Ibrutinib
(previously untreated chronic lymphocytic leukaemia)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A23-04 Version: 1.0 Status: 24 April 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Ibrutinib (nicht vorbehandelte chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Ibrutinib (previously untreated chronic lymphocytic leukaemia) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

26 January 2023

Internal Project No.

A23-04

Address of publisher

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Christa Knebel.

IQWiG thanks the respondent for participating in the written exchange about how she experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Keywords

Ibrutinib, Venetoclax, Leukemia – Lymphocytic – Chronic – B-Cell, Benefit Assessment, NCT03462719

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
FCR	fludarabine in combination with cyclophosphamide and 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
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small lymphocytic lymphoma
SPC	Summary of Product Characteristics
TP53	tumour protein p53

I 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 (in combination with venetoclax). 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 26 January 2023.

Research question

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

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of ibrutinib + venetoclax

Therapeutic indication	**ACT[a]**
Adult patients with previously untreated CLL[b,c]	Ibrutinib or Ibrutinib in combination with rituximab or obinutuzumab or FCR[d, e] or Bendamustine in combination with rituximab[e, f] or **Chlorambucil in combination with** rituximab or **obinutuzumab**[e, f]
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. In the present therapeutic indication, patients presumably require treatment (e.g. Binet stage C). c. For the present therapeutic indication, allogeneic stem cell transplantation is presumably not indicated at the time of treatment. d. Only for patients who (1) have no genetic risk factors, (2) are < 65 years of age, and (3) are eligible for FCR therapy based on their general health and comorbidities. e. According to current medical knowledge, the following factors are deemed genetic risk factors: presence of 17p deletion / TP53 mutation / unmutated IGHV. f. Only for patients without genetic risk factors who are ineligible for FCR therapy. According to the G-BA, this includes both patients ≥ 65 years of age and patients < 65 years of age who, based on their general health and comorbidities, are ineligible for FCR therapy. 17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of tumour protein p53	

The company followed the ACT specified by the G-BA and, from the options mentioned, chose chlorambucil in combination with obinutuzumab.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Randomized controlled trials (RCTs) are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The study pool for the benefit assessment consists of the GLOW study. This study is an ongoing open-label RCT directly comparing ibrutinib + venetoclax versus chlorambucil + obinutuzumab.

The study enrolled adults with previously untreated CLL / small lymphocytic lymphoma (SLL) without deletion in the short arm of chromosome 17 (17p deletion) or mutation of tumour protein p53 (TP53 mutation). Patients had to require treatment as per the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (as of 2008). In addition, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 2; further, they had to be ≥ 65 years of age or – if younger – exhibit a certain level of comorbidities (Cumulative Illness Rating Scale [CIRS] > 6) or renal insufficiency. A total of 106 patients were randomized to the intervention arm of ibrutinib + venetoclax and 105 patients to the comparator arm of chlorambucil + obinutuzumab.

The GLOW study enrolled patients irrespective of whether or not they were eligible for treatment with fludarabine in combination with cyclophosphamide and rituximab (FCR). The company's dossier presents evaluations of a subpopulation eligible for chlorambucil and obinutuzumab treatment according to various criteria (age, renal function, thrombocytopenia, anaemia, autoimmune cytopenia, general condition, comorbidities, and mutation status of 17p, TP53, and the immunoglobulin heavy chain variable region [IGHV]). This subpopulation included 23 patients in the ibrutinib + venetoclax arm and 24 patients in the chlorambucil + obinutuzumab arm.

Ibrutinib + venetoclax in the intervention arm and chlorambucil and obinutuzumab in the comparator arm were used in accordance with the respective Summaries of Product Characteristics (SPCs).

Primary outcome of the GLOW study is progression-free survival (PFS). Secondary outcomes are overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Data cutoffs

At the time of the benefit assessment, 4 data cutoffs have been implemented. The 1st data cutoff had been predefined and was conducted on 26 February 2021. The 2nd data cutoff had not been predefined and was conducted on 19 August 2021. The 3rd data cutoff on 17 January 2022 had not been predefined and was required by the European Medicines Agency (EMA) as part of the European regulatory process. The 4th data cutoff dated 25 August 2022 had not been predefined and was conducted for the purposes of a scientific publication.

Data cutoff presented by the company is unsuitable for the benefit assessment

The company's dossier presents the results of the relevant subpopulation for the non-predefined 4th data cutoff dated 25 August 2022. For the patient-reported outcomes on morbidity and health-related quality of life, Module 4 A of the company's dossier presents analyses of the 1st data cutoff dated 26 February 2021 because these outcomes were not further surveyed. Because the 4th data cutoff was neither predefined nor required by a regulatory authority, reporting bias cannot be ruled out. Consequently, the subpopulation results presented by the company are unusable for the benefit assessment.

Company's dossier is incomplete in content

According to the module templates, the dossier is to present the results of the data cutoffs which were either predefined or required by the regulatory authorities. Consequently, the subpopulation results at the 3rd data cutoff dated 17 January 2022 are primarily relevant because this data cutoff was required by the EMA in the context of the European approval process. Since the company's dossier does not present these results, it is incomplete.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of added benefit of ibrutinib in combination with venetoclax 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]

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

[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)

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with previously untreated CLL[b,c]	Ibrutinib Or Ibrutinib in combination with rituximab or obinutuzumab Or FCR[d, e] Or Bendamustine in combination with rituximab[e, f] Or C**hlorambucil in combination with** rituximab or **obinutuzumab**[e, f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. In the present therapeutic indication, patients presumably require treatment (e.g. Binet stage C).
c. In the present therapeutic indication, allogeneic stem cell transplantation is presumably not indicated at the time of treatment.
d. Only for patients without any genetic risk factors and < 65 years of age who, based on their general health and comorbidities, are eligible for FCR therapy.
e. According to current medical knowledge, the following factors are deemed genetic risk factors: presence of 17p deletion / TP53 mutation / unmutated IGHV.
f. Only for patients without genetic risk factors who are ineligible for FCR therapy. According to the G-BA, this includes both patients ≥ 65 years of age and patients < 65 years of age who, based on their general health and comorbidity, are ineligible for FCR therapy.

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; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of tumour protein p53

The G-BA decides on the added benefit.

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].

I 2 Research question

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

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of ibrutinib + venetoclax

Therapeutic indication	**ACT**[a]
Adult patients with previously untreated CLL[b,c]	Ibrutinib or Ibrutinib in combination with rituximab or obinutuzumab or FCR[d, e] or Bendamustine in combination with rituximab[e, f] or **Chlorambucil in combination with** rituximab or **obinutuzumab**[e, f]
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. In the present therapeutic indication, patients presumably require treatment (e.g. Binet stage C). c. In the present therapeutic indication, allogeneic stem cell transplantation is presumably not indicated at the time of treatment. d. Only for patients who (1) have no genetic risk factors, (2) are < 65 years of age, and (3) are eligible for FCR therapy based on their general health and comorbidities. e. According to current medical knowledge, the following factors are deemed genetic risk factors: presence of 17p deletion / TP53 mutation / unmutated IGHV. f. Only for patients without genetic risk factors who are ineligible for FCR therapy. According to the G-BA, this includes both patients ≥ 65 years of age and patients < 65 years of age who, based on their general health and comorbidities, are ineligible for FCR therapy. 17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of tumour protein p53	

The company followed the ACT specified by the G-BA and, from the options mentioned, chose chlorambucil in combination with obinutuzumab.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ibrutinib (status: 5 December 2022)
- bibliographical literature search on ibrutinib (last search on 5 December 2022)
- search in trial registries / trial results databases for studies on ibrutinib (last search on 5 December 2022)
- search on the G-BA website for ibrutinib (last search on 5 December 2022)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 9 February 2023); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the company's study pool identified not only the GLOW study, but also the potentially relevant studies CLL17 [3] and ERADIC [4], but no results are available from these studies at this time.

The CLL17 study is a 3-arm RCT comparing ibrutinib + venetoclax versus ibrutinib monotherapy and versus obinutuzumab + venetoclax. In total, 897 patients with previously untreated CLL are to be included in the study. Primary outcome of the CLL17 study is PFS. Secondary outcomes are from the morbidity and side effects categories. Potentially relevant for the benefit assessment are the results on the comparison of ibrutinib + venetoclax versus ibrutinib. The study is sponsored by the German CLL Study Group. At the time of the benefit assessment, no results are available for the CLL17 study. The final analysis of the primary outcome is expected in March 2027.

The ERADIC RCT, which has been ongoing since 2019, compares ibrutinib + venetoclax versus FCR. The study has enrolled 120 patients with previously untreated CLL who have no genetic risk factors. Primary outcome of the study is minimal residual disease. Secondary outcomes are from the categories of mortality, morbidity, and side effects. The study is conducted by the French Innovative Leukemia Organisation, with the company being one of the sponsors. First study results are expected in December 2023.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab

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 and other sources[c] (yes/no [citation])
CLL3011 (GLOW[d])	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8,9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
GLOW	RCT, open-label, parallel	Adult patients with untreated CLL/SLL requiring treatment[b] and lymph node enlargement measurable by computed tomography (CT)[c] ▪ Without 17p deletion or known TP53 mutation[d] ▪ ≥ 65 years of age or < 65 years of age meeting 1 of the following criteria: ▫ CIRS > 6 or ▫ estimated creatinine clearance < 70 mL/min[e] ▪ ECOG-PS ≤ 2	Ibrutinib + venetoclax (N = 106) Chlorambucil + obinutuzumab (N = 105) Relevant subpopulation thereof[f]: Ibrutinib + venetoclax (n = 23) Chlorambucil + obinutuzumab (n = 24)	Screening: 30 days Treatment: ▪ 15 cycles in the intervention arm and 6 cycles in the comparator arm or ▪ Until progression of disease, unacceptable toxicity, or treatment discontinuation at the investigator's or the patient's discretion Observation: Outcome-specific, at most until end of study	67 study sites in Belgium, Canada, Czech Republic, Denmark, France, Israel, Netherlands, Poland, Russia, Spain, Sweden, Turkey, United Kingdom, and United States 04/2018 ongoing 1st data cutoff: 26/02/2021[g] 2nd data cutoff: 19/08/2021[h] 3rd data cutoff: 17/01/2022[i] 4th data cutoff: 25/08/2022[j]	Primary: progression-free survival Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data only the basis of the information provided by the company's Module 4.
b. Diagnosis and need for treatment according to iwCLL criteria (2008) [10].
c. ≥ 1 lymph nodes with a diameter > 1.5 cm.
d. In > 10% of the cells.
e. According to Cockcroft-Gault formula.
f. Patients without genetic risk factors who are ineligible for FCR therapy.
g. Predefined interim analysis, planned to be conducted after 71 PFS events (actually carried out after 89 PFS events).
h. Referred to by the company as a data cutoff for the expanded follow-up.
i. Data cutoff conducted in the context of the European approval process.
j. Data cutoff with the goal of scientific publication.

AE: adverse event; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; CT: computed tomography; 17p deletion: deletion in the short arm of chromosome 17; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FCR: treatment with fludarabine in combination with cyclophosphamide and rituximab; IGHV: immunoglobulin heavy chain variable segments; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; TP53: tumour protein p53

Table 7: Characteristics of the intervention – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study	Intervention	Comparison
GLOW	Ibrutinib 420 mg, orally, once daily for 15 cycles[a] + venetoclax, orally, once daily, starting with Cycle 4 The dose is incrementally increased for 5 weeks: Cycle 4, days 1–7: 20 mg/day Cycle 4, Week 2: 50 mg/day Cycle 4, Week 3: 100 mg/day Cycle 4, Week 4: 200 mg/day From Cycle 5: 400 mg/day In cycles with venetoclax combination treatment: simultaneous administration of ibrutinib and venetoclax	Chlorambucil, 0.5 mg per kg body weight, orally for 6 cycles[c] each on Day 1 and Day 15 + Obinutuzumab i.v., for 6 cycles [a] Cycle 1 ▪ Day 1: 100 mg ▪ Day 2: 900 mg[b] ▪ Days 8 and 15: 1000 mg Cycles 2–6: 1000 mg on Day 1
	Dose adjustments / treatment interruptions[c]	
	Ibrutinib: ▪ Treatment interruptions for ≤ 28 days[d] and dose reductions in case of AEs with CTCAE grade ≥ 3 or development of liver dysfunction with subsequent dose adjustment after resumption of therapy[d] Venetoclax: ▪ Dose adjustments[e] and treatment interruptions[f] due to toxicities as per SPC	Chlorambucil: Treatment interruptions for ≤ 28 days in case of cytopoenia[g] or uncontrollable, nonhaematological toxicity CTCAE grade ≥ 3 with subsequent dose adjustments after resumption of therapy[h] Obinutuzumab: ▪ Treatment interruptions for ≤ 28 days[i] in case of toxicity ▪ No dose adjustments allowed
	Prior treatment <u>Disallowed</u> ▪ Antileukaemic treatment for CLL or SLL ▪ Chronic administration of corticosteroids ≥ 20 mg/day ≤ 7 days before the 1st dose of the study medication and during the study ▪ Live vaccines within ≤ 4 weeks prior to the 1st dose of study medication and during study treatment **Premedication and concomitant treatment** ▪ Fluid administration ▪ Electrolyte balancing ▪ Venetoclax: mandatory TLS prophylaxis: fluid administration; allopurinol or other xanthine oxidase inhibitors ▪ Obinutuzumab: recommended prophylaxis of infusion reactions: analgesics, antipyretics, antihistamines, corticosteroidsj	

Table 7: Characteristics of the intervention – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study	Intervention	Comparison
	Further permitted concomitant treatment ▪ Appropriate supportive concomitant treatment during the study ▪ Haematopoietic growth factors (e.g. filgrastim, pegfilgrastim) ▪ Transfusions ▪ Antimicrobial prophylaxis (e.g. sulfamethoxazole, trimethoprim) ▪ Corticosteroids (≤ 100 mg/day prednisone or equivalent) for treatment for non-cancer medical reasons (< 14 days) **Disallowed concomitant treatment** ▪ Anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon) in the comparator arm ▪ Potent CYP3A inhibitors in the intervention arm ▪ Any leukaemia therapy	

a. One treatment cycle comprises 28 days.
b. If well tolerated, the remaining 900 mg were allowed to be administered as early as Day 1.
c. If 1 therapy component was discontinued, the other was continued as planned.
d. If toxicity was present > 28 days, ibrutinib was to be permanently discontinued unless treatment continuation was approved by the sponsor.
e. If interrupted due to AEs, dose adjustment or resumption of therapy was dependent on the number of times the AE had previously occurred.
f. Discontinuation of venetoclax treatment was to be weighed in case of dose reduction to < 100 mg for > 2 weeks.
g. Either absolute neutrophil count < 500/µL for ≥ 7 days or platelet count < 50 000/µL (with bleeding) or platelet count < 25 000/µL or haemoglobin < 8.0 g/dL.
h. Treatment continuation at 75% of the original dose after the 1st interruption; treatment continuation at 50% of the original dose after the 2nd interruption.
i. In case of toxicity for > 28 days, obinutuzumab was to be permanently discontinued unless treatment continuation was approved by the medical monitor.
j. Before the first administration of obinutuzumab, mandatory administration of 100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone i.v.

AE: adverse events; CLL: chronic lymphatic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; CYP3A: cytochrome P450 3A; i.v.: intravenous; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; SPC: Summary of Product Characteristics; TLS: tumour lysis syndrome

The GLOW study is an open-label, multicentre RCT directly comparing ibrutinib + venetoclax versus chlorambucil + obinutuzumab. The study is ongoing.

The GLOW study enrolled adults with previously untreated CLL/SLL without a deletion in the short arm of chromosome 17 (17p deletion) or a mutation of tumour protein p53 (TP53 mutation). Patients had to require treatment according to the iwCLL criteria (as of 2008) [10]. Furthermore, patients were to have an ECOG-PS of ≤ 2 and be ≥ 65 years of age or, if younger, meet at least 1 of the following criteria:

- Presence of comorbidities (CIRS > 6)

- presence of renal impairment (creatinine clearance < 70 mL/min, estimated using the Cockcroft-Gault equation)

A total of 106 patients were randomized to the intervention arm of ibrutinib + venetoclax and 105 patients to the comparator arm of chlorambucil + obinutuzumab. Randomization was stratified by IGHV mutation status (mutated versus unmutated versus not evaluable) and by the presence of a deletion on chromosome 11 (11q deletion) (yes versus no). Only a subpopulation of the GLOW study is relevant for the present benefit assessment (further explanations are found below).

The use of ibrutinib + venetoclax in the intervention arm corresponds to the SPC [11,12].

In the comparator arm, chlorambucil and obinutuzumab were administered according to the SPC. However, the description of the combination therapy of chlorambucil + obinutuzumab, including the dosing of chlorambucil, is found in the obinutuzumab SPC [13,14].

After discontinuation of the study medications (e.g. due to disease progression), subsequent therapies were allowed without restrictions. Patients of both study arms were allowed to switch to ibrutinib monotherapy after progression. For the relevant subpopulation, no information is available on how many patients this affects or on other follow-up therapies received after discontinuation/termination of the study medication. This information would be required, however, to interpret the overall survival results in the relevant subpopulation.

The primary outcome of the GLOW study is PFS. Secondary outcomes are overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Subpopulation presented by the company

The GLOW study enrolled patients irrespective of whether or not FCR therapy was an option for them. According to the G-BA, however, the chemoimmunotherapy administered in the comparator arm, consisting of chlorambucil and obinutuzumab, is suitable only for patients without genetic risk factors for whom FCR therapy is not an option (see Table 4). Therefore, the company's dossier presents evaluations of a subpopulation which, in its opinion, meets the criteria for treatment with chlorambucil and obinutuzumab.

Company's approach for defining the relevant subpopulation

To form the relevant subpopulation from the GLOW study's total population, the company used various criteria (age, renal function, thrombocytopenia, anaemia, autoimmune cytopoenia, general health, comorbidities, 17p mutation status,TP53 mutation status, and IGHV mutation status) which may render patients ineligible for FCR therapy. When forming this subpopulation, the company took these criteria into account as follows:

- Sufficient criteria (if ≥ 1 criteria are met, FCR therapy is no longer an option)
  - 17p deletion / TP53 mutation
  - unmutated IGHV status
  - presence of renal impairment (creatinine clearance < 70 mL/min)
  - presence of autoimmune cytopenia
- Composite criteria (if at least 2 criteria are met, FCR therapy is no longer an option)
  - age > 65 years
  - general health: ECOG PS ≥ 2
  - comorbidities: CIRS > 6
  - anaemia and/or reduced platelet count

Taking into account the above criteria, the company therefore analysed 47 (22.3%) of the 211 GLOW participants (ibrutinib + venetoclax arm: N = 23; chlorambucil + obinutuzumab arm: N = 24) for the present research question.

Assessment of the company's approach for defining the relevant subpopulation

No consistent scientific consensus exists regarding criteria for the suitability or unsuitability of FCR therapy for patients with CLL. In its approach, the company takes into account criteria cited in guidelines as well as in prior benefit assessment procedures conducted in the same therapeutic indication [15-17]. The criteria used by the company are thus deemed suitable for adequately representing the subpopulation relevant for the present research question.

Data cutoffs

The GLOW study is still ongoing. At the time of the benefit assessment, 4 data cutoffs have been implemented:

- 1st data cutoff dated 26 February 2021: predefined primary analysis conducted after reaching 89 PFS events (planned to occur after 71 events)
- 2nd data cutoff dated 19 August 2021: non-predefined follow-up analysis
- 3rd data cutoff dated 17 January 2022: data cutoff which was not predefined but required by the EMA in the context of the European approval process
- 4th data cutoff dated 25 August 2022: non-predefined data cutoff conducted for the purposes of scientific publication [18]

Data cutoff presented by the company is unsuitable for the benefit assessment

The company's dossier presents the results of the relevant subpopulation for the non-predefined 4th data cutoff dated 25 August 2022. For the patient-reported outcomes on morbidity and health-related quality of life, Module 4 A of the company's dossier presents analyses of the 1st data cutoff dated 26 February 2021 because these outcomes were not further surveyed. Because the 4th data cutoff was neither predefined nor required by a regulatory authority, reporting bias cannot be ruled out. Consequently, the subpopulation results presented by the company are unusable for the benefit assessment.

Company's dossier is incomplete in content

According to the module templates, the dossier is to present the results of the data cutoffs which were either predefined or required by the regulatory authorities. Consequently, the subpopulation results at the 3rd data cutoff dated 17 January 2022 are primarily relevant because this data cutoff was required by the EMA in the context of the European approval process. Since the company's dossier does not present these results, it is incomplete.

Inadequate application of elevation rule

For the benefit assessment of ibrutinib + venetoclax, the company applies the elevation rule. The company describes that the formation of the subpopulation reduces power. The probability of detecting an actual effect in the relevant subpopulation on the basis of the sample size is reportedly lower than it would be if the complete study population was used. The company argues that, under certain conditions, the elevation rule could be leveraged by conducting a test in a relevant subpopulation of a study to measure the effect with the higher significance level of 15% – rather than the conventional 5%. The company explains that it has checked compliance with formal criteria of the elevation rule for all outcomes in each case.

It is true that, according to the elevation rule, the treatment effect in the relevant subpopulation may be tested at the elevated significance level of 15% under certain conditions [19].

In the present situation, the company argues that the relevant subpopulation and the total study population are medically comparable patient populations, hence fulfilling a necessary prerequisite for the use of the elevation rule. However, this is not the case in the GLOW study. In the comparator arm with chlorambucil + obinutuzumab, the non-target population of the GLOW study receive therapy which does not correspond to the ACT specified by the G-BA for this population. As per G-BA, chlorambucil + obinutuzumab is suitable only for patients without genetic risk factors who are also ineligible for FCR therapy. For instance, 109 patients (66.5%) in the non-target population had unmutated IGHV status, and 9 patients (5.5%) had a TP53 mutation and hence genetic risk factors. Therefore, the company's approach for applying the elevation rule is not appropriate.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of ibrutinib in combination with venetoclax in comparison with the ACT in adult patients with previously untreated CLL. This results in no hint of an added benefit of ibrutinib in combination with venetoclax in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 8 summarizes the result of the assessment of added benefit of ibrutinib + venetoclax in comparison with the ACT.

Table 8: Ibrutinib + venetoclax – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with previously untreated CLL[b,c]	Ibrutinib or Ibrutinib in combination with rituximab or obinutuzumab or FCR[d, e] or Bendamustine in combination with rituximab[e, f] or **Chlorambucil in combination with** rituximab or **obinutuzumab**[e, f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. In the present therapeutic indication, patients presumably require treatment (e.g. Binet stage C).
c. In the present therapeutic indication, allogeneic stem cell transplantation is presumably not indicated at the time of treatment.
d. Only for patients without any genetic risk factors and < 65 years of age who, based on their general health and comorbidities, are eligible for FCR therapy.
e. According to current medical knowledge, the following factors are deemed genetic risk factors: presence of 17p deletion / TP53 mutation / unmutated IGHV.
f. Only for patients without genetic risk factors who are ineligible for FCR therapy. According to the G-BA, this includes both patients ≥ 65 years of age and patients < 65 years of age who, based on their general health and comorbidities, are ineligible for FCR therapy.

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; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of the tumour protein p53

The assessment described above departs from that by the company, which derived an indication of considerable added benefit based on the results of the GLOW study.

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

I 6 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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