IQWiG Reports – Commission No. A21-64

Obinutuzumab (chronic lymphocytic leukaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Obinutuzumab (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 August 2021). 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
Obinutuzumab (chronic lymphocytic leukaemia) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
12 May 2021

Internal Commission No.
A21-64

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

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.

IQWiG employees involved in the dossier assessment

- Christina Keksel
- Charlotte Guddat
- Marco Knelangen
- Stefan Kobza
- Christopher Kunigkeit
- Katrin Nink
- Sabine Ostlender
- Katharina Wölke

Keywords: Obinutuzumab, Chlorambucil, Leukemia – Lymphocytic – Chronic – B-Cell, Benefit Assessment, NCT02053610

Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CD	cluster of differentiation
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRR	infusion-related reaction
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
MedDRA	Medical Dictionary for Regulatory Activities
PFS	progression-free survival
PT	Preferred Term
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

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 obinutuzumab. 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 12 May 2021.

Research question

The aim of this report is to assess the added benefit of obinutuzumab in combination with chlorambucil (hereinafter obinutuzumab + chlorambucil) in comparison with the appropriate comparator therapy (ACT) in patients with previously untreated chronic lymphocytic leukaemia (CLL) for whom treatment with full-dose fludarabine is not an option due to comorbidities.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of obinutuzumab + chlorambucil

Indication[a]	**ACT**[b]
Adult patients with previously untreated CLL for whom treatment with full-dose fludarabine is not an option due to comorbidities	Rituximab + bendamustine or Rituximab + chlorambucil
a. The G-BA assumes that patients with 17p deletion and/or TP53 mutation are to be disregarded because chemoimmunotherapy is generally not indicated for these patients. For this therapeutic indication, it is assumed that patients require treatment (e.g. Binet stage C) and that allogeneic stem cell transplantation is not indicated at the time of therapy. b. Presented is the ACT specified by the G-BA. 17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee; TP53 mutation: mutation of the p53 tumour protein	

The company followed the G-BA's specification of the ACT. The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

Study pool and study design

For assessing the added benefit of obinutuzumab + chlorambucil in comparison with the ACT, the CLL study was included.

However, the study results presented in the company's dossier are incomplete and were inadequately compiled. This makes it impossible to adequately assess the study data, and consequently, none of the results of the CLL11 study have been for the benefit assessment.

Study design

The CLL11 study is a randomized, 3-arm, unblinded phase III study comparing obinutuzumab + chlorambucil, rituximab + chlorambucil, and chlorambucil monotherapy. For the present assessment, the obinutuzumab + chlorambucil and rituximab + chlorambucil treatment arms are relevant.

The study included adult patients with previously untreated cluster of differentiation (CD)20^+ CLL who required treatment as per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria (2008). In addition, patients had to have a Cumulative Illness Rating Scale (CIRS) score > 6 and/or creatinine clearance < 70 mL/min.

In a 2-stage randomization procedure, 333 patients were allocated to treatment with obinutuzumab + chlorambucil and 330 patients to rituximab + chlorambucil.

The study was not explicitly designed to include patients for whom treatment with full-dose fludarabine is not an option. For the outcome categories of mortality, morbidity, and health-related quality of life, but not the outcome category of side effects, the company presented analyses of a relevant subpopulation for whom treatment with full-dose fludarabine is not an option. At the final data cut-off (2017), this subpopulation included 256 patients in the obinutuzumab + chlorambucil arm and 242 patients in the rituximab + chlorambucil arm.

In both treatment arms, treatment was largely in line with the Summary of Product Characteristics (SPC). Over the course of the study, however, several changes in the study protocol were made with respect to the premedication and to splitting up the 1st obinutuzumab dose in an effort to reduce the risk of infusion-related reactions. Therefore, the premedication of patients receiving obinutuzumab was not fully in line with the SPC until version G of the study protocol.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms outcomes, health-related quality of life, and adverse events (AEs).

Incomplete submitted results

The results of the CLL11 study as presented by the company's dossier are incomplete and were inadequately compiled. It is therefore impossible to adequately assess the study data, and consequently, none of the results of the CLL11 study are usable for the benefit assessment. The rationale is provided below.

Incomplete data for the final data cut-off

The final analysis of the CLL11 study used the data cut-off of 10 October 2017. For this final data cut-off, the company's Module 4 A provides analyses on the outcome categories of mortality and side effects. However, for patient-reported outcomes of the morbidity and health-related quality of life categories, the company presented analyses only from the interim data

cut-off 9 May 2013. In departure from the dossier template's specifications, therefore, no data cut-off, particularly not the final data cut-off, offered analyses of all surveyed relevant outcomes. In this context, a considerable volume of additional data on patient-reported outcomes presumably becomes available at the final data cut-off.

No side effects analyses for the relevant subpopulation

In Module 4 A, the company presented analyses on the outcome category of side effects only for the study's total population, whereas it presented analyses of the relevant subpopulation for the other outcome categories.

The relevant subpopulation defined by the company includes only about 75% of patients of the total population. The company failed to convincingly argue that the total population's results on side effects are applicable to the relevant subpopulation.

Incomplete data on common AEs

Irrespective of the above-described problem regarding the analysed population, the information on common AEs as presented by the company is incomplete, even for the total population. The dossier template specifies that alongside the total rates of AEs, results must be provided on all AEs (operationalized as System Organ Class [SOC] and Preferred Terms [PT] as per Medical Dictionary for Regulatory Activities [MedDRA]), provided they meet a minimum prevalence threshold. A complete presentation of these common AEs (broken down AEs without further differentiation serious AEs (SAEs), and AEs and differentiated by severity) is essential for assessing side effects profiles as well as for selecting specific AEs.

Module 4 A of the company's dossier, however, presents only AEs with an incidence ≥ 10% in one study arm as well as SAEs and severe AEs (Common-Terminology-Criteria-for-Adverse-Events [CTCAE] grade ≥ 3) with an incidence ≥ 5% in at least one study arm. As per dossier template, however, all events that occurred in ≥ 10 patients and ≥ 1% of a study arm are to be additionally reported without regard to severity. Hence, the information provided in the company's dossier on common AEs is incomplete. For the benefit assessment, this makes it impossible to present common AEs or to select specific AEs on the basis of the AEs which occurred in the CLL11 study.

Final evaluation and consequences

Taken altogether, the above-described deficiencies of the dossier are deemed major. The presented data are incomplete, particularly due to the lack of results on patient-reported outcomes at the final data cut-off and the presentation of common AEs differing from the dossier template.

Overall, therefore, no usable data are available for assessing any added benefit of obinutuzumab + chlorambucil in comparison with the ACT in adult patients with previously untreated CLL for whom treatment with full-dose fludarabine is not an option due to comorbidities.

Consequently, there is no hint of an added benefit of obinutuzumab + chlorambucil 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 presents a summary of the probability and extent of added benefit of obinutuzumab + chlorambucil.

Table 3: Obinutuzumab + chlorambucil – probability and extent of added benefit

Indication[a]	ACT [b]	Probability and extent of added benefit
Adult patients with previously untreated CLL for whom treatment with full-dose fludarabine is not an option due to comorbidities	Rituximab + bendamustine or Rituximab + chlorambucil	Added benefit not proven

a. The G-BA assumes that patients with 17p deletion and/or TP53 mutation are to be disregarded because chemoimmunotherapy is generally not indicated for these patients. For this therapeutic indication, it is assumed that patients require treatment (e.g. Binet stage C) and that allogeneic stem cell transplantation is not indicated at the time of therapy.
b. Presented is the ACT specified by the G-BA.

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

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the G-BA's assessment conducted in the context of the market launch in 2014, wherein the G-BA had found an unquantifiable added benefit of obinutuzumab + chlorambucil. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization due to the special status of orphan drugs, regardless of the underlying data.

[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].

2.2 Research question

The aim of this report is to assess the added benefit of obinutuzumab in combination with chlorambucil (hereinafter obinutuzumab + chlorambucil) in comparison with the ACT in patients with previously untreated CLL for whom treatment with full-dose fludarabine is not an option due to comorbidities.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of obinutuzumab + chlorambucil

Indication[a]	**ACT**[b]
Adult patients with previously untreated CLL for whom treatment with full-dose fludarabine is not an option due to comorbidities	Rituximab + bendamustine or Rituximab + chlorambucil
a. The G-BA assumes that patients with 17p deletion and/or TP53 mutation are to be disregarded because chemoimmunotherapy is generally not indicated for these patients. For this therapeutic indication, it is assumed that patients require treatment (e.g. Binet stage C) and that allogeneic stem cell transplantation is not indicated at the time of therapy. b. Presented is the ACT specified by the G-BA. 17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee; TP53 mutation: mutation of the p53 tumour protein	

The company followed the G-BA's specification of the ACT. The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on obinutuzumab + chlorambucil (as of 16 February 2021)
- Bibliographic literature search on obinutuzumab + chlorambucil (most recent search on 16 February 2021)
- Search in trial registries / study results databases on obinutuzumab + chlorambucil (most recent search on 23 February 2021)
- Search on the G-BA website for obinutuzumab + chlorambucil (most recent search on 19 February 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on obinutuzumab (most recent search on 31 May 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

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

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
BO21004 (CLL11[d])	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8-12]

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 tables below, the study will be referred to using this short name.

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

The study pool used for the benefit assessment is consistent with that of the company, which presented the CLL11 study for deriving any added benefit of obinutuzumab + chlorambucil in comparison with rituximab + chlorambucil.

The CLL11 study is viewed as generally relevant for answering the present research question. Therefore, it is included in the benefit assessment and characterized below. However, the study results presented in the company's dossier are incomplete and were inadequately compiled. Therefore, it is impossible to adequately assess the study data, and consequently, none of the results of the CLL11 study have been included in the benefit assessment (see Section 2.4.2).

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: obinutuzumab + chlorambucil vs. rituximab + chlorambucil (multipage table)

Study	Study design	Population	Interventions (number of randomized[a] patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[b]
CLL11	RCT, open-label, parallel-group	Adult patients with previously untreated CD20$^+$ CLL[c] requiring treatment and with clinically relevant comorbidities[d]	Obinutuzumab + chlorambucil (N = 333) Rituximab + chlorambucil (N = 330) Chlorambucil[e] (N = 118) Relevant subpopulations thereof: Obinutuzumab + chlorambucil (n = 255) Rituximab + chlorambucil (n = 242)	Screening: ≤ 28 days Treatment: maximum of 6 (28-day) cycles or until confirmed progression, occurrence of unacceptable toxicity, or death Observation[g]: outcome-specific, after progression and until the start of a new leukaemia therapy, for a maximum of 8 years after inclusion of the last patients	189 centres[h] in Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Hong Kong, Italy, Mexico, New Zealand, Romania, Russia, Slovakia, Spain, Switzerland, Thailand, United Kingdom, United States 12/2009–08/2017 Data cut-off dates[h]: 09/05/2013[i] 11/05/2015[j] 10/10/2017[k] (final)	Primary: PFS Secondary: overall survival, symptoms, morbidity, health-related quality of life, AEs

Table 6: Characterization of the included study – RCT, direct comparison: obinutuzumab + chlorambucil vs. rituximab + chlorambucil (multipage table)

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

a. Patients were allocated to the treatment arms in a 2-stage randomization procedure. For the present benefit assessment, relevant results are those from patients of the relevant subpopulation who were allocated in both randomization stages to the treatment arms of obinutuzumab + chlorambucil and rituximab + chlorambucil, and hence only the results of "stage 2".
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Diagnosis and need for therapy as per IWCLL criteria (2008) [13].
d. CIRS score > 6 and/or creatinine clearance < 70 mL/min.
e. The arm is not relevant for the assessment and is not presented in the tables below. At the investigator's discretion, patients with confirmed disease progression during or within 6 months after chlorambucil treatment were allowed to switch to obinutuzumab + chlorambucil treatment. The change is of no consequence since it does not affect the analyses potentially relevant for this benefit assessment.
f. 256 patients at data cut-off 10/10/2017
g. Outcome-specific data are provided in Table 8.
h. Data for "stage 2" of the study.
i. Planned after 300 PFS events.
j. Not predefined; the company's dossier does not present any analyses on this data cut-off. The data cut-off is not relevant for the assessment and is not presented in the tables below.
k. Planned to take place after 406 PFS events.

AE: adverse event; CD: cluster of differentiation; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; IWCLL: International Workshop on Chronic Lymphocytic Leukaemia; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characterization of the intervention – RCT, direct comparison: obinutuzumab + chlorambucil vs. rituximab + chlorambucil

Study	Intervention	Comparison
CLL11	Obinutuzumab i.v. for 6 cycles [a] ▪ Cycle 1: 1000 mg each on Days 1[b], 8, and 15 ▪ Cycles 2–6: 1000 mg on Day 1 + Chlorambucil 0.5 mg/kg[c] orally on Days 1 and 15 for 6 cycles[a] The premedication before the infusions was in line with the SPC[d] [14,15].	Rituximab i.v. for 6 cycles[a] ▪ Cycle 1: 375 mg/m² on Day 1 ▪ Cycles 2–6: 500 mg/m² on Day 1 +
	Treatment interruptions Permitted for all 3 drugs, even for > 4 weeks **Dose adjustments and treatment interruptions** Obinutuzumab and rituximab: no dose reductions permitted for either of them Chlorambucil: after 1st interruption for cytopenia grade 3 or 4, continue therapy at 75% of original dose; after 2nd interruption, continue therapy at 50% of original dose; after chlorambucil discontinuation, treatment continuation with obinutuzumab and/or rituximab was permitted.	
	Nonpermitted prior treatment ▪ Any CLL therapy **Nonpermitted concomitant treatment** ▪ Other chemotherapy or investigational substances ▪ Immunotherapy or radioimmunotherapy ▪ Radiotherapy	

a. One treatment cycle equals 28 days.
b. As per study protocol amendment G dated 9 December 2011, the 1st dose was split into 100 mg on Day 1 and 900 mg on Day 2 for all patients to prevent IRR.
c. Patients with a BMI > 35 kg/m² received the dose of a patient of the same height and a BMI of 35 kg/m².
d. For obinutuzumab, fully compliant with SPC only after study protocol amendment G dated 9 December 2011, which came into effect after inclusion of the 1st patient on 21 December 2009. It is unclear how many patients received insufficient premedication. For a more detailed description, see the text below.

BMI: body mass index; CLL: chronic lymphocytic leukaemia; IRR: infusion-related reactions; i.v.: intravenous; RCT: randomized controlled trial

The CLL11 study is a randomized, 3-arm, nonblinded phase III study comparing obinutuzumab + chlorambucil, rituximab + chlorambucil, and chlorambucil monotherapy. For the present assessment, the obinutuzumab + chlorambucil and rituximab + chlorambucil treatment arms are relevant.

The study included adult patients with previously untreated $CD20^+$ CLL requiring treatment as per IWCLL criteria (2008) [13] . In addition, patients had to have a CIRS score > 6 and/or creatinine clearance < 70 mL/min.

In a 2-stage randomization procedure, 333 patients were allocated to treatment with obinutuzumab + chlorambucil and 330 patients to rituximab + chlorambucil. Randomization was stratified by Binet stage (A versus B versus C) and 5 geographic regions.

Both treatment arms received treatment for a maximum of 6 cycles taking 28 days each as long as no confirmed disease progression or unacceptable toxicities occurred. Rituximab was largely administered in line with the SPC [15]. The obinutuzumab dosing was in compliance with the SPC [14]. Over the course of the study, however, several changes in the study protocol were made with respect to the premedication and to splitting up the 1st obinutuzumab dose. Therefore, the premedication of patients receiving obinutuzumab was not fully in line with the SPC until version G of the study protocol.

The changes were intended to reduce the risk of infusion-related reactions (IRRs). As per the company's dossier, version D of the study protocol had been in effect at the start of the randomized part of the study. Accordingly, corticosteroid premedication was to be administered before the infusion to patients in the obinutuzumab + chlorambucil arm who were at high risk of IRR as well as patients in the rituximab + chlorambucil arm who had a lymphocyte count $> 25 \times 10^9$/L. Protocol amendments E through G (9 December 2011) successively intensified corticosteroid premedication for patients in the obinutuzumab + chlorambucil arm. In addition, starting with these protocol amendments, antihypertensive agents were withheld in the morning before and during obinutuzumab infusion, and the dose of the 1st obinutuzumab infusion was spread over 2 days (100 mg on Day 1; 900 mg on Day 2) for all patients. The company did not submit any information as to how many patients were treated with obinutuzumab before version G of the study protocol came into effect and hence how many did not receive premedication fully in compliance with the SPC. This is irrelevant for the present assessment because all results of the CLL11 study were disregarded for the benefit assessment.

In both treatment arms of the study, chlorambucil was administered at a dose of 0.5 mg/kg body weight on Days 1 and 15 of each cycle. According to the company, the chlorambucil dosing was derived from the experience gained in the CLL5 study [16]. For CLL therapy, the chlorambucil SPC provides dosing information only for monotherapy; beyond that, it refers to established treatment protocols [17]. For the combination with obinutuzumab, the chlorambucil dose used in the CLL11 study is in line with the obinutuzumab SPC [14]. Regarding the combination with rituximab, the SPC [15] does not provide any information on chlorambucil dosing. The recommendations on anticancer drug therapy for CLL as issued by the Germany Society of Haematology and Medical Oncology (DGHO) likewise refer to the dosage used in the CLL11 study [18]. Hence, there is no evidence of chlorambucil in combination with rituximab being administered differently than in the CLL11 study.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, symptoms outcomes, health-related quality of life, and AEs.

Relevant subpopulation

The CLL11 study included patients with clinically relevant comorbidities, but the study was not explicitly designed to include patients for whom treatment with full-dose fludarabine is not an option. However, only patients for whom therapy with full-dose fludarabine is not an option are relevant for the present assessment.

For the outcome categories of mortality, morbidity, and health-related quality of life, but not for the outcome category of side effects, the company's dossier presents analyses of a subpopulation for whom, in its view, treatment with full-dose fludarabine was not an option.

Company's approach for defining the relevant subpopulation

To define the relevant subpopulation from the total population of the CLL11 study, the company used various criteria which possibly render therapy with full-dose fludarabine an unsuitable option. The company stated that chemoimmunotherapy is unsuitable for patients with a 17p deletion and/or mutation of the p53 tumour protein (TP53 mutation) and that these patients were therefore excluded from the subpopulation of patients for whom treatment with full-dose fludarabine is not an option. When defining the subpopulation, the company viewed the further criteria as follows:

- Sufficient criteria
  - Presence of renal dysfunction (creatinine clearance < 70 mL/min, estimated using Cockroft-Gault formula)
  - Presence of autoimmune cytopenia
- Combination criteria (if ≥ 2 criteria are met, patients were included in the relevant subpopulation, provided none of the sufficient criteria was met)
  - Age ≥ 65 years
  - General condition: Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≥ 2
  - Comorbidities: CIRS > 6
  - Anaemia and/or reduced platelet count

At the final data cut-off (2017) and taking into account the above-mentioned criteria, the company analysed 498 (75.1%) of the 663 patients from the relevant study arms (obinutuzumab + chlorambucil arm: N = 256; rituximab + chlorambucil arm: N = 242).

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

No scientific consensus exists regarding the criteria for suitability or unsuitability of full-dose fludarabine therapy in patients with CLL. The company's approach took into account criteria for the decision on a suitable therapy as mentioned, e.g., in guidelines [19,20].

The company justified its choice of criteria based on a previous benefit assessment procedure in the same therapeutic indication [21-23]. As per its research question, patients were included for whom treatment with fludarabine + cyclophosphamide + rituximab was not an option. In the present assessment, in contrast, the relevant population is patients for whom full-dose fludarabine treatment is not an option. However, the criteria used by the company are assumed to be sufficient to adequately represent the relevant subpopulation of this assessment.

As a sufficient approximation of the subpopulation relevant for the research question, the subpopulation defined by the company was used in the present benefit assessment. In deviation from the company's approach, however, analyses of the relevant subpopulation are needed for all outcome categories (see Section 2.4.2).

Data cut-offs and analyses

For the CLL11 study, the company's dossier provides results on 2 data cut-offs:

- Interim data cut-off of 9 May 2013 (planned to occur upon reaching a total of 300 PFS events)
- Final data cut-off 10 October 2017 (planned to occur upon reaching a total of 406 PFS events)

Both data cut-offs were predefined. In the dossier, the company presents analyses of different outcome categories at the data cut-offs. In departure from the specifications of the dossier template [24], complete analyses, i.e., analyses of all surveyed relevant outcomes, are not available for any data cut-off, particularly not for the final data cut-off. As a result, the dossier provides incomplete information (see Section 2.4.2).

Treatment duration and follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CLL11	
Mortality	
Overall survival	Until death or study end
Morbidity	
Symptoms (EORTC QLQ-C30)	Until progression and start of a subsequent therapy, for a maximum of 5 years after inclusion of the last patient
Health-related quality of life (EORTC QLQ C30)	Until progression and start of a subsequent therapy, for a maximum of 5 years after inclusion of the last patient
Side effects	
AEs	Until 28 days after the last dose of the study drug[a]
SAEs[b]	Until 12 months after the last dose of the study medication or until the start of a subsequent therapy[c], whichever is first
Severe AEs[d]	Until 6 months after the last dose of the study medication or until the start of a subsequent therapy[c], whichever is first

a. Data from Table 9 and the schedule of study protocol version J; according to the company's Module 4 A, the outcome is followed up for 28 days after the last dose of the study drug or until the start of a subsequent therapy.
b. Unrelated to the study drug; SAEs related to the study drug were followed up for up to 8 years after the inclusion of the last patient.
c. Information from the company's Module 4 A and Table 9 of the study protocol version J; as per study protocol schedule, the outcome of SAEs was followed up for up to 12 months after the last dose of the study drug or until progression. The schedule provides no information on severe AEs.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire Core 30; RCT: randomized controlled trial; SAE: serious adverse event

Although the follow-up of symptoms and health-related quality of life was not continued throughout the study, it was, after all, continued for up to a maximum of 5 years after inclusion of the last patient.

The follow-up observation periods for the side effects outcomes have been systematically shortened; this is because they were surveyed beyond the treatment end, but not to the study end. To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire period.

Information on subsequent therapies

There is no evidence of any limitations regarding the subsequent therapy. Module 4 A, however, does not provide any information on subsequent therapies for the relevant subpopulation.

Characterization of the relevant subpopulation

Table 9 shows the patient characteristics of the relevant subpopulation of the included CLL11 study.

Table 9: Characterization of the study population – RCT, direct comparison: obinutuzumab + chlorambucil vs. rituximab + chlorambucil (relevant subpopulation) (multipage table)

Study Characteristic Category	Obinutuzumab + chlorambucil N[a] = 255[b]	Rituximab + chlorambucil N[a] = 242
CLL11		
Age [years], mean (SD)	73 (7)	74 (7)
Sex [f/m], %	38/62	39/61
Ancestry		
White	246 (96)	231 (95)
Other	9 (4)	11 (5)
Geographic region, n (%)		
North America	12 (5)	13 (5)
Central and South America	3 (1)	2 (< 1)
Western Europe	175 (69)	165 (68)
Asia Pacific	20 (8)	18 (7)
Other	45 (18)	44 (18)
Disease duration: Period from initial diagnosis to randomization [months], n (%)		
≤ 12 months	60 (24)	70 (29)
13–24 months	41 (16)	31 (13)
> 24 months	153 (60)	141 (58)
CIRS score, n (%)		
≤ 6 points	63 (25)	75 (31)
> 6 points	192 (75)	167 (69)
Creatinine clearance, n (%)		
< 70 mL/min	178 (70)	176 (73)
≥ 70 mL/min	77 (30)	66 (27)
ECOG-PS, n (%)		
0	91 (36)	85 (35)
1	136 (53)	111 (46)
2	27 (11)	43 (18)
3	1 (< 1)	2 (1)
4	0 (0)	0 (0)
Binet stage, n (%)		
A	59 (23)	57 (24)
B	104 (41)	85 (35)
C	92 (36)	100 (41)

Table 9: Characterization of the study population – RCT, direct comparison: obinutuzumab + chlorambucil vs. rituximab + chlorambucil (relevant subpopulation) (multipage table)

Study Characteristic Category	Obinutuzumab + chlorambucil N[a] = 255[b]	Rituximab + chlorambucil N[a] = 242
B symptoms, n (%)		
Fever		
Yes	8 (3)	7 (3)
No	247 (97)	234 (97)
Night sweat		
Yes	76 (30)	69 (29)
No	178 (70)	172 (71)
Weight loss		
Yes	31 (12)	36 (15)
No	224 (88)	205 (85)
Molecular genetic and cytogenetic factors, n (%)		
17p deletion or TP53 mutation	0 (0)	0 (0)
12q trisomy	45 (18)	44 (18)
11q deletion	46 (18)	43 (18)
13q deletion	79 (31)	75 (31)
No abnormality	65 (25)	58 (24)
Other	20 (8)	22 (9)
Treatment discontinuation, n (%)	ND[c]	ND[c]
Study discontinuation, n (%)	ND[d]	ND[d]

a. Number of analysed patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. Compared to the interim data cut-off (2013), 1 further person is included in the analyses on the final data cut-off (2017).
c. Based on the total population, 20% of patients in the intervention arm and 13% of the patients in the comparator arm had discontinued treatment by the final data cut-off (2017).
d. Based on the total population, 78% of patients in the intervention arm and 88% of patients in the comparator arm had discontinued the study by the final data cut-off (2017). Most study discontinuations were due to disease progression, death, and other, unspecified reasons.

11q/13q deletion: deletion of the long arm of chromosome 11/13; 12q trisomy: trisomy of the long arm of chromosome 12; 17p deletion: deletion of the short arm of chromosome 17; CIRS: Cumulative Illness Rating Scale; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TP53 mutation: mutation of the p53 tumour protein

Patient characteristics are sufficiently comparable between treatment arms. Mean patient age was 73 and 74 years, respectively, and the majority of study participants was male. Almost all patients were white and had an ECOG-PS ≤ 2. The CIRS score was > 6 in more than 2/3 of patients, and about 70% of patients had a creatinine clearance of < 70 mL/min. No data are available on treatment or study discontinuation in the relevant subpopulation.

Data on the course of the study

Table 10 shows the mean/median patient treatment duration in the relevant subpopulation as well as the mean/median duration of follow-up observation for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: obinutuzumab + chlorambucil vs. rituximab + chlorambucil (relevant subpopulation)

Study **Duration of the study phase** **Outcome category**	**Obinutuzumab + chlorambucil**	**Rituximab + chlorambucil**
CLL11		
Data cut-off of 09/05/2013		
Treatment duration [months]	**N = 260**[a]	**N = 236**[a]
Median [min; max]	5.08 [0.02; 8.53][b]	5.08 [0.02; 7.66][b]
Mean (SD)	4.55 (1.89)[b]	4.92 (1.17)[b]
Follow-up duration [months]	**N = 255**	**N = 242**
Overall survival		
Median [min; max]	ND [0.03; 36.21]	ND [0.79; 35.84]
Mean (SD)	19.06 (ND)	19.37 (ND)
Morbidity, health-related quality of life	ND	ND
Side effects	ND	ND
Data cut-off of 10/10/2017		
Treatment duration [months][c]	**N = 260**[a]	**N = 236**[a]
Median [min; max]	5.08 [0.02; 8.53][b]	5.08 [0.02; 7.66][b]
Mean (SD)	4.55 (1.89)[b]	4.92 (1.17)[b]
Follow-up duration [months]	**N = 256**	**N = 242**
Overall survival		
Median [min; max]	ND [0.03; 85.09]	ND [0.79; 83.71]
Mean (SD)	53.30 (ND)	51.57 (ND)
Morbidity, health-related quality of life	ND	ND
Side effects	ND	ND

a. Patients who had received at least one dose of the medication were analysed according to the actually received medication ("as treated").
b. IQWiG calculations: conversion from weeks to months.
c. Since according to the company, all patients had already discontinued treatment at the interim data cut-off (2013), the company did not calculate treatment duration for the final data cut-off (2017). However, 1 further person was included in the analysis of the observation durations at the final data cut-off when compared to the interim data cut-off.

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

At the interim data cut-off (2013), the treatment arms have a sufficiently similar treatment duration. The same is true for the final data cut-off (2017) since according to the company, all patients had already terminated treatment at the interim data cut-off. Except for mean overall

survival, no data are available on the mean/median observation duration for individual outcomes.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Symptoms, measured with the symptom scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)
  - B symptoms
- Health-related quality of life
  - Surveyed with the EORTC QLQ-Hepatocellular Carcinoma / Primary Liver Cancer Module 18 (EORTC QLQ-HCC18) functioning scales
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Infections
  - Infusion-related reactions
  - Further specific AEs, if any

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

For the G-BA's assessment as part of the marketing authorization in 2014, the company's dossier had included post hoc analyses on the non-predefined outcome of absence of all B symptoms. This outcome was included as relevant by the G-BA. The company did not present the outcome in the current dossier. The outcome of B symptoms is generally patient-relevant, and corresponding results from a suitable analysis of all patients were taken into account.

Since the results presented by the company were not used for the benefit assessment (see Section 2.4.2), an assessment of the risk of bias at study and outcome levels for the CLL11 study was foregone.

2.4.2 Usability of the study results for the benefit assessment

The results of the CLL11 study as presented by the company's dossier are incomplete and were inadequately compiled. It is therefore impossible to adequately assess the study data, and consequently, none of the results of the CLL11 study are usable for the benefit assessment. The rationale is provided below.

Incomplete data for the final data cut-off

The final analysis of the CLL11 study relied on the data cut-off of 10 October 2017. For this final data cut-off, the company's Module 4 A provides analyses on the outcome categories of mortality and side effects. However, for patient-reported outcomes of the morbidity and health-related quality of life categories, the company presented analyses only from the interim data cut-off 9 May 2013. The company referred to this data cut-off as final or confirmatory for these outcomes. Nonetheless, it is unclear why the company considers these outcomes as final. In departure from the specifications of the dossier template [24], therefore, analyses for all surveyed relevant outcomes are not available for any data cut-off, particularly not the final data cut-off. In this context, a considerable volume of additional data on patient-reported outcomes presumably becomes available at the final data cut-off. According to the study protocol, the EORTC QLQ-C30 questionnaire was administered up to progression and start of a subsequent therapy, for a maximum of 5 years after inclusion of the last patient. According to Module 4 A, the survey was continued until Month 84 of follow-up (= 7 years).

At the time of the interim data cut-off (2013), patients had been followed-up for a maximum of 3.5 years. In addition, only a small percentage of patients of the total population had started a subsequent therapy (16.5% in the intervention arm and 26.1% in the comparator arm) at this data cut-off. If one assumes that no relevant percentage of patients had discontinued the study by the interim data cut-off date, this suggests that a large percentage of patients (including in the relevant subpopulation) were still on follow-up observation. Consequently, a meaningful volume of data was presumably still being collected at the final data cut-off for patient-reported outcomes of the morbidity and health-related quality of life categories. The benefit assessment lacks results based on these data.

Adequate analyses needed on EORTC QLQ-C30

Besides being flawed in terms of completeness, as discussed above, the company's analyses provided in the dossier invite criticism in the following respects: The company submitted responder analyses (relative risk [RR]). In addition to results from the only analysis time point during treatment (Day 1 of Cycle 4), the company presented results from Follow-Up Month 3. It is unclear on which basis the company chose the analysis time point of Follow-Up Month 3, particularly since it was not predefined in any analysis of the patient-reported outcomes. In addition, it is intransparent why available surveys that extend even to Follow-Up Month 84 (provided no subsequent therapy had been started) were disregarded. In addition, data are missing on the durations of outcome-specific follow-up. These durations are needed at the final

data cut-off to estimate whether an analysis via RR was adequate, particularly regarding later survey time points.

For the analysis of continuous data, the company apparently allocated results surveyed at different time points from randomization to a constructed time point (Follow-up Day 28 and Follow-up Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 42, 48, 54, 60, 66, 72, 78, 84 after treatment end). This approach can result in serious bias, particularly in progressive courses of disease with different treatment durations. Therefore, the surveyed values should be presented with the time from randomization. In the present situation, however, this aspect seems negligible since the treatment durations of the two arms had an identical median and very similar mean.

Overall, drawing any conclusions on added benefit requires the results on patient-reported outcomes at the final data cut-off in the form of a suitable analysis, e.g. responder analyses during treatment and at the latest possible time point at which an adequate analysis is possible [1] or analyses of continuous data covering the entire study period. Responder analyses are preferred:

As discussed in IQWiG General Methods [1], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change that is perceivable for patients [25]). Irrespective of the above, for a transition period until the revised module templates for the dossier enter into force, primarily analyses with the previously accepted response threshold of 10 points are used for the EORTC QLQ-C30 and all additional EORTC modules (see Frequently Asked Questions from the G-BA: [26]).

No side effects analyses for the relevant subpopulation

In Module 4 A, the company presented analyses on the outcome category of side effects only for the study's total population, whereas it presented analyses of the relevant subpopulation for the other outcome categories. This approach is inadequate.

The relevant subpopulation defined by the company (see Section 2.3.2) accounts for only about 75% of patients of the total population. According to the Institute's General Methods, studies in which the population inclusion criterion was met by fewer than 80% of patients included in the study are used only if analyses of the relevant subpopulation are available or if it is sufficiently plausible or proven that results obtained in the study are applicable to the target population [1]. The company did not present the results on the relevant subpopulation, nor did it convincingly argue that the total population's side effects results are applicable to the relevant subpopulation.

Moreover, additional points of criticism arising from the company's analyses are as follows: The company presented analyses using RR, but not HR. No data were available on the outcome-specific follow-up duration for these outcomes. The planned follow-up observation for SAEs

as well as severe AEs (CTCAE grade ≥ 3), however, ends either after a defined period or with the start of a subsequent therapy (see Table 8). Therefore, the outcome-specific follow-up durations are needed for estimating whether the use of RR is adequate in these cases. For the outcome of discontinuation due to AEs, the company's dossier also fails to specify whether this involves the discontinuation of at least 1 component or of both components. For the following benefit assessment, the discontinuation of at least 1 component is an adequate operationalization.

Incomplete data on common AEs

Irrespective of the above-described problem regarding the analysed population, the information on common AEs as presented by the company is incomplete, even for the total population. According to the dossier template, alongside the total rates of AEs, results on all AEs (operationalized as SOC and PT as per MedDRA) must be presented, provided they exceed a minimum prevalence [24]. A complete presentation of these common AEs (separately by AEs without further differentiation, SAEs, AEs differentiated by severity) is essential for assessing the AE profile as well as for selecting specific AEs [1].

However, Module 4 A of the company's dossier presents only a subset of these AEs, namely AEs that occurred at an incidence ≥ 10% in a study arm as well as SAEs and severe AEs (CTCAE grade ≥ 3) at an incidence of ≥ 5% in at least one study arm. As per dossier template, however, all events that occurred in ≥ 10 patients and ≥ 1% of a study arm are to be additionally reported without regard to severity. Hence, the information provided in the company's dossier on common AEs is incomplete. For the benefit assessment, this makes it impossible to present common AEs or to select specific AEs on the basis of the AEs which occurred in the CLL11 study.

Further points of criticism

As already described above, the company's dossier also lacks information on outcome-specific follow-up durations as well as on the subsequent therapies used in the study. Alongside the incompletely presented results, this issue further complicates the interpretation of study data.

Final evaluation and consequences

Taken altogether, the above-described deficiencies of the dossier are deemed major. The presented data are incomplete, particularly due to the lack of results on patient-reported outcomes at the final data cut-off and the presentation of common AEs differing from the dossier template.

Due to the incomplete data, it is therefore impossible to adequately weigh benefit and harm and hence to assess the added benefit of obinutuzumab + chlorambucil in comparison with the ACT. A presentation of usable study results presented in the dossier is foregone as well.

No usable data are available for assessing any added benefit of obinutuzumab + chlorambucil in comparison with the ACT in adult patients with previously untreated CLL for whom

treatment with full-dose fludarabine is not an option due to comorbidities. Consequently, there is no hint of an added benefit of obinutuzumab + chlorambucil in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 11 presents a summary of the results of the benefit assessment of obinutuzumab + chlorambucil in comparison with the ACT.

Table 11: Obinutuzumab + chlorambucil – probability and extent of added benefit

Indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Adult patients with previously untreated CLL for whom treatment with full-dose fludarabine is not an option due to comorbidities	Rituximab + bendamustine or Rituximab + chlorambucil	Added benefit not proven
a. The G-BA assumes that patients with 17p deletion and/or TP53 mutation are to be disregarded because chemoimmunotherapy is generally not indicated for these patients. For this therapeutic indication, it is assumed that patients require treatment (e.g. Binet stage C) and that allogeneic stem cell transplantation is not indicated at the time of therapy. b. Presented is the ACT specified by the G-BA. 17p deletion: deletion of the short arm of chromosome 17; G-BA: Federal Joint Committee; TP53 mutation: mutation of the p53 tumour protein		

The assessment described above deviates from that by the company, which derived proof of minor benefit based on the results of the CLL11 study. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the G-BA's assessment conducted in the context of the market launch in 2014, wherein the G-BA had found an unquantifiable added benefit of obinutuzumab + chlorambucil. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization due to the special status of orphan drugs, regardless of the underlying data.

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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