adults (between 18 and 70 years of age) with CLL according to iwCLL criteria (2008) [8] or SLL according to the WHO criteria [9], each previously untreated and in need of treatment. The patients had to have an ECOG PS between 0 and 2 and no 17p deletion.

A total of 529 patients were randomly assigned in a ratio of 2:1, either to treatment with ibrutinib + rituximab (354 patients) or to treatment with FCR (175 patients). Stratification factors were age (< 60 years versus ≥ 60 years) ECOG PS (0 or 1 versus 2), Rai stage (I–II

versus III–IV) and cytogenetic status at study inclusion (deletion of the long arm of chromosome 11 [11q deletion] versus others).

Only a subpopulation of the ECOG-E1912 study is relevant to the present research question (see Section 2.3.1.3.3).

In the intervention arm, treatment with ibrutinib + rituximab was given in compliance with the SPC for ibrutinib [10]. Accordingly, ibrutinib was given until disease progression or until the occurrence of unacceptable intolerances. The administration of rituximab in the intervention arm was limited to cycles 2 to 7. In the control arm, treatment was given in cycles 1 to 6, with fludarabine and cyclophosphamide being given as combination partners of rituximab, which is in compliance with the SPC for rituximab [11]. The administration of rituximab deviates from the recommendations of the SPC, as the dose for cycle 1 was not administered as a total dose of 375 mg/m² BSA IV on day 1, but had been divided into 2 subdoses (50 mg/m² BSA IV on day 1 and 325 mg/m² BSA IV on day 2). This deviation has no consequence for the present benefit assessment.

The primary outcome is PFS. Patient-relevant secondary outcomes are overall survival, morbidity, and AEs.

2.3.1.3.2 Planned treatment duration and follow-up observation

Treatment with rituximab (in addition to ibrutinib) in the intervention arm and with FCR in the control arm was for 6 cycles of 28 days each or until the occurrence of at least one of the following discontinuation criteria: disease progression (assessed using the 2008 iwCLL criteria [8]), death, occurrence of unacceptable toxicity, or withdrawal of consent. If rituximab was discontinued, treatment with the other components could be continued. After the end of treatment with rituximab in the intervention arm, treatment with ibrutinib as monotherapy was continued until at least one of the discontinuation criteria occurred. Supportive treatments (e.g. antiemetics, corticosteroids) were given in addition to the study treatment. Further supportive treatments (e.g. with neutrophil growth factors) were also allowed. If patients in the control arm experienced progression after completion of the study treatment, they could be treated at the discretion of the investigator.

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ECOG-E1912	
Mortality	
Overall survival	Until death or end of study
Morbidity	
FACT-Leu TOI[a]	Up to 3 years after study inclusion, independent of disease progression
Health-related quality of life	Not recorded[b]
Side effects	
AEs, severe AEs[c] and AEs leading to treatment discontinuation	Up to 30 days after end of therapy or 1 day before start of follow-up therapy (whichever occurred first)[d]

a. The FACT-Leu TOI is assigned to morbidity because it does not cover all dimensions of health-related quality of life.
b. Of the FACT-Leu, only the PWB and FWB subscales and the leukaemia-specific Leu module were completed (see also Section 2.3.2.1).
c. Operationalized as CTCAE grade ≥ 3.
d. Observation of certain toxicities and secondary malignancies was continued beyond the 30 days after the end of therapy. The information provided by the company in Module 4 A, according to which AEs were documented up to 10 years after study inclusion, cannot be verified on the basis of the study documents.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia; FCR: fludarabine + cyclophosphamide + rituximab; FWB: functional wellbeing; PWB: physical wellbeing; RCT: randomized controlled trial; TOI: Trial Outcome Index; vs.: versus

The observation periods for the outcomes of morbidity and side effects were systematically shortened. The data on side effects were only recorded for the period of treatment with the study medication (plus 30 days), whereas the data on morbidity were recorded up to 3 years after study inclusion (regardless of disease 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.

2.3.1.3.3 Data cut-offs

Results on 2 data cut-offs are available for the ECOG-E1912 study. The first data cut-off was scheduled for 24 to 27 months after completion of recruitment and was conducted on 17 July 2018. All outcomes were analysed. The second data cut-off was performed at the request of the European Medicines Agency; it included only PFS and overall survival and was conducted on 2 August 2019. With the exception of overall survival, the results of the first data cut-off were used to derive the added benefit.

The study is ongoing. According to the statistical analysis plan (SAP), further annual analyses for overall survival are to be conducted until the criteria for the premature end of the study or 125 deaths have occurred.

2.3.1.3.4 Method of analysis

There are 2 versions of the SAP for the ECOG-E1912 study, and it is unclear whether they were prepared with knowledge of the publication of results on overall survival and PFS by Shanafelt 2018 [12]. The company stated in Module 4 A that it did not gain access to the data until 2 August 2019 and thus after finalization of version 2 of the SAP (26 March 2019). In addition, all analyses of the SAP versions had already been outlined in Protocol Amendments 6 (dated 1 December 2016) and 8 (dated 25 May 2018).

However, there are 2 changes in particular between the two SAP versions that are not based on any protocol changes outlined earlier:

- For overall survival, stratified analyses were replaced by an unstratified log-rank test and an unstratified Cox regression citing the number of death events.
- The analysis of covariance (ANCOVA), which was planned for the FACT-Leu TOI and was not specified further, was replaced by a mixed-effects model with repeated measures (MMRM) without further explanations.

Since for overall survival, both the stratified and the unstratified analysis are available for the total population of the ECOG-E1912 study at the first data cut-off, and the 2 results do not differ, this change is not assumed to have an effect on the overall survival data relevant to this assessment. The effect of the change in the analyses of the FACT-Leu TOI, on the other hand, cannot be estimated on the basis of the available information. This is taken into account when determining the risk of bias of the results on the FACT-Leu TOI (see Section 2.3.2.2).

2.3.1.3.5 Characteristics of the population

For the dossier assessment, the company used the criteria specified by the G-BA [13] to check for which patients in the ECOG-E1912 study treatment with FCR was an option, and presented the results for this subpopulation as the main analysis and the results of the entire study population as supplementary information.

The company used the following criteria (cut-off values) to select the relevant subpopulation: TP53 mutation (unmutated), creatinine clearance (≥ 70 mL/min), age (≤ 65 years), ECOG PS (< 2), Cumulative Illness Rating Scale (CIRS) (≤ 6), platelet count (≥ 100 000/µL) and haemoglobin (≥ 10 g/dL).

The criteria and cut-off values used by the company are consistent with the information in the SPC for fludarabine [14] and cyclophosphamide [15], the German S3 guideline [16] and the G-BA [13]. They are therefore suitable for selecting the relevant subpopulation. Therefore, the results of the relevant subpopulation were used to derive the added benefit.

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

Table 9: Characteristics of the study population – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Study **Characteristic** **Category**	**Ibrutinib + rituximab** **N = 141**	**FCR** **N = 65**
ECOG-E1912		
Age [years], mean (SD)	55 (7)	54 (7)
Sex [F/M], %	28/72	31/69
Family origin, n (%)		
White	131 (93)	58 (89)
Not white or missing	10 (7)[a]	7 (11)[a]
Disease duration: time from diagnosis to randomization [months], median [Q1; Q3]	9.7 [1.3; 36.0]	17.0 [1.2; 48.4]
Histology, n (%)		
CLL	116 (82)	59 (91)
SLL	25 (18)	6 (9)
Rai stage, n (%)		
0/I/II	117 (83)	56 (86)
III/IV	24 (17)	9 (14)
Bulky disease, n (%)		
≥ 10 cm	11 (8)	5 (8)
≥ 5 cm	51 (36)	25 (38)
Unknown	4 (3)	3 (5)
Cytopenia[b], n (%)	31 (22)	12 (18)
ECOG PS (0 or 1), n (%)	141 (100)	65 (100)
Creatinine clearance (≥ 70 mL/min), n (%)	141 (100)	65 (100)
Beta 2 microglobulin (mg/L), n (%)		
≤ 3.5	80 (57)	35 (54)
> 3.5	61 (43)	30 (46)
11q deletion, n (%)		
Yes	37 (26)	15 (23)
No	103 (73)	50 (77)
Unknown	1 (1)	0 (0)
IGHV, n (%)		
Unmutated	98 (70)	32 (49)
Mutated	28 (20)	20 (31)
Unknown	15 (11)	13 (20)
CIRS ≤ 6, n (%)	141 (100)	65 (100)
Treatment discontinuation, n (%)[c]	26 (18)	16 (25)
Study discontinuation, n (%)	3 (2)	15[d] (23)

a. Institute's calculation.
b. Haemoglobin ≤ 110 g/L or platelets ≤ 100 x 10^9/L or absolute neutrophil count ≤ 1.5 x 10^9/L
c. Information on the first data cut-off from 17 July 2018.
d. Including 6 deaths.

Table 9: Characteristics of the study population – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Study Characteristic Category	Ibrutinib + rituximab N = 141	FCR N = 65
11q deletion: deletion of the long arm of chromosome 11; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FCR: fludarabine + cyclophosphamide + rituximab; IGHV: immunoglobulin heavy-chain variable region; M: male; n: number of patients in the category; N: number of randomized patients; Q1: first quartile or 25% quantile; Q3: third quartile or 75% quantile; RCT: randomized controlled trial; SD: standard deviation; SLL: small lymphocytic lymphoma; vs.: versus		

The patient characteristics are largely comparable between the treatment arms. The mean age was 55 years and the proportion of men was about 70%; most patients (90%) were of white family origin. The majority of patients (about 85%) had mild disease (Rai stage 0, I or II). CLL was present in 82% of patients in the intervention arm and 91% of patients in the control arm.

Notable differences between the treatment arms were shown in particular for the characteristics of disease duration and immunoglobulin heavy-chain variable region (IGHV) mutation status. The median duration of disease at study inclusion was 9.7 months in the intervention arm and 17.0 months in the control arm. In 70% versus 49% of patients, there was an unfavourable prognosis due to unmutated IGHV (see for example [16,17]).

The different proportions of patients with mutated and unmutated IGHV probably did not have a relevant effect on the study result. The subgroup analyses presented by the company in Module 4 A (Section 4.3.1.3.2) at least show no statistically significant interaction due to the IGHV mutation status (mutated versus unmutated).

The notable differences have no consequences for the benefit assessment.

2.3.1.3.6 Treatment duration and observation period as well as subsequent therapies

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 + rituximab vs. FCR (patients for whom FCR therapy is an option)

Study **Duration of the study phase** **Outcome category**	**Ibrutinib + rituximab** **N = 141**	**FCR** **N = 65**
ECOG-E1912		
Treatment duration [months]		
Median [Q1; Q3]	ND	ND
Observation period [months]		
Overall survival (DCO 1)[a]		
Median (95% CI)	37.5 (ND)	35.5 (ND)
Overall survival (DCO 2)[a]		
Median (95% CI)	47.5 (ND)	42.7 (ND)
Morbidity (FACT-Leu TOI[b], DCO 1)[c]		
Median [Q1; Q3]	30.7 (ND)	24.0 (ND)
Health-related quality of life	Not recorded	
Side effects[d] (DCO 1)		
Median [Q1; Q3]	34.1 (ND)	4.8 (ND)

a. Per inverse Kaplan-Meier method: Censorings in the observation of overall survival are treated as events, death events as censorings.
b. The FACT-Leu TOI is assigned to morbidity because it does not cover all dimensions of health-related quality of life.
c. Median of the observed values of the observation periods based on the last period used in the MMRM analyses.
d. Time since treatment start to discontinuation date + 30 days or data cut-off date, whichever was first, using the median of the observed values of the observation periods.

DCO: data cut-off; FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia; FCR: fludarabine + cyclophosphamide + rituximab; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; Q1: first quartile or 25% quantile; Q3: first quartile or 75% quantile; RCT: randomized controlled trial; TOI: Trial Outcome Index; vs.: versus

There is no information on the treatment duration. Observation of the outcomes for overall survival and morbidity was slightly longer in the intervention arm than in the control arm. The fixed treatment duration in the control arm and linking the observation period for side effects to the treatment duration led to a notably longer observation period for the side effect outcomes in the intervention arm (median 34 months) than in the control arm (median 5 months). This difference in observation periods was taken into account when deriving the outcome-specific risk bias of some outcomes (see Section 2.3.2.2).

There are no data on subsequent therapies after the end of the study medication; an assessment of the frequency of subsequent therapies and the type of subsequent therapies used is therefore not possible. Since the study protocol did not restrict the administration of subsequent therapies, there is no consequence for the present benefit assessment.

2.3.1.3.7 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 + rituximab vs. FCR (patients for whom FCR therapy is an option)

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			
ECOG-E1912	Yes	Yes	No	No	Yes	Yes	Low
FCR: fludarabine + cyclophosphamide + 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 in Section 2.3.2 with the outcome-specific risk of bias.

2.3.1.3.8 Transferability of the study results to the German health care context

When discussing the transferability of the ECOG-E1912 study, which was conducted exclusively in the USA, the company referred to the high proportion of Caucasian patients and stated that the treatment regimen used in the ECOG-E1912 study is common in Germany.

In addition, the company compared the results on overall survival of FCR treatment in the control arm of the ECOG-E1912 study with the results of FCR treatment in 2 studies [18,19] that were conducted by the German CLL study group in patients with previously untreated CLL and mainly in Germany. The company derived the transferability of the results of the ECOG-E1912 study on the basis of the survival rate after 3 years and the proportion of patients with treatment discontinuation due to side effects.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - FACT-Leu TOI
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - haemorrhage
    - major haemorrhage (SMQ haemorrhage terms [excl laboratory terms][4], severe AEs [CTCAE grade ≥ 3])
    - haemorrhage (SMQ haemorrhage terms [excl laboratory terms][1], AEs)
  - infections and infestations (SOC, AEs)
  - cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

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

[4] "Excluding laboratory terms" means that the SMQ does not include any PTs resulting from laboratory investigations.

Table 12: Matrix of outcomes – ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option)

Study	Outcomes										
	Overall survival	Morbidity (FACT-Leu TOI)[a]	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Major haemorrhage (SMQ haemorrhage terms [excl laboratory terms][c], severe AEs)[b]	Haemorrhage (SMQ haemorrhage terms [excl laboratory terms][c], AEs)	Infections and infestations (SOC, AEs)	Cardiac disorders (SOC, severe AEs[b])	Further specific AEs[d]
ECOG-E1912	Yes[e]	Yes	No[f]	No[g]	Yes	Yes	No[h]	No[i]	Yes	Yes	Yes

a. The FACT-Leu TOI is assigned to morbidity because it does not cover all dimensions of health-related quality of life.
b. Operationalized as CTCAE grade ≥ 3.
c. "Excluding laboratory terms" means that the SMQ does not include any PTs resulting from laboratory investigations.
d. The following events are considered (MedDRA coding): nausea (PT, AEs), constipation (PT, AEs), vomiting (PT, AEs), decreased appetite (PT, AEs), upper respiratory tract infection (PT, AEs), contusion (PT, AEs), pollakiuria, lymphocyte count decreased (PT, severe AEs [CTCAE grade ≥ 3]), white blood cell count decreased (PT, severe AEs [CTCAE grade ≥ 3]), febrile neutropenia (PT, severe AEs [CTCAE grade ≥ 3]), platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3]), leucocytosis (PT, severe AEs [CTCAE grade ≥ 3]), lymphocyte count increased (PT, severe AEs [CTCAE grade ≥ 3]), hyperglycaemia (PT, severe AEs [CTCAE grade ≥ 3]).
e. Results are not only available for the first data cut-off, but also for the second data cut-off.
f. Not recorded.
g. No data available, see below.
g. No results available.
i. In view of the differences in observation periods between the arms, a survival time analysis would be necessary; this is not available.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia; FCR: fludarabine + cyclophosphamide + 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; TOI: Trial Outcome Index; vs.: versus

In deviation from the company's approach, the FACT-Leu TOI was assigned to morbidity and not to health-related quality of life, as the FACT-Leu modules of social/family and emotional wellbeing were not used, and thus not all dimensions of health-related quality of life were recorded.

No results are available for the outcome "SAEs", as the data recording does not allow an analysis of the comparison of the 2 treatment arms. This is partly because the case report form was not designed to distinguish serious from non-serious AEs within all AEs recorded. In

addition, the criterion of whether an event is serious was included for the expedited reporting of AEs only in the intervention arm but not in the control arm. In the control arm, only events that were of CTCAE grade ≥ 4 were subject to expedited reporting; and of the CTCAE grade 4 events, only unexpected AEs that were at least likely to have a causal relationship with the treatment in the investigator's opinion were to be reported.

2.3.2.2 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 – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option)

Study	Study level	Outcomes										
		Overall survival	Morbidity (FACT-Leu TOI)[a]	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Major haemorrhage (SMQ haemorrhage terms [excl laboratory terms], severe AEs)[b, c]	Haemorrhage (SMQ haemorrhage terms [excl laboratory terms][c])	Infections and infestations (SOC, AEs)	Cardiac disorders (SOC, severe AEs[b])	Further specific AEs[d]
ECOG-E1912	L	L	H[e, f]	–[g]	–[h]	H[i]	H[e, i]	–[j]	–[k]	H[e, i]	H[i]	H[e, i]

a. The FACT-Leu TOI is assigned to morbidity because it does not cover all dimensions of health-related quality of life.
b. Operationalized as CTCAE grade ≥ 3.
c. "Excluding laboratory terms" means that the SMQ does not include any PTs resulting from laboratory investigations.
d. The following events are considered (MedDRA coding): nausea (PT, AEs), constipation (PT, AEs), vomiting (PT, AEs), decreased appetite (PT, AEs), upper respiratory tract infection (PT, AEs), contusion (PT, AEs), pollakiuria, lymphocyte count decreased (PT, severe AEs [CTCAE grade ≥ 3]), white blood cell count decreased (PT, severe AEs [CTCAE grade ≥ 3]), febrile neutropenia (PT, severe AEs [CTCAE grade ≥ 3]), platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3]), leucocytosis (PT, severe AEs [CTCAE grade ≥ 3]), lymphocyte count increased (PT, severe AEs [CTCAE grade ≥ 3]), hyperglycaemia (PT, severe AEs [CTCAE grade ≥ 3]).
e. Lack of blinding in subjective recording of outcomes. For the other specific side effects, this aspect only contributes to a high risk of bias if these are not severe side effects of CTCAE grade ≥ 3.
f. Notable decrease in questionnaire return rate over the course of the study (except for death or censorings due to reaching the data cut-off) with differences between the treatment arms for unknown and thus potentially informative reasons. In addition, the company changed the analysis model from ANCOVA to MMRM without justification, after at least data on overall survival had already been published.
g. Not recorded.
h. No data available, see explanation to Table 12.
i. When interpreting the results on side effects, it should be noted that the fixed treatment duration and the associated discontinuation of observation in the control arm mean that the hazard ratio only reflects approximately the first 9 months after randomization.
j. No results available.
k. No usable results available; in view of the differences in observation periods between the arms, a survival time analysis would be necessary; this is not available.

AE: adverse event; ANCOVA: analysis of covariance; CTCAE: Common Terminology Criteria for Adverse Events; FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia; FCR: fludarabine + cyclophosphamide + rituximab; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MMRM: mixed-effects model with repeated measures; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; TOI: Trial Outcome Index; vs.: versus

In line with the company, a high risk of bias of the results was assumed for all included outcomes except overall survival.

The open-label study design alone caused a high risk of bias of the results for the morbidity outcomes and the side effect outcomes that were not classified as severe AEs (CTCAE grade ≥ 3). In addition, there was a high risk of bias for all side effect outcomes due to the limitation of the observation periods in the control arm to the 6 cycles of chemo-immunotherapy. For the FACT-Leu TOI, there is also the fact that the questionnaire return rate differed greatly between the treatment arms during the course of the study and the analysis model was changed in the SAP after at least data on overall survival had already been published (see Section 2.3.1.3.4).

2.3.2.3 Results

Table 14 and Table 15 summarize the results on the comparison of ibrutinib + rituximab with FCR in patients with previously untreated CLL. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves for the event time analyses can be found in Appendix A, and the tables for the common side effects in Appendix B of the full dossier assessment. No Kaplan-Meier curves are available for the outcome "major haemorrhage" (SMQ haemorrhage terms [excl laboratory terms], "severe AEs [CTCAE grade ≥ 3])" and "haemorrhage" (SMQ haemorrhage terms [excl laboratory terms], AEs).

Table 14: Results (mortality, side effects) – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Study **Outcome category** **Outcome**	**Ibrutinib + rituximab**		**FCR**		**Ibrutinib + rituximab vs. FCR**
	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][a]; p-value from Wald test[b]**
ECOG-E1912					
Mortality					
Overall survival (main analysis DCO 1[c])	*141*	*NA* *0 (0)*	*65*	*NA* *6 (9.2)*	*NC;* *< 0.001*[d]
Overall survival (main analysis DCO 2[e])	141	NA 0 (0)	65	NA 7 (10.8)	NC; < 0.001[d]
Overall survival (sensitivity analysis DCO 2[f])	141	NA 1 (0.7)	65	NA 7 (10.8)	0.06 [0.01; 0.48]; < 0.001[d]
Side effects					
AEs (supplementary information)	141	1.0 [NC; NC] 141 (100.0)	65	1.0 [NC; NC] 65 (100.0)	–
SAEs	No results available				
Severe AEs[g]	141	1.9 [1.0; 1.9] 126 (89.4)	65	1.0 [1.0; 1.9] 59 (90.8)	0.71 [0.52; 0.97]; 0.035
Discontinuation due to AEs (≥ 1 component)	141	NA 15 (10.6)	65	NA 8 (12.3)	0.29 [0.10; 0.86]; 0.025
Haemorrhage					
Major haemorrhage (SMQ haemorrhage terms [excl laboratory terms][h], severe AEs[g])				ND	
Haemorrhage (SMQ haemorrhage terms [excl laboratory terms][h], AEs)	141	ND 66 (46.8)	65	ND 6 (9.2)	ND
Contusion (PT, AEs)	141	NA 41 (29.1)	65	NA 3 (4.6)	4.47 [1.36; 14.70]; 0.014
Infections and infestations (SOC, AEs)	141	21.2 [12.9; 26.7] 90 (63.8)	65	NA [5.6; NC] 24 (36.9)	0.78 [0.48; 1.28]; 0.323
Upper respiratory tract infection (PT, AEs)	141	NA [40,5; NC] 50 (35.5)	65	NA 17 (26.2)	0.31 [0.15; 0.63]; 0.001

Table 14: Results (mortality, side effects) – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Study Outcome category Outcome	Ibrutinib + rituximab N	Ibrutinib + rituximab Median time to event in months [95% CI] Patients with event n (%)	FCR N	FCR Median time to event in months [95% CI] Patients with event n (%)	Ibrutinib + rituximab vs. FCR HR [95% CI][a]; p-value from Wald test[b]
Cardiac disorders (SOC, severe AEs[g])	141	NA 11 (7.8)	65	NA 0 (0)	NC; 0.266[d]
Nausea (PT, AEs)	141	37.8 [12.9; NC] 69 (48.9)	65	1.0 [1.0; 2.8] 45 (69.2)	0.42 [0.28; 0.62]; < 0.001
Constipation (PT, AEs)	141	NA 29 (20.6)	65	NA 22 (33.8)	0.33 [0.18; 0.61]; < 0.001
Vomiting (PT, AEs)	141	NA 28 (19.9)	65	NA 20 (30.8)	0.30 [0.15; 0.58]; < 0.001
Decreased appetite (PT, AEs)	141	NA 21 (14.9)	65	NA 17 (26.2)	0.37 [0.18; 0.74]; 0.005
Pollakiuria (PT, AEs)	141	NA 8 (5.7)	65	NA 8 (12.3)	0.18 [0.05; 0.63]; 0.007
Lymphocyte count decreased (PT, severe AEs[g])	141	NA 12 (8.5)	65	2.8 [1.9; 3.7] 49 (75.4)	0.03 [0.01; 0.08]; < 0.001
White blood cell count decreased (PT, severe AEs[g])	141	NA 11 (7.8)	65	NA [5.6; NC] 25 (38.5)	0.06 [0.02; 0.17]; < 0.001
Febrile neutropenia (PT, severe AEs[g])	141	NA 1 (0.7)	65	NA 8 (12.3)	0.05 [0.01; 0.41]; 0.005
Platelet count decreased (PT, severe AEs[g])	141	NA 2 (1.4)	65	NA 4 (6.2)	0.11 [0.01; 0.97]; 0.047
Leucocytosis (PT, severe AEs[g])	141	NA 21 (14.9)	65	NA 1 (1.5)	8.02 [1.07; 60.28]; 0.043
Lymphocyte count increased (PT, severe AEs[g])	141	1.9 [1.9; NC] 78 (55.3)	65	NA 17 (26.2)	2.16 [1.28; 3.66]; 0.004
Hyperglycaemia (PT, severe AEs[g])	141	NA 6 (4.3)	65	NA 4 (6.2)	0.15 [0.02; 0.96]; 0.045

a. Unstratified Cox model.
b. Unstratified.
c. 17 July 2018; data cut-off is presented as supplementary information and is not used for the derivation of the added benefit.
a. p-value from log-rank test, unstratified.
e. 2 August 2019.
f. Assuming an event in the intervention arm immediately after randomization.
g. Operationalized as CTCAE grade ≥ 3.
h. "Excluding laboratory terms" means that the SMQ does not include any PTs resulting from laboratory investigations.

Table 14: Results (mortality, side effects) – RCT, direct comparison: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Study Outcome category Outcome	Ibrutinib + rituximab N	Ibrutinib + rituximab Median time to event in months [95% CI] Patients with event n (%)	FCR N	FCR Median time to event in months [95% CI] Patients with event n (%)	Ibrutinib + rituximab vs. FCR HR [95% CI][a]; p-value from Wald test[b]

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; FCR: fludarabine + cyclophosphamide + rituximab; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; 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 + rituximab vs. FCR (patients for whom FCR therapy is an option)

Study Outcome category Outcome	Ibrutinib + rituximab N[a]	Ibrutinib + rituximab Values at baseline mean (SD)	Ibrutinib + rituximab Mean change in the course of the study mean[b] (SE)	FCR N[a]	FCR Values at baseline mean (SD)	FCR Mean change in the course of the study mean[b] (SE)	Ibrutinib + rituximab vs. FCR MD [95% CI]; p-value[b]
ECOG-E1912							
Morbidity							
FACT-Leu TOI[c]	139	93.2 (19.0)	6.0 (1.0)	64	93.5 (17.4)	8.1 (1.5)	−2.04 [−5.58; 1.50]; 0.258
PWB	*140*	*22.8 (5.4)*	*0.4 (0.3)*	*65*	*23.5 (4.2)*	*0.5 (0.4)*	*−0.08 [−1.11; 0.95]*
FWB	*140*	*20.6 (5.7)*	*1.1 (0.3)*	*65*	*20.3 (5.5)*	*1.8 (0.4)*	*−0.74 [−1.77; 0.30]*
Leu	*139*	*49.6 (9.9)*	*4.5 (0.5)*	*64*	*49.8 (9.5)*	*5.9 (0.8)*	*−1.41 [−3.27; 0.46]*
Health-related quality of life						Not recorded	

a. According to the company, only patients with one value at baseline and at least one subsequent value were considered in the MMRM analysis; this contradicts the information that only 127 vs. 57 patients had one value at baseline.
b. MMRM analysis, using the change from baseline value as the dependent variable; the independent variables used in the model were baseline value, visit, treatment, and interaction between treatment arm and documentation time. A compound symmetry matrix was used as the correlation structure.
c. The FACT-Leu TOI is assigned to morbidity because it does not cover all dimensions of health-related quality of life. Higher (increasing) values indicate better wellbeing; positive effects (intervention minus control) indicate an advantage for the intervention.

CI: confidence interval; FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia; FCR: fludarabine + cyclophosphamide + rituximab; FWB: functional wellbeing; Leu: leukaemia-specific module of the FACT-Leu; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; PWB: physical wellbeing; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; TOI: Trial Outcome Index; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcome "overall survival". Due to the high risk of bias, at most a hint, e.g. of an added benefit, can be determined for the morbidity outcome.

Despite the high risk of bias, indications, e.g. of greater harm, can partly be determined for the outcomes of the outcome category of side effects because the certainty of results was partly not reduced due to the large number of early events and the clear difference between the treatment arms. Further information can be found in the description of the results below.

Mortality

Overall survival

Both the main analysis and the sensitivity analysis showed a statistically significant advantage of ibrutinib + rituximab in comparison with FCR for the outcome "overall survival". This resulted in an indication of an added benefit of ibrutinib + rituximab in comparison with FCR.

This concurs with the company's assessment.

Morbidity

FACT-Leu TOI

No statistically significant difference between the 2 treatment arms was shown for the morbidity outcome "FACT-Leu TOI". Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; an added benefit is therefore not proven.

The result of this assessment concurs with that of the company, which assigned the FACT-Leu TOI to health-related quality of life, however.

Health-related quality of life

Deviating from the company's approach, the FACT-Leu TOI was assigned to morbidity and not to health-related quality of life. Thus, no data for health-related quality of life were available. Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; an added benefit is therefore not proven.

The result of this assessment concurs with that of the company, which derived no added benefit on the basis of the FACT-Leu TOI.

Side effects

When interpreting the results on side effects, it should be noted that the fixed treatment duration and the associated discontinuation of observation in the control arm mean that the hazard ratio only reflects approximately the first 9 months after randomization.

SAEs

For the reasons described in Section 2.3.2.1, no results are available for the outcome "SAEs".

Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

The result of this assessment concurs with that of the company, which stated that SAEs were not systematically documented in the ECOG-E1912 study.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

This concurs with the company's assessment.

Discontinuation due to AEs (≥ 1 component)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the outcome "discontinuation due to AEs (≥ 1 component)". This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

This concurs with the company's assessment.

Haemorrhage

Major haemorrhage (SMQ haemorrhage terms [excl laboratory terms], severe AEs [CTCAE grade ≥ 3])

No results are available for the outcome "major haemorrhage" (SMQ haemorrhage terms [excl laboratory terms], severe AEs [CTCAE grade ≥ 3]). Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

Haemorrhage (SMQ haemorrhage terms [excl laboratory terms], AEs)

The company only presented the proportions of patients with event per study arm for the outcome "haemorrhage" (SMQ haemorrhage terms [excl laboratory terms], AEs). The company did not present an effect estimation and a p-value based on an event time analysis. No effect estimation on the basis of the aggregated data can be carried out by the Institute. There were therefore no usable results available. Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

Contusion (PT, AEs)

A statistically significant difference to the disadvantage of ibrutinib + rituximab was shown for the specific AEs "contusion" (PT, AEs), which is part of the SMQ haemorrhage terms (excl laboratory terms). This resulted in a hint of greater harm of ibrutinib + rituximab in comparison with FCR.

This deviates from the company, which only included a subset of haemorrhage events (SMQ haemorrhage terms [excl laboratory terms]) for the outcome "haemorrhage" and derived a hint of lesser harm across all side effect outcomes.

Infections and infestations (SOC, AEs)

No statistically significant difference between the treatment arms was shown for the outcome "infections and infestations" (SOC, AEs). Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

This concurs with the assessment of the company, which did not consider this outcome separately.

Upper respiratory tract infection (PT, AE)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the specific AEs "upper respiratory tract infection" (PT, AEs). This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])

No statistically significant difference between the treatment arms was shown for the outcome "cardiac disorders" (SOC, severe AEs [CTCAE grade ≥ 3]). Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with FCR; lesser or greater harm is therefore not proven.

This deviates from the assessment of the company, which did not include this outcome in the derivation of the added benefit, but presented the effect without information on the added benefit and derived a hint of lesser harm across all side effect outcomes.

The results of all other specific AEs are described below in summary form according to the direction of effect. The comparison with the assessment of the company for the specific AEs is carried out subsequently.

Further specific AEs in favour of ibrutinib + rituximab

Cytopenias: lymphocyte count decreased, white blood cell count decreased, febrile neutropenia and platelet count decreased (each PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for each of the following specific AEs: lymphocyte count decreased, white blood cell count decreased, febrile neutropenia, and platelet count decreased (each PT, severe AEs [CTCAE grade ≥ 3]).

This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR for each of the outcomes "febrile neutropenia" and "platelet count decreased" (each PT, severe AEs [CTCAE grade ≥ 3]). For the outcomes "lymphocyte count decreased" and "white blood cell count decreased" (each PT, severe AEs [CTCAE grade ≥ 3]), there was an indication of lesser

harm of ibrutinib + rituximab in comparison with FCR due to the size of the respective observed effects.

Hyperglycaemia (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the specific AEs "hyperglycaemia" (PT, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Nausea, constipation, vomiting and decreased appetite (each PT, AE)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the following specific AEs: nausea, constipation, vomiting and decreased appetite (each PT, AEs). In each case, this resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Pollakiuria (PT, AEs)

A statistically significant difference in favour of ibrutinib + rituximab in comparison with FCR was shown for the outcome "pollakiuria" (PT, AEs). This resulted in a hint of lesser harm of ibrutinib + rituximab in comparison with FCR.

Further specific AEs to the disadvantage of ibrutinib + rituximab

Lymphocyte count increased and leucocytosis (each PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of ibrutinib + rituximab was shown for each of the specific AEs "lymphocyte count increased" and "leucocytosis" (each PT, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of greater harm of ibrutinib + rituximab in comparison with FCR.

Comparison with the assessment of the company for the specific AEs

The assessment of the added benefit in the specific AEs deviates from the assessment of the company, which did not include these outcomes in the derivation of the added benefit, but presented the effects without information on the added benefit and derived a hint of lesser harm across all side effect outcomes.

2.3.2.4 Subgroups and other effect modifiers

For the present benefit assessment, age (< 60, ≥ 60 years), sex (female, male) and disease severity at study inclusion (Rai stage 0/I/II versus III/IV) were considered as potential effect modifiers.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one 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.

In accordance with the methods described, no relevant effect modification by age, sex or disease severity at study inclusion was identified for the outcomes for which usable analyses were available.

2.3.3 Probability and extent of added benefit

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

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

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 16).

Determination of the outcome category of 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.

The outcome “discontinuation due to AEs” was assigned to the outcome category of serious/severe side effects, as it was estimated that more than 50% of the discontinuations were of CTCAE grade ≥ 3.

Table 16: Extent of added benefit at outcome level: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Outcome category **Outcome**	**Ibrutinib + rituximab vs. FCR** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival (DCO 2)	Main analysis median: NA vs. NA 0 (0) vs. 7 (10.8) patients HR: NC p < 0.001 Sensitivity analysis median: NA vs. NA 1 (0.7) vs. 7 (10.8) patients HR: 0.06 [0.01; 0.48]; p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
FACT-Leu TOI	Mean (change in the course of study): 6.0 vs. 8.1 MD: −2.04 [−5.58; 1.50] p = 0.258	Lesser benefit/added benefit not proven
Health-related quality of life		
	The FACT-Leu TOI does not fully represent health-related quality of life and was therefore assigned to morbidity	Lesser benefit/added benefit not proven
Side effects		
SAEs	No results available	Greater/lesser harm not proven
Severe AEs[c]	Median: 1.9 vs. 1.0 months HR: 0.71 [0.52; 0.97] p = 0.035 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Discontinuation due to AEs (≥ 1 component)	Median: NA vs. NA HR: 0.29 [0.10; 0.86] p = 0.025 probability: "hint"	Outcome category: serious/severe side effects $0.85 \leq CI_u < 0.95$ lesser harm, extent: "considerable"
Haemorrhage		
Major haemorrhage (SMQ haemorrhage terms [excl laboratory terms], severe AEs[c])	ND	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Outcome category **Outcome**	**Ibrutinib + rituximab vs. FCR** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Haemorrhage (SMQ haemorrhage terms [excl laboratory terms])	Median: ND 66 (46.8) vs. 6 (9.2) patients HR: ND p = ND	Greater/lesser harm not proven
Contusion (PT, AEs)	Median: NA vs. NA HR: 4.47 [1.36; 14.70] HR: 0.22 [0.07; 0.74][d] p = 0.014 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Infections and infestations (SOC, AEs)	Median: 21.2 vs. NA months HR: 0.78 [0.48; 1.28] p = 0.323	Greater/lesser harm not proven
Upper respiratory tract infection (PT, AEs)	Median: NA vs. NA HR: 0.31 [0.15; 0.63]; p = 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Cardiac disorders (SOC, severe AEs[c])	Median: NA vs. NA 11 (7.8) vs. 0 (0) patients HR: NC p = 0.266	Greater/lesser harm not proven
Nausea (PT, AEs)	Median: 37.8 vs. 1.0 months HR: 0.42 [0.28; 0.62] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Constipation (PT, AEs)	Median: NA vs. NA HR: 0.33 [0.18; 0.61] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Vomiting (PT, AEs)	Median: NA vs. NA HR: 0.30 [0.15; 0.58] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Decreased appetite (PT, AEs)	Median: NA vs. NA HR: 0.37 [0.18; 0.74] p = 0.005 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"

Table 16: Extent of added benefit at outcome level: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Outcome category **Outcome**	**Ibrutinib + rituximab vs. FCR** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Pollakiuria (PT, AEs)	Median: NA vs. NA HR: 0.18 [0.05; 0.63] p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Cytopenias		
Lymphocyte count decreased (PT, severe AEs[c])	Median: NA vs. 2.8 HR: 0.03 [0.01; 0.08] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
White blood cell count decreased (PT, severe AEs[c])	Median: NA vs. NA HR: 0.06 [0.02; 0.17] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Febrile neutropenia (PT, severe AEs[c])	Median: NA vs. NA HR: 0.05 [0.01; 0.41] p = 0.005 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Platelet count decreased (PT, severe AEs[c])	Median: NA vs. NA HR: 0.11 [0.01; 0.97] p = 0.047 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Leucocytosis (PT, severe AEs[c])	Median: NA vs. NA HR: 8.02 [1.07; 60.28] HR: 0.12 [0.02; 0.94][d] p = 0.043 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Lymphocyte count increased (PT, severe AEs[c])	Median: 1.9 vs. NA HR: 2.16 [1.28; 3.66] HR: 0.46 [0.27; 0.78][d] p = 0.004 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Hyperglycaemia (PT, severe AEs[c])	Median: NA vs. NA HR: 0.15 [0.02; 0.96] p = 0.045 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"

Table 16: Extent of added benefit at outcome level: ibrutinib + rituximab vs. FCR (patients for whom FCR therapy is an option) (multipage table)

Outcome category **Outcome**	**Ibrutinib + rituximab vs. FCR** **Median time to event (months) or proportion of events (%) or mean (change in the course of the study)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. Operationalized as CTCAE grade ≥ 3. d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia; FCR: fludarabine + cyclophosphamide + rituximab; HR: functional wellbeing; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; TOI: Trial Outcome Index; vs.: versus		

2.3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of ibrutinib + rituximab in comparison with FCR (patients for whom FCR therapy is an option)

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of added benefit – extent: "major"	–
Serious/severe side effects[a] ▪ Severe AEs: hint of lesser harm – extent: "minor" including ▫ Cytopenias - lymphocyte count decreased - white blood cell count decreased in each case indication of lesser harm – extent: "major" - febrile neutropenia hint of lesser harm – extent: "major" - platelet count decreased hint of lesser harm – extent: "minor" ▫ Hyperglycaemia hint of lesser harm – extent: "minor" ▪ Discontinuation due to AEs (≥ 1 component): hint of lesser harm – extent: "considerable"	Serious/severe side effects[a] ▫ Lymphocyte count increased (severe AEs): hint of greater harm – extent: "considerable" ▫ Leucocytosis (severe AEs): hint of greater harm – extent: "minor"
Non-serious/non-severe side effects[a] ▪ Nausea ▪ Constipation ▪ Vomiting ▪ Decreased appetite ▪ Upper respiratory tract infection ▪ Pollakiuria in each case hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects[a] ▪ Contusion[b]: hint of greater harm – extent: "considerable"
No outcome for health-related quality of life was recorded in the study included.	

a. When interpreting the results on side effects, it should be noted that the great differences in observation periods between the treatment arms mean that the hazard ratio only reflects approximately the first 9 months.
b. Contusion is the only event of the side effect "haemorrhage" for which usable results are available.
AE: adverse event; FCR: fludarabine + cyclophosphamide + rituximab;

In the overall assessment, there are positive and negative effects, which, with the exception of the outcomes "overall survival", "lymphocyte count decreased" and "white blood cell count decreased" (each indication) have the probability of a hint.

There was an indication of a major added benefit for the outcome "overall survival". At the level of side effects, there was lesser harm of minor extent for the overall rate of severe AEs (CTCAE grade ≥ 3), and lesser harm of considerable extent for discontinuations due to AEs, each with the probability of a hint.

Within the severe side effects (CTCAE-grade ≥ 3), there were mainly positive and individual negative effects; these mainly concerned events on the number of immune cells.

At the level of non-serious/non-severe side effects, there were also more positive than negative effects; these mainly concerned gastrointestinal events.

There were no results for the outcome category of health-related quality of life.

In summary, there is an indication of a major added benefit of ibrutinib + rituximab in comparison with the ACT FCR for patients with previously untreated CLL for whom treatment with FCR is an option.

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for this research question.

2.4 Research question 2: patients for whom treatment with FCR is not an option

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ibrutinib (status: 3 August 2020)
- bibliographical literature search on ibrutinib (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on ibrutinib (last search on 3 August 2020)
- search on the G-BA website for ibrutinib (last search on 7 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 8 October 2020)

The check identified no relevant RCT for a direct or indirect comparison. The company also did not identify any suitable studies for a direct comparison. The company did not conduct an information retrieval for RCTs for an adjusted indirect comparison via a common comparator, as the population relevant to research question 2 was not sufficiently covered in the study presented by the company (ECOG-E1912).

2.4.2 Results on added benefit

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

2.4.3 Probability and extent of added benefit

Since the company did not present any data for the assessment of the added benefit of ibrutinib + rituximab in patients for whom treatment with FCR is not an option, an added benefit of ibrutinib + rituximab for this population is not proven.

This concurs with the company's assessment.

2.5 Research question 3: patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

2.5.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ibrutinib (status: 3 August 2020)
- bibliographical literature search on ibrutinib (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on ibrutinib (last search on 3 August 2020)
- search on the G-BA website for ibrutinib (last search on 7 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 8 October 2020)

The check identified no relevant RCT for a direct or indirect comparison. The company also did not identify any suitable studies for a direct comparison. The company did not conduct an information retrieval for RCTs for an adjusted indirect comparison via a common comparator, as the population relevant to research question 3 was not sufficiently covered in the study presented by the company (ECOG-E1912).

2.5.2 Results on added benefit

The company presented no data for the assessment of the added benefit of ibrutinib + rituximab in comparison with the ACT for patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons. This resulted in no hint of an added benefit of ibrutinib + rituximab 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 data for the assessment of the added benefit of ibrutinib + rituximab in patients with 17p deletion and/or TP53 mutation or for whom chemo-

immunotherapy is not indicated for other reasons, an added benefit of ibrutinib + rituximab is not proven for this population.

This concurs with the company's assessment.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ibrutinib + rituximab in comparison with the ACT is summarized in Table 18.

Table 18: Ibrutinib + rituximab – probability and extent of added benefit

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
1	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR	Indication of major added benefit
2	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Bendamustine in combination with rituximab or chlorambucil in combination with rituximab or obinutuzumab	Added benefit not proven
3	Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	Added benefit not proven

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA.

17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

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

References for English extract

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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