IQWiG Reports – Commission No. A20-39

Venetoclax (chronic lymphocytic leukaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Venetoclax (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 July 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
17p	short arm of chromosome 17
ACT	appropriate comparator therapy
AE	adverse event
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
DGHO	Deutsche Gesellschaft für Hämatologie und Onkologie (German Society for Haematology and Medical Oncology)
EMA	European Medicines Agency
FCR	fludarabine in combination with cyclophosphamide and rituximab
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IGHV	immunoglobulin heavy-chain variable
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)
SPC	Summary of Product Characteristics
TP53	gene of the tumour suppressor protein p53

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 venetoclax. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 3 April 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is to assess the added benefit of venetoclax in combination with obinutuzumab in comparison with the appropriate comparator therapy (ACT) in adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

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

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

Research question	**Subindication[a]**	**ACT[b]**
1	Adult patients with previously untreated CLL for whom treatment with FCR is an option	Fludarabine in combination with cyclophosphamide and rituximab
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. It is assumed 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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein 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 in combination with cyclophosphamide and rituximab (FCR) is an option (FCR therapy suitable)
- Research question 2: patients for whom FCR therapy is not an option (FCR therapy unsuitable)
- Research question 3: patients with deletion on the short arm of chromosome 17 (17p deletion) and/or a mutation of the gene of the tumour suppressor protein p53 (TP53) or for whom chemo-immunotherapy is not indicated for other reasons (chemo-immunotherapy unsuitable)

The company followed the G-BA's specification of the ACT for all 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: FCR therapy suitable

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

Results for research question 2: FCR therapy unsuitable

For the derivation of the added benefit for research question 2, the company used a subpopulation (subpopulation 2) of the CLL14 study included by the company.

The CLL14 study is unsuitable for the derivation of an added benefit for research question 2, however. In addition, the subpopulation 2 formed by the company is not a complete representation of the population of research question 2.

The CLL14 study is an open-label, randomized parallel-group study on the comparison of venetoclax + obinutuzumab versus chlorambucil + obinutuzumab. It included patients with previously untreated CLL requiring treatment, and comorbidities.

In the CLL14 study, chlorambucil was administered initially for 6 cycles in combination with obinutuzumab, followed by monochemotherapy with chlorambucil for a further 6 cycles. The Summary of Product Characteristics (SPC) of chlorambucil does not contain any explicit information on the duration of therapy. However, the S3 guideline recommends conducting a combination therapy with chlorambucil and obinutuzumab over 6 cycles in patients with CLL. Longer administration of chlorambucil over a total of 12 cycles can have an effect on both benefit and harm outcomes. The company did not provide sufficient data to allow the

conclusion that longer administration of chlorambucil has no effect on the occurrence of adverse events (AEs) in the control arm

The company formed 2 subpopulations out of the total number of patients included. Subpopulation 2 includes 148 patients for whom, according to the company, FCR therapy is not an option; this subpopulation was used by the company for research question 2. Subpopulation 3 includes 258 patients for whom, according to the company, chemo-immunotherapy is not indicated; this subpopulation was used by the company for research question 3.

All patients in the CLL14 study for whom there are no reasons against chemo-immunotherapy are eligible for research question 2. Besides the presence of 17p deletion and/or TP53 mutation and age (> 65 years), the company also used the immunoglobulin heavy-chain variable (IGHV) mutation status as a criterion for differentiating between patients for whom chemo-immunotherapy is suitable and those for whom chemo-immunotherapy is unsuitable. Thus, it assigned all patients (> 65 years) with mutated IGHV gene, but without 17p deletion or TP53 mutation to research question 2. It assigned patients with unmutated IGHV gene or 17p deletion or TP53 mutation, regardless of age, to research question 3. This leads to patients being assigned to subpopulation 3 (patients for whom chemo-immunotherapy is unsuitable) solely on the basis of their IGHV mutation status, which is considered not appropriate.

There is not yet sufficient evidence that patients with an unmutated IGHV gene should generally not receive chemo-immunotherapy. For research question 2, a subpopulation of the CLL14 study was to be analysed regardless of their IGHV mutation status.

Overall, the results on research question 2 are unusable, as it cannot be estimated what effect the longer administration of chlorambucil in the comparator arm had on harm and benefit outcomes. In addition, the company's subpopulation 2 might not be a complete representation of the population of patients for whom FCR therapy is unsuitable, but who could be treated with chemo-immunotherapy.

This resulted in no hint of an added benefit in comparison with the ACT. An added benefit is therefore not proven.

Results for research question 3: chemo-immunotherapy unsuitable

The company identified no study that allowed a direct comparison of venetoclax + obinutuzumab in comparison with ibrutinib, the ACT specified by the G-BA. However, the company argued that the CLL14 study also included patients for whom chemo-immunotherapy is not indicated and who would therefore be suitable for research question 3. The company delimited this subpopulation by means of the presence of 17p deletion and/or TP53 mutation and the IGHV mutation status.

Since the CLL14 study conducted no comparison with the corresponding ACT, this study is unsuitable for deriving an added benefit for research question 3.

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 venetoclax + obinutuzumab in comparison with the ACT are assessed as follows:

Research question 1: FCR therapy suitable

The company presented no data for the assessment of the added benefit of venetoclax + obinutuzumab in comparison with the ACT in patients for whom FCR therapy is an option. An added benefit of venetoclax + obinutuzumab for research question 1 is therefore not proven.

Research question 2: FCR therapy unsuitable

The company presented no usable data for the assessment of the added benefit of venetoclax + obinutuzumab in comparison with the ACT in patients for whom FCR therapy is not an option. An added benefit of venetoclax + obinutuzumab for research question 2 is therefore not proven.

Research question 3: chemo-immunotherapy unsuitable

The company presented no data for the assessment of the added benefit of venetoclax + obinutuzumab in comparison with the ACT in patients for whom chemo-immunotherapy is not indicated. An added benefit of venetoclax + obinutuzumab for research question 3 is therefore not proven.

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

[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: Venetoclax + obinutuzumab – 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	Added benefit not proven
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. It is assumed 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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein p53

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of venetoclax in combination with obinutuzumab in comparison with the ACT in adult patients with previously untreated CLL.

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

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

Research question	**Subindication**[a]	**ACT**[b]
1	Adult patients with previously untreated CLL for whom treatment with FCR is an option	Fludarabine in combination with cyclophosphamide and rituximab
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. It is assumed 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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein 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 (FCR therapy suitable)
- Research question 2: patients for whom FCR therapy is not an option (FCR therapy unsuitable)
- Research question 3: patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons (chemo-immunotherapy unsuitable)

The company followed the G-BA's specification of the ACT for all 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: FCR therapy suitable

2.3.1 Information retrieval and study pool (research question 1 – FCR therapy suitable)

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 venetoclax + obinutuzumab (status: 22 January 2020)
- bibliographical literature search on venetoclax + obinutuzumab (last search on 22 January 2020)
- search in trial registries/trial results databases for studies on venetoclax + obinutuzumab (last search on 3 February 2020)
- search on the G-BA website for venetoclax + obinutuzumab (last search on 3 February 2020)

To check the completeness of the study pool:

- search in trial registries for studies on venetoclax + obinutuzumab (last search on 16 April 2020)

No relevant study was identified from the check. The company also identified no suitable studies.

2.3.2 Results on the added benefit (research question 1 – FCR therapy suitable)

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

2.3.3 Probability and extent of added benefit (research question 1 – FCR therapy suitable)

The company presented no data for the assessment of the added benefit of venetoclax + obinutuzumab in comparison with the ACT in patients for whom FCR therapy is an option. An added benefit of venetoclax + obinutuzumab for research question 1 is therefore not proven.

This concurs with the company’s assessment.

2.4 Research question 2: FCR therapy unsuitable

2.4.1 Information retrieval and study pool (research question 2 – FCR therapy unsuitable)

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 venetoclax + obinutuzumab (status: 22 January 2020)
- bibliographical literature search on venetoclax + obinutuzumab (last search on 22 January 2020)
- search in trial registries/trial results databases for studies on venetoclax + obinutuzumab (last search on 3 February 2020)
- search on the G-BA website for venetoclax + obinutuzumab (last search on 3 February 2020)

To check the completeness of the study pool:

- search in trial registries for studies on venetoclax + obinutuzumab (last search on 16 April 2020)

No additional relevant study was identified from the check.

Study pool of the company

For the derivation of the added benefit for research question 2, the company used a subpopulation (subpopulation 2) of the CLL14 study included by the company.

The CLL14 study is unsuitable for the derivation of an added benefit for research question 2. In addition, the company's subpopulation was not adequately formed and is not a complete representation of the population of research question 2. The CLL14 study, the company's approach to forming the subpopulation and the reasons why the presented subpopulation 2 only partially represents the population of research question 2 are described in detail below.

Study characteristics of the CLL14 study included by the company

Table 5 and Table 6 describe the CLL14 study included by the company.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CLL14	RCT, open-label, parallel	Adult patients with previously untreated CLL requiring treatment[b], and comorbidities ▪ CIRS > 6 or ▪ creatinine clearance < 70 mL/min and ≥ 30 mL/min	Venetoclax + obinutuzumab (N = 216) chlorambucil + obinutuzumab (N = 216)	Screening: ≤ 28 days Treatment: 12 cycles (of 28 days) in total ▪ 6 cycles of venetoclax or chlorambucil in combination with obinutuzumab, followed by ▪ 6 cycles of venetoclax or chlorambucil as monotherapy Observation: outcome-specific, at most until 5 years after inclusion of the last patient	130 centres in Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Croatia, Denmark, Estonia, France, Germany, Italy, Mexico, New Zealand, Poland, Romania, Russia, Switzerland, Spain, United Kingdom, United States 8/2015–ongoing First data cut-off: 17 Aug 2018 (primary analysis) Second data cut-off: 17 Jan 2019 (only AE outcomes, at FDA's request) Third data cut-off: 23 Aug 2019 (at EMA's request)	Primary: PFS Secondary: symptoms, health-related quality of life, overall survival, 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. Diagnosis and treatment requirement according to the IWCLL criteria (2008) [3].

AE: adverse event; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; EMA: European Medicines Agency; FDA: Food and Drug Administration; IWCLL: International Workshop on Chronic Lymphocytic Leukemia; N: number of randomized (included) patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 6: Characteristics of the intervention – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study	Intervention	Comparison
CLL14	Venetoclax, orally, for 12 cycles [a] (cycles 1–6 in combination with obinutuzumab, cycles 7–12 as monotherapy) ▪ cycle 1: ▫ days 22–28: 20 mg/day ▪ cycle 2: ▫ days 1–7: 50 mg/day ▫ days 8–14: 100 mg/day ▫ days 15–21: 200 mg/day ▫ days 22–28: 400 mg/day ▪ cycles 3–12: 400 mg/day + obinutuzumab, 1000 mg, IV, over cycles[a] 1–6 ▪ cycle 1: 1000 mg on days 1, 8 and 15 ▪ cycles 2–6: 1000 mg on day 1 of each cycle	chlorambucil 0.5 mg/kg BW, orally, for 12 cycles[a], on days 1 and 15 (cycles 1–6 in combination with obinutuzumab, cycles 7–12 as monotherapy)
	Dose adjustments and treatment interruptions Dose adjustments, treatment interruptions and treatment discontinuation due to toxicity allowed[c] ▪ Dose reduction for obinutuzumab was excluded. ▪ In case of discontinuation of treatment with venetoclax or chlorambucil due to toxicity, treatment with obinutuzumab also had to be discontinued.	
	Premedication and concomitant treatment Obinutuzumab: prophylaxis of tumour lysis syndrome in patients with high tumour load: high fluid intake before each dose, allopurinol or alternative **Prohibited prior/concomitant treatment** ▪ radiotherapy, immunotherapy, and any other antineoplastic therapy during treatment with the study medication and ≤ 5 half-lives prior to treatment with venetoclax; biologic agents for antineoplastic treatment ≤ 8 weeks prior to treatment with venetoclax ▪ hormonal therapy (other than contraceptives, hormone replacement therapy or megestrol acetate) during treatment with the study medication ▪ steroids (except inhaled steroids for asthma, topical steroids, or replacement corticosteroids) during treatment with the study medication ▪ moderate to strong CYP3A inhibitors and inducers ≤ 7 days prior to treatment with venetoclax and during venetoclax up-titration phase; grapefruit, grapefruit products, bitter oranges and star fruit ≤ 3 days prior to treatment with venetoclax	

a. One treatment cycle has 28 days.
b. The infusion on day 1 could be divided into 2 infusion bags (100 mg and 900 mg). If the first infusion was administered without modifications of the infusion rate and without interruptions, the second bag could be administered on the same day; otherwise, the second bag had to be administered on day 2.
c. Toxicity-related dose adjustments up to treatment discontinuation were made without relevant deviation from the requirements of the SPC. In case of permanent discontinuation of treatment with obinutuzumab, administration of venetoclax or chlorambucil could be continued.

BW: body weight; CYP3A: cytochrome P450 3A; IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The CLL14 study is an open-label, randomized parallel-group study on the comparison of venetoclax + obinutuzumab versus chlorambucil + obinutuzumab. It included patients with previously untreated CLL requiring treatment according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria (2008) [3]. In addition, the patients had to have comorbidities, defined by a Cumulative Illness Rating Scale (CIRS) score > 6 or impaired renal function (creatinine clearance < 70 mL/min).

A total of 432 patients were included and randomly allocated in a 1:1 ratio to treatment with venetoclax + obinutuzumab (N = 216) or to treatment with chlorambucil + obinutuzumab (N = 216). Randomization was stratified by Binet stage (A versus B versus C) and geographical region (United States/Canada/Central America versus Australia/New Zealand versus Western Europe versus Central and Eastern Europe versus Latin America).

The company formed 2 subpopulations out of the total number of patients included. Subpopulation 2 includes 148 patients for whom, according to the company, FCR therapy is not an option, and whom the company therefore considered relevant for research question 2. Subpopulation 3 includes 258 patients for whom, according to the company, chemo-immunotherapy is not indicated. A detailed discussion of the inclusion criteria of both subpopulations can be found below.

Treatment with venetoclax and obinutuzumab was in compliance with the SPCs [4,5]. Treatment with chlorambucil, in contrast, did not comply with the recommendations, as is described further below.

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

A total of 3 data cut-offs were conducted for the CLL14 study.

- The first data cut-off was to take place after prespecified 110 PFS events and was performed on 17 August 2018 after 107 PFS events.
- A second data cut-off was conducted on 17 January 2019 at the request of the Food and Drug Administration (FDA) for AE outcomes.
- The third data cut-off was conducted on 23 August 2019 at the request of the European Medicines Agency (EMA) in the framework of the EU authorization procedure.

The third data cut-off was used by the company in the present dossier for the benefit assessment.

Chlorambucil administration not in compliance with guideline recommendations, effect on results unclear

In the comparator arm, chlorambucil was administered initially over 6 cycles in combination with obinutuzumab. Administration of chlorambucil was then continued as monochemotherapy for a further 6 cycles. The SPC of chlorambucil does not contain any explicit information on

the duration of therapy [6]. However, the S3 guideline [7] recommends conducting a combination therapy with chlorambucil and obinutuzumab over 6 cycles in patients with CLL. However, there is no recommendation in the guideline for further therapy with chlorambucil.

The company argued that dosing and duration of chlorambucil administration were heterogeneous in studies and everyday health care. To illustrate this, it presented a list of studies in CLL, indicating the number of cycles and the dosage of chlorambucil. The company added that administration over 12 cycles in the CLL14 study was associated with a tendency of further improved response measured using minimal residual disease (MRD) negativity after cycle 6 [8]. It referred to a presentation showing data on various outcomes, including MRD negativity, of the CLL14 study. This improved response was not associated with a deterioration in tolerability. Instead, there was even a decrease in AEs over the course of the 12 cycles.

The company's reasoning is not substantive. From the presentation of the CLL studies, it is clear that the only studies that allowed a maximum of 12 cycles of chlorambucil were those in which chlorambucil was continuously given as monotherapy. In only 2 of the studies presented, chlorambucil was given in combination with obinutuzumab, including the approval study of obinutuzumab [9]. In both studies, chlorambucil was given for only 6 cycles.

Longer administration of chlorambucil or initial treatment as combination therapy followed by monotherapy over a total of 12 cycles can have an effect on both benefit and harm outcomes. To assess whether the administration of chlorambucil over 12 cycles is comparable with the administration of chlorambucil over 6 cycles with regard to the occurrence of AEs, studies would be needed that would allow such a comparison, namely a comparison between patients who were treated with chlorambucil for 6 or 12 cycles, with analyses at different time points. The company did not provide such data, however. In order to be able to estimate the effects on AE outcomes based on the results of the CLL14 study, at least Kaplan-Meier curves on specific AEs would be required to estimate how the occurrence of AEs develops over time in the chlorambucil arm and whether a longer administration of chlorambucil possibly leads to an increased occurrence of AEs after cycle 6. However, the company only presented raw overall rates for superordinate AE outcomes and specific AEs, which did not differ significantly between treatment arms for the relevant superordinate AE outcomes. It cannot be deduced from the analyses presented that longer treatment with chlorambucil has no negative effects on the occurrence of AEs. If, for example, more AEs occur in the comparator arm after 6 cycles, this will not be reflected in the respective overall rates.

IGHV mutation status is an unsuitable criterion to differentiate between patients suitable for chemo-immunotherapy and those unsuitable for chemo-immunotherapy

The G-BA differentiated between 3 therapeutic situations for the present benefit assessment. Research question 2 includes patients for whom FCR therapy is not an option, but for whom other chemo-immunotherapy is an option (subpopulation 2). For research question 3, patients were to be considered for whom chemo-immunotherapy is not an option (subpopulation 3). The company cited the following criteria for the delimitation of this subpopulation 3: presence of

17p deletion and/or TP53 mutation, or patients for whom chemo-immunotherapy is not indicated for other reasons. The G-BA added that patients for whom chemo-immunotherapy is not indicated for other reasons are, for example, patients for whom, according to the generally recognized state of knowledge, no sufficient response to chemo-immunotherapy can be expected due to their mutation status, or who cannot be treated with chemo-immunotherapy due to a reduced general condition.

Besides the presence of 17p deletion and/or TP53 mutation and age (> 65 years), the company also used the IGHV mutation status as a criterion for differentiating between patients for whom chemo-immunotherapy is suitable and those for whom chemo-immunotherapy is unsuitable. Thus, it assigned all patients (> 65 years) with mutated IGHV gene, but without 17p deletion or TP53 mutation to research question 2. It assigned patients with unmutated IGHV gene or 17p deletion or TP53 mutation, regardless of age, to research question 3.

However, the IGHV mutation status is not yet an established factor in the choice of therapy. There is not yet sufficient evidence that patients with an unmutated IGHV gene should generally not receive chemo-immunotherapy. The German Society for Haematology and Medical Oncology (DGHO) recommends treatment with ibrutinib or chemo-immunotherapy for unfit patients with an unmutated IGHV gene [10]. In the evidence-based S3 guideline, the IGHV mutation status of patients is not described as a decision criterion for the choice of therapy [7].

The company's approach of using the IGHV mutation status as a decision criterion for identifying patients for whom chemo-immunotherapy is unsuitable leads to patients being assigned to subpopulation 3 (patients for whom chemo-immunotherapy is unsuitable) solely on the basis of their IGHV mutation status. It is possible that chemo-immunotherapy is a treatment option for a large proportion of these patients, so that they would have to be assigned to subpopulation 2 (patients unsuitable for FCR). The company included 258 patients of the CLL14 study with 17p deletion and/or TP53 mutation and/or unmutated IGHV gene in subpopulation 3. Out of these patients, 12% had 17p deletion, 16% had TP53 mutation, and 95% had an unmutated IGHV status. Even if there is no overlap between the different genetic factors, the vast majority of patients were included in subpopulation 3 solely because of an unmutated IGHV gene. Of all 258 patients in subpopulation 3, at least 174 patients had neither 17p deletion nor TP53 mutation. It is unclear how many of these patients would have to be assigned also to research question 2. For research question 2, a subpopulation of the CLL14 study was to be analysed regardless of their IGHV mutation status.

Summary

Overall, the results on research question 2 are unusable, as it cannot be estimated what effect the longer administration of chlorambucil in the comparator arm had on the results on patient-relevant outcomes. In addition, the company's subpopulation 2 might not be a complete representation of the population of those patients for whom FCR therapy is unsuitable, but who could be treated with another chemo-immunotherapy.

2.4.2 Results on the added benefit (research question 2 – FCR therapy unsuitable)

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

2.4.3 Probability and extent of added benefit (research question 2 – FCR therapy unsuitable)

The company presented no usable data for the assessment of the added benefit of venetoclax + obinutuzumab in comparison with the ACT in patients for whom FCR therapy is not an option. An added benefit of venetoclax + obinutuzumab for research question 2 is therefore not proven.

This deviates from the assessment of the company, which derived an indication of a considerable added benefit under consideration of the results of the CLL14 study.

2.5 Research question 3: chemo-immunotherapy unsuitable

2.5.1 Information retrieval and study pool (research question 3 – chemo-immunotherapy unsuitable)

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 venetoclax + obinutuzumab (status: 22 January 2020)
- bibliographical literature search on venetoclax + obinutuzumab (last search on 22 January 2020)
- search in trial registries/trial results databases for studies on venetoclax + obinutuzumab (last search on 3 February 2020)
- search on the G-BA website for venetoclax + obinutuzumab (last search on 3 February 2020)

To check the completeness of the study pool:

- search in trial registries for studies on venetoclax + obinutuzumab (last search on 16 April 2020)

No relevant study was identified from the check. The company also did not identify any study in comparison with the ACT specified by the G-BA.

2.5.2 Results on the added benefit (research question 3 – chemo-immunotherapy unsuitable)

The company identified no study that allowed a direct comparison of venetoclax + obinutuzumab in comparison with ibrutinib, the ACT specified by the G-BA. However, the company argued that the CLL14 study also included patients for whom chemo-immunotherapy is not indicated and who would therefore be suitable for research question 3. The company delimited this subpopulation by means of the presence of 17p deletion and/or TP53 mutation and the IGHV mutation status. A detailed discussion of the suitability of these criteria can be found in Section 2.4.1.

Since the CLL14 study conducted no comparison with the corresponding ACT, this study is unsuitable for deriving an added benefit for research question 3. In addition, the question arises whether a patient population defined by the company itself as not eligible for chemo-immunotherapy was adequately treated with the chemo-immunotherapy chlorambucil + obinutuzumab in the comparator arm of the study.

2.5.3 Probability and extent of added benefit (research question 3 – chemo-immunotherapy unsuitable)

The company presented no data for the assessment of the added benefit of venetoclax + obinutuzumab in comparison with the ACT in patients for whom chemo-immunotherapy is not indicated. An added benefit of venetoclax + obinutuzumab for research question 3 is therefore not proven.

This assessment deviates from that of the company, which derived a hint of a non-quantifiable added benefit based on a direct comparison of venetoclax + obinutuzumab versus the comparator therapy chlorambucil + obinutuzumab, which does not concur with the ACT specified by the G-BA.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of venetoclax + obinutuzumab in comparison with the ACT is summarized in Table 7.

Table 7: Venetoclax + obinutuzumab – 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	Added benefit not proven
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. It is assumed 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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein p53

The approach for the derivation of 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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