IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-60

Ibrutinib (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 *Ibrutinib (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 December 2016). 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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[3] 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
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BR	(combination therapy of) bendamustine and rituximab
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
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Levels
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PEI	Paul-Ehrlich-Institut
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ibrutinib in combination with bendamustine and rituximab (ibrutinib + BR). 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 23 September 2016.

Research question

The aim of this report was to assess the added benefit of ibrutinib + BR in comparison with the appropriate comparator therapy (ACT) specified by the G-BA for adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy and for whom chemotherapy is indicated.

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

Therapeutic indication	**ACT**[a]
Patients with CLL who have received at least one prior therapy and for whom chemotherapy indicated is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; BR: bendamustine + rituximab; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee	

The company followed the ACT specified by the G-BA for the present research question; it considered the BR combination to be the most adequate and the most common treatment option for the majority of patients with pretreated CLL.

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

Results

Study pool and patient population

The randomized, placebo-controlled approval study HELIOS was included in the present benefit assessment. The study had a double-blind design, but blinding was not completely maintained: Patients in the control arm who switched to the intervention arm of the study because of progression were unblinded. In addition, the study was unblinded after the first interim analysis.

Adult patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) with at least one prior systemic therapy were included.

A total of 578 patients were randomly allocated to treatment with ibrutinib or placebo (each in combination with BR). Patients were stratified according to whether they were refractory to purine analogues (yes/no) and by number of prior therapies (1/> 1).

The results of the BR population were used for the present benefit assessment. The BR population comprised those patients who were refractory to purine analogue treatment and had received at least 2 prior systemic therapies. These were 106 patients (53 patients in the ibrutinib arm and 53 patients in the placebo arm). These criteria were principally suitable to form a patient population for which BR constitutes an optimized chemotherapy in combination with rituximab in the sense of the ACT specified by the G-BA.

The evidence provided by the company therefore allowed conclusions on the added benefit of ibrutinib + BR for the subgroup of patients who have received at least 2 prior therapies and for whom BR is the individually optimized chemotherapy in combination with rituximab. The company presented no usable data for further patients of the target population (patients with only 1 prior therapy and patients for whom other treatments than BR are the individually optimized treatment).

Risk of bias

The risk of bias at the study level was rated as low for the HELIOS study. At outcome level, the risk of bias was rated as high for all outcomes (overall survival, symptoms, health status, health-related quality of life and all adverse event [AE] outcomes). The data for the outcome "discontinuation due to AEs" were incomplete.

All-cause mortality

A statistically significant difference in favour of ibrutinib + BR in comparison with placebo + BR was shown for the outcome "overall survival". This resulted in an indication of an added benefit of ibrutinib + BR in comparison with placebo + BR. Despite the high risk of bias caused by treatment switching from the control to the intervention group, in this concrete situation, the survival advantage of ibrutinib would only be challenged by several extreme assumptions (including, for example, the assumption of an increased mortality risk from ibrutinib after the treatment switching). The certainty of conclusions of the result ("indication") is therefore not compromised.

Health-related quality of life

Health-related quality of life was measured with the functional scales and the global health status of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). A statistically significant difference between the treatment groups in favour of ibrutinib + BR was only shown for the item of social functioning, and only for the operationalization "time to deterioration". There was no

statistically significant difference between the treatment groups for the operationalization "time to improvement of social functioning".

In the overall consideration of all domains of health-related quality of life and the respective operationalization as time to deterioration and time to improvement as well as of the data on symptoms and health status, the result on deterioration of social functioning was an isolated finding. Important information for the BR subpopulation, such as time course curves (including information on the area under the curve), were missing for the interpretation of this result. In the overall consideration, no added benefit of ibrutinib + BR can therefore be derived for the outcome "social functioning".

Side effects

No statistically significant differences between the treatment groups were shown for the outcomes "serious adverse events (SAEs)" and "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). There were only incomplete data for the outcome "discontinuation due to AEs".

The large proportion of patients with treatment switching from the control to the intervention group resulted in a high risk of bias for the outcomes mentioned. The Kaplan-Meier curve for severe AEs shows that a large proportion of the events were already observed in the first 3 months and therefore before progression. It is not plausible that an elimination of the potential bias by treatment switching after progression would have resulted in a statistically significant disadvantage in severe AEs (CTCAE grade ≥ 3).

The Kaplan Meier curve for SAEs shows that the majority of the events occurred after 3 months. Hence this outcome is potentially biased due to the treatment switching from the control to the intervention group. Despite this potential high bias, in this concrete situation, a statistically significant disadvantage of ibrutinib + BR in SAEs would only result under several extreme assumptions.

Overall, there was no hint of greater or lesser harm from ibrutinib + BR in comparison with placebo + BR; greater or lesser harm is therefore not proven.

Further outcomes

There was no statistically significant difference between the treatment groups for the remaining outcomes (EORTC QLQ-C30 symptom scales, Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) of the outcome categories of morbidity. An added benefit is not proven for any outcome of these outcome categories.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug ibrutinib + BR in comparison with the ACT for the subpopulation of patients with CLL who have received at least 2 prior therapies and for whom BR is an individually optimized chemotherapy in combination with rituximab is assessed as follows:

For the BR population, the indication of considerable added benefit resulted in a positive effect for the outcome "overall survival". The positive effect on overall survival is not accompanied by a negative effect.

The company presented no usable data for further patients of the target population (patients with 1 prior therapy and patients for whom other treatments than BR are the individually optimized treatment). The added benefit is not proven for this patient population.

Overall, there is an indication of considerable added benefit of ibrutinib + BR versus BR, one treatment option within the ACT, for patients with CLL who have received at least 2 prior therapies and for whom BR is an individually optimized chemotherapy in combination with rituximab.

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

[4] 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, no added benefit, or less benefit). For further details see [1,2].

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

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Patients with CLL who have received at least one prior therapy and for whom chemotherapy indicated is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	*Patients with at least 2 prior therapies and for whom BR is an individually optimized chemotherapy in combination with rituximab:* indication of considerable added benefit *Further patients of the target population*[b]*:* added benefit not proven
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: Patients with only 1 prior therapy and patients for whom other treatments than BR are the individually optimized treatment. ACT: appropriate comparator therapy; BR: bendamustine + rituximab; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee		

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

2.2 Research question

The aim of this report was to assess the added benefit of ibrutinib + BR in comparison with the ACT specified by the G-BA for adult patients with CLL who have received at least one prior therapy and for whom chemotherapy is indicated.

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

Therapeutic indication	**ACT**[a]
Patients with CLL who have received at least one prior therapy and for whom chemotherapy indicated is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; BR: bendamustine + rituximab; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee	

The company followed the ACT specified by the G-BA for the present research question; it considered the BR combination to be the most adequate and the most common treatment option for the majority of patients with pretreated CLL (see Section 2.7.1 of the full dossier assessment).

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

- study list on ibrutinib (status: 26 July 2016)
- bibliographical literature search on ibrutinib (last search on 26 July 2016)
- search in trial registries for studies on ibrutinib (last search on 27 July 2016)
- bibliographical literature search on the ACT (last search on 26 July 2016)
- search in trial registries for studies on the ACT (last search on 27 July 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 20 October 2016)

No additional relevant study was identified from the check of the completeness of the study pool.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CLL3001 (HELIOS[b, c])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
c: Only a subpopulation of the study (BR population) is relevant for the present benefit assessment.
BR: bendamustine + rituximab; RCT: randomized controlled trial; vs.: versus

Section 2.6 contains a reference list for the studies included.

The HELIOS study on the comparison of ibrutinib + BR versus placebo + BR with 289 patients in each treatment arm (578 patients in total) was included in the present benefit assessment. Since BR is not an individually optimized chemotherapy in combination with rituximab in the sense of the ACT specified by the G-BA for all patients, the company presented the data of a subpopulation of the HELIOS study with 53 patients in each treatment arm (hereinafter referred to as "BR population") in addition to the results of the total population. The BR population comprised those patients in the HELIOS study who were refractory to purine analogue treatment and had received at least 2 prior systemic therapies. From the company's point of view, these 2 criteria (which were also stratification factors of the study) ensured that BR is the optimized chemotherapy in combination with rituximab for the selected population.

The criteria used by the company are principally suitable to form a patient population for which BR is an optimized treatment. It can be assumed that BR is also the suitable treatment for individual patients who do not fulfil these criteria. This error was not considered to be so large that it would challenge the suitability of the BR population for the present benefit assessment, however.

The evidence provided by the company therefore allowed conclusions on the added benefit of ibrutinib + BR for the subgroup of patients who have received at least 2 prior therapies and for whom BR is the individually optimized chemotherapy in combination with rituximab. The company presented no usable data for further patients of the target population (patients with only 1 prior therapy and patients for whom other treatments than BR are the individually optimized treatment).

Furthermore, the conclusions on the added benefit versus the ACT in the present benefit assessment were drawn with reservations regarding the questionable approval status of BR because an enquiry at the higher federal authorities Federal Institute for Drugs and Medical Devices (BfArM) and Paul Ehrlich Institute (PEI) did not result in clarification as to whether the BR combination therapy is approved in CLL or not (see Section 2.7.1 of the full dossier assessment).

The study characteristics and the results of the BR population of the HELIOS study (if usable analyses were available) are presented and described below.

2.3.1 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 + BR vs. placebo + BR

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
HELIOS	RCT, double-blind, parallel	Adult patients with relapsed or refractory CLL or SLL, active disease (according to iwCLL criteria), at least one prior systemic therapy (at least 2 cycles), ECOG PS ≤ 1, measurable lymph node disease (at least one lymph node > 1.5 cm), without 17p deletion (17p in ≥ 20% of examined cells)	Ibrutinib + BR (N = 289) placebo + BR (N = 289) Relevant subpopulation thereof[b]: ibrutinib + BR (n = 53) placebo + BR (n = 53)	Screening: ≤ 30 days before randomization Treatment with ibrutinib/placebo until disease progression or occurrence of unacceptable toxicity[c] Treatment with BR for a maximum of 6 cycles of 28 days[d] Follow-up: until death, loss to follow-up, withdrawal of consent or end of study	133 study centres in Argentina, Belgium, Brazil, Canada, Columbia, Czech Republic, France, Germany, Greece, Israel, Mexico, Poland, Portugal, Russia, South Korea, Spain, Sweden, Turkey, Ukraine, United Kingdom, USA 9/2012–ongoing Data cut-offs: 12 Jan 2015 1 Oct 2015	Primary: progression-free survival Secondary: overall survival, health-related quality of life, disease-related symptoms, health status, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment from the M4 A of the dossier.
b: Adult patients with active CLL/SLL who are refractory to purine analogue treatment and have received ≥ 2 prior therapies.
c: Placebo arm: possibility of treatment switching to ibrutinib after confirmed disease progression.
d: The first cycle lasted 29 days to allow administration of rituximab before administration of bendamustine.
e: At this data cut-off, only data for the following outcomes were reported: overall survival, progression-free survival, overall response and side effects.

AE: adverse event; BR: bendamustine + rituximab; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; N: number of randomized patients; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study	Intervention	Comparison	Prior and concomitant medication
Direct comparison ibrutinib + BR vs. placebo + BR			
HELIOS	Ibrutinib 420 mg/day orally (starting on day 2 of the first cycle)[a] Background medication: bendamustine 70 mg/m^2 IV (maximum of 6 cycles)[b] ▪ cycle 1: day 2 and 3 ▪ cycles 2–6: day 1 and 2 rituximab IV (maximum of 6 cycles) ▪ cycle 1, day 1: 375 mg/m^2 ▪ cycles 2–6, day 1: 500 mg/m^2	Placebo orally (starting on day 2 of the first cycle)[a] Background medication: bendamustine 70 mg/m^2 IV (maximum of 6 cycles)[b] ▪ cycle 1: day 2 and 3 ▪ cycles 2–6: day 1 and 2 rituximab IV (maximum of 6 cycles) ▪ cycle 1, day 1: 375 mg/m^2 ▪ cycles 2–6, day 1: 500 mg/m^2	Concomitant medication allowed: ▪ antiemetics ▪ standard medication for supportive treatment ▪ growth factors (filgrastim and pegfilgrastim) ▪ antimicrobial prophylaxis (e.g. sulfamethoxazole, trimethoprim) ▪ patients at risk of TLS: treatment for lowering uric acid levels (allopurinol or febuxostat) ▪ patients at risk of leukostasis: leukapheresis Non-permitted concomitant medication: ▪ other chemotherapy than BR ▪ immunotherapy ▪ corticosteroids (> 20 mg/day prednisone equivalent) ▪ radiotherapy ▪ strong CYP3A4/5 inducers or inhibitors ▪ warfarin and vitamin K antagonists

a: Medication with ibrutinib/placebo was administered until disease progression or occurrence of persistent unacceptable toxicities. In case of toxicities grade ≥ 3, medication was temporarily discontinued for a maximum of 28 days or until improvement to grade ≤ 1 or to baseline status. Then treatment was resumed with a low dosage of the medication. In case of persistent toxicity for longer than 28 days, ibrutinib/placebo was permanently stopped. Basic medication (bendamustine and rituximab) could be continued during this period.

b: Dose reduction or temporary discontinuation of the medication in case of toxicities according to the SPC.

BR: bendamustine + rituximab; CYP3A4/5: cytochrome P450 liver enzymes, IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; TLS: tumour lysis syndrome; W: weeks; vs.: versus

The HELIOS study was a randomized, placebo-controlled approval study. The study had a double-blind design, but blinding was not completely maintained: Patients in the control arm who switched to the intervention arm of the study because of progression were unblinded. In addition, the study was unblinded after the first interim analysis.

Adult patients with relapsed or refractory CLL or SLL with at least one prior systemic therapy were included. In addition, patients had to have measurable lymph node disease and no 17p deletion. Regarding their physical status, the patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1 at the start of the study. Patients with higher ECOG PS were excluded.

A total of 578 patients were randomly allocated to treatment with ibrutinib or placebo (each in combination with BR). Patients were stratified according to whether they were refractory to purine analogues (yes/no) and by number of prior therapies (1/> 1). The patient population relevant for the present benefit assessment (BR population) comprised those patients of the total population who were refractory to purine analogue treatment and had received at least 2 prior systemic therapies. These were 106 patients (53 patients in the ibrutinib arm and 53 patients in the placebo arm).

The patients were allowed to receive supportive treatment with restrictions. Other chemotherapeutic regimens than BR, immunotherapies, corticosteroids (> 20 mg/day prednisone equivalent), radiotherapies, strong cytochrome P450 inducers and inhibitors, warfarin and vitamin K antagonists were not allowed.

Treatment with BR was administered in 6 cycles of 28 days. The patients additionally received 420 mg ibrutinib or placebo daily until disease progression or occurrence of persistent unacceptable toxicities. By protocol extension 17 months after initiation of the study, patients in the control group had the option to switch to the intervention group after disease progression. Until the first data cut-off (12 January 2015) – about 12 months after the protocol extension – 34% of the patients had switched from the control to the intervention groups. Until the second data cut-off (1 October 2015) – about 20 months after the protocol extension – the proportion of patients who had switched treatment had increased in the control group to 43%.

Planned duration of follow-up

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

Table 8: Planned duration of follow up – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study **Outcome category** **Outcome**	**Planned follow-up**
HELIOS	
Mortality	
Overall survival	Until death, end of study or loss to follow-up
Morbidity	
EORTC QLQ-C30 symptom scales	Until progression, death, end of study or loss to follow-up
Health status (EQ-5D-5L VAS)	Until death, end of study, loss to follow-up or 48 weeks after progression
FACIT-Fatigue	Until progression, death, end of study or loss to follow-up
Health-related quality of life	
Recorded with the EORTC QLQ-C30 functional scales	Until progression, death, end of study or loss to follow-up
Side effects	
AEs/SAEs/discontinuation due to AEs/AEs CTCAE grade ≥ 3	Until 30 days after the end of treatment

AE: adverse event; BR: bendamustine + rituximab; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACIT: Functional Assessment of Chronic Illness Therapy; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Follow-up for the outcome “overall survival” was planned until death, end of study or loss to follow-up. The outcomes on morbidity and health-related quality of life, in contrast, were only recorded until progression (or end of study, loss to follow-up or death). The outcome “health status” was additionally recorded for another 48 weeks after progression. Side effects were recorded until 30 days after the end of treatment. For patients who switched to the ibrutinib arm, the side effects were also recorded until 30 days after the end of ibrutinib treatment.

The observation periods for the outcomes “side effects”, “morbidity” and “health-related quality of life” were therefore systematically shortened because they were only recorded until progression or for the time period of the treatment (plus 30 days or 48 weeks). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

Table 9 shows the characteristics of the BR population in the HELIOS study.

Table 9: Characteristics of the BR population – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study **Characteristics** **Category**	**Ibrutinib + BR**	**Placebo + BR**
HELIOS (BR population)	**N[a] = 53**	**N[a] = 53**
Age [years], median [min; max]	62 [31; 79]	62 [40; 79]
Sex [F/M], %	30/70	40/60
Ethnicity, %		
White	94	91
Non-white	4[b]	9[b]
Unknown	2	0
Time since diagnosis [months] median [min; max]	87.6 [14; 216]	74.8 [6; 263]
Histology at diagnosis, n (%)		
CLL	48 (91)	45 (85)
SLL	5 (9)	8 (15)
Rai stage at screening, n (%)		
0–II	29 (55)[b]	21 (40)[b]
III–IV	16 (30)[b]	23 (43)[b]
Missing	8 (15)[b]	9 (17)[b]
ECOG PS, n (%)		
0	19 (36)	19 (36)
1	34 (64)	34 (64)
Tumour mass, n (%)		
< 5 cm	23 (43)	16 (30)
≥ 5 cm	30 (57)	37 (70)
Number of CLL/SLL treatments received, median [min; max]	3 [2; 11]	3 [2; 7]
Purine analogue treatment received, n (%)	51 (96)	53 (100)
Purine analogue refractory	17 (32)	21 (40)
Relapse after purine analogue	34 (64)[b]	32 (60)[b]
Relapse after < 6 months	9 (17)	19 (36)
Relapse after ≥ 6 to < 12 months	17 (32)	11 (21)
Relapse after ≥ 12 to < 24 months	3 (6)	0
Relapse after ≥ 24 months	5 (9)	2 (4)
Chromosome anomaly del11q, n (%)	13 (25)	9 (17)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients; values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Institute's calculation.

BR: bendamustine + rituximab; CLL: chronic lymphocytic leukaemia; 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: non data; RCT: randomized controlled trial; SD: standard deviation; SLL: small lymphocytic lymphoma; vs.: versus

The patient characteristics between the treatment groups were mostly balanced in the BR population. The median age of the patients was 62 years. The median time since diagnosis was 88 months for patients in the intervention group and 75 months for patients in the control group.

Noteworthy differences were found regarding the Rai disease stage. Whereas only 30% of the patients in the intervention group had a Rai disease stage of ≥ III, this was the case in 43% of the patients in the control group. More patients in the control group (70%) than in the intervention group (57%) had a tumour mass of ≥ 5 cm.

There was no information on treatment and study discontinuations for the BR population.

Treatment duration and observation period

No information was available for the treatment duration or for the observation period for the BR population.

As described above, the outcomes on symptoms and health-related quality of life were recorded until progression; health status was recorded until 48 weeks after progression. The observation period of these outcomes was therefore determined by progression. The Kaplan-Meier curves on progression-free survival (PFS) in Module 4 A (Section 4.3.1.3.1.2) show that the median time to progression was 9.4 months in the control group, whereas in the intervention group it was not yet achieved after 27 months. Based on these differences, it can be assumed that the observation periods for the outcomes on symptoms and health-related quality of life differed at least by a factor of about 3 between the study arms.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
HELIOS	Yes	Yes	Unclear[a]	Unclear[a]	Yes	Yes	Low

a: Unblinding after ending the randomized study medication due to progression as well as after the first interim analysis. Hence blinding was not completely ensured. This was considered in the assessment of the risk of bias at outcome level.

BR: bendamustine + rituximab; RCT: randomized controlled trial; vs.: versus

The risk of bias at the study level was rated as low for the HELIOS study. This concurs with the company's assessment.

Deviating from the company's assessment, no complete blinding can be assumed for the HELIOS study: The study was unblinded after the first interim analysis with an amendment to the study protocol from 13 April 2015. Furthermore, patients who switched from the control to the intervention group were unblinded.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, measured with the symptom scales of the EORTC QLQ-C30
  - health status, measured with the European Quality of Life-5 Dimensions 5 Levels visual analogue scale (EQ-5D-5L VAS)
  - fatigue, measured with FACIT-Fatigue
- Health-related quality of life
  - measured with the functional scales and the global health status of the EORTC QLQ-C30
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs CTCAE grade ≥ 3

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 11 shows for which outcomes and data cut-offs data for the BR population were available in the HELIOS study.

Table 11: Matrix of outcomes – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30 symptom scales)[a]	Health status (EQ-5D-5L VAS)	Fatigue (FACIT-Fatigue)	Health-related quality of life (EORTC QLQ-C30 functional scales)[b]	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
HELIOS (BR population)								
First data cut-off (12 January 2015)	Yes	Yes	Yes	Yes	Yes	Yes	(Yes)[b]	Yes
Second data cut-off (1 October 2015)	Yes	No	No	No	No	Yes	(Yes)[b]	Yes

a: EORTC QLQ-C30 questionnaire version 3.
b: Data incomplete. Only analyses on the discontinuation of ibrutinib or placebo are available for the outcome "discontinuation due to AEs". No information on the discontinuation of all drug components of a treatment group is available.

AE: adverse event; BR: bendamustine + rituximab; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACIT: Functional Assessment of Chronic Illness Therapy; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

For the first data cut-off, data were available for all outcomes. For the second data cut-off, complete data were only available for the outcomes "overall survival", "SAEs" and "severe AEs". The data on the outcome "discontinuation due to AEs" were incomplete.

2.4.2 Risk of bias

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study	Study level	Outcomes							
		Overall survival	Symptoms (EORTC QLQ-C30 symptom scales)	Health status (EQ-5D-5L VAS)	Fatigue (FACIT-Fatigue)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
HELIOS (BR population)	L	H[a]	H[b]	H[a, b, c]	H[b]	H[b]	H[a, d]	–[e]	H[a, d]

a: Large proportion (43%) of patients with treatment switching from the comparator group (placebo + BR) to the intervention group (ibrutinib + BR)
b: Potential informative censoring.
c: Due to incomplete blinding in subjective recording of outcomes.
d: Deviation from the analysis planned a priori, see Section 2.7.2.4.2 of the full dossier assessment.
e: Data incomplete. Only analyses on the discontinuation of ibrutinib or placebo are available for the outcome "discontinuation due to AEs". No information on the discontinuation of all drug components of a treatment group is available.

AE: adverse event; BR: bendamustine + rituximab; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

For the outcome "overall survival", the risk of bias was rated as high due to the large proportion of patients who switched treatment from the control to the intervention group. This concurs with the company's assessment.

In contrast to the company's assessment, the risk of bias for all other outcomes was rated as high. For the outcomes based on the instruments EORTC QLQ-C30 and FACIT-Fatigue, this was due to the potential informative censoring. The outcome "health status" was potentially highly biased because of the treatment switching, informative censoring and incomplete blinding. For the outcomes of the outcome category "side effects", the company deviated from the approach for the outcome "overall survival" and did not use the predefined Cox proportional hazards model stratified by refractoriness to purine analogues and number of prior therapies specified. Instead, it used the unstratified Cox proportional hazards model without further explanation. Particularly given the low patient numbers, this can potentially cause bias in the BR population. Together with the large proportion of patients who switched treatment, these aspects resulted in a high risk of bias in the outcomes on side effects. For the

outcome “discontinuation due to AEs”, only incomplete data were available (see Section 2.7.2.4.3 of the full dossier assessment).

2.4.3 Results

Table 13 summarizes the results on the comparison of ibrutinib + BR with placebo + BR for the BR population of the HELIOS study. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) of the BR population – RCT, direct comparison: ibrutinib + BR vs. placebo + BR

Study Outcome category Outcome	Ibrutinib + BR		Placebo + BR		Ibrutinib + BR vs. Placebo + BR
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
HELIOS (BR population)					
Mortality					
Overall survival					
Second data cut-off (1 October 2015)	53	NA ND	53	34.49 [12.56; 34.49] ND	0.43 [0.21; 0.89]; 0.022[b, c]
Morbidity					
EORTC QLQ-C30 symptom scales – time to improvement of symptoms[d, e]					
Fatigue	53	NA 25 (47.2)	53	NA 25 (47.2)	1.0 [0.57; 1.73]; 0.987
Nausea and vomiting	53	NA 11 (20.8)	53	NA 6 (11.3)	1.93 [0.72; 5.23]; 0.194
Pain	53	NA 20 (37.7)	53	NA 21 (39.6)	0.97 [0.53; 1.79]; 0.921
Dyspnoea	53	NA 16 (30.2)	53	NA 18 (34.0)	0.93 [0.48; 1.83]; 0.841
Insomnia	53	19.6 26 (49.1)	53	4.0 28 (52.8)	0.97 [0.57; 1.65]; 0.902
Appetite loss	53	NA 14 (26.4)	53	NA 17 (32.1)	0.87 [0.43; 1.76]; 0.687
Constipation	53	NA 9 (17.0)	53	NA 14 (26.4)	0.63 [0.27; 1.46]; 0.283
Diarrhoea	53	NA 10 (18.9)	53	NA 5 (9.4)	2.09 [0.72; 6.13]; 0.177
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms[d, e]					
Fatigue	53	6.5 [ND] 32 (60.4)	53	7.1 [ND] 29 (54.7)	1.19 [0.72; 1.97]; 0.498
Nausea and vomiting	53	11.4 [ND] 26 (49.1)	53	NA 19 (35.8)	1.56 [0.87; 2.82]; 0.140
Pain	53	NA 22 (41.5)	53	13.9 [ND] 26 (49.1)	0.81 [0.46; 1.44]; 0.474
Dyspnoea	53	NA 21 (39.6)	53	NA 15 (28.3)	1.57 [0.81; 3.05]; 0.180

(continued)

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) of the BR population – RCT, direct comparison: ibrutinib + BR vs. placebo + BR (continued)

Study Outcome category Outcome	Ibrutinib + BR		Placebo + BR		Ibrutinib + BR vs. Placebo + BR
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Insomnia	53	NA 16 (30.2)	53	NA 12 (22.6)	1.44 [0.68; 3.04]; 0.341
Appetite loss	53	NA 17 (32.1)	53	NA 16 (30.2)	1.11 [0.56; 2.20]; 0.767
Constipation	53	NA 16 (30.2)	53	NA 10 (18.9)	1.68 [0.76; 3.71]; 0.197
Diarrhoea	53	NA 15 (28.3)	53	NA 19 (35.8)	0.78 [0.40; 1.54]; 0.473
FACIT-Fatigue – time to deterioration[e, f]					
	53	14.5 [ND] 27 (50.9)	53	NA 25 (47.2)	1.23 [0.71; 2.12]; 0.456
FACIT-Fatigue – time to improvement[e, f]					
	53	6.5 [ND] 34 (64.2)	53	2.9 [ND] 33 (62.3)	0.96 [0.60; 1.55]; 0.869
Health status (EQ-5D-5L VAS)[e] – time to deterioration					
MID 7 mm	53	NA 24 (45.3)	53	9.0 [ND] 29 (54.7)	0.80 [0.47; 1.38]; 0.428
MID 10 mm	53	NA 21 (39.6)	53	12 27 (50.9)	0.72 [0.41; 1.28]; 0.264
Health status (EQ-5D-5L VAS)[e] – time to improvement					
MID 7 mm	53	5.8 [ND] 33 (62.3)	53	6.5 [ND] 29 (54.7)	1.18 [0.72; 1.95]; 0.508
MID 10 mm	53	11.1 [ND] 29 (54.7)	53	14.6 [ND] 27 (50.9)	1.10 [0.65; 1.86]; 0.715
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to improvement of health-related quality of life[d, e]					
Global health status	53	8.3 [ND] 28 (52.8)	53	14.7 [ND] 27 (50.9)	1.13 [0.67; 1.92]; 0.654
Role functioning	53	NA 23 (43.4)	53	NA 23 (43.4)	1.0 [0.56; 1.78]; > 0.999
Emotional functioning	53	NA 22 (41.5)	53	NA 19 (35.8)	1.22 [0.66; 2.26]; 0.521

(continued)

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) of the BR population – RCT, direct comparison: ibrutinib + BR vs. placebo + BR (continued)

Study Outcome category Outcome	Ibrutinib + BR		Placebo + BR		Ibrutinib + BR vs. Placebo + BR
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Physical functioning	53	NA 20 (37.7)	53	NA 22 (41.5)	0.91 [0.49; 1.66]; 0.746
Cognitive functioning	53	NA 19 (35.8)	53	NA 18 (34.0)	1.06 [0.56; 2.01]; 0.867
Social functioning	53	NA 24 (45.3)	53	NA 21 (39.6)	1.22 [0.68; 2.19]; 0.508
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life[d, e]					
Global health status	53	NA 17 (32.1)	53	NA 19 (35.8)	0.89 [0.46; 1.72]; 0.737
Role functioning	53	8.5 [ND] 29 (54.7)	53	NA 22 (41.5)	1.46 [0.84; 2.55]; 0.179
Emotional functioning	53	NA 16 (30.2)	53	NA 17 (32.1)	0.97 [0.49; 1.92]; 0.931
Physical functioning	53	NA 21 (39.6)	53	NA 24 (45.3)	0.85 [0.47; 1.53]; 0.595
Cognitive functioning	53	NA 23 (43.4)	53	NA 23 (43.4)	1.09 [0.61; 1.94]; 0.771
Social functioning	53	NA 16 (30.2)	53	7.1 [ND] 27 (50.9)	0.54 [0.29; 0.996]; 0.049
Side effects[g]					
AEs (supplementary information)	52	0.1[h] [ND] 51 (98.1)	53	0.2[h] [ND] 52 (98.1)	–
SAEs	52	13.4[h] [ND] 37 (71.2)	53	11.4[h] [ND] 25 (47.2)	0.96 [0.57; 1.62]; 0.874[i]
Discontinuation due to AEs	Data presented incomplete[j]				
Severe AEs (CTCAE ≥ 3)	52	2.3[h] [ND] 46 (88.5)	53	1.6[h] [ND] 48 (90.6)	0.67 [0.44; 1.02]; 0.064[i]

(continued)

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) of the BR population – RCT, direct comparison: ibrutinib + BR vs. placebo + BR (continued)

a: HR, 95% CI and p-value from Cox proportional hazards model stratified by refractoriness to purine analogues and number of prior therapies.
b: Result after censoring at treatment switching: HR [95% CI]; p-value: 0.35 [0.17; 0.73]; 0.004.
c: Effect at the first data cut-off (12 January 2015): HR [95% CI]; p-value: 0.40 [0.18; 0.88]; 0.022.
d: Time to deterioration/improvement of the score by at least 10 points versus the baseline value.
e: Data cut-off used: 12 January 2015.
f: Time to deterioration/improvement of the score by at least 3 points versus the baseline value.
g: Data cut-off used: 1 October 2015.
h: Institute's calculation from weeks to months.
i: HR, 95% CI and p-value from unstratified Cox proportional hazards model.
j: Only information on the discontinuation of ibrutinib or placebo is available for the outcome "discontinuation due to AEs" (results not statistically significant; HR [95% CI]; p-value: 0.39 [0.15; 1.01]; 0.052). No information on the discontinuation of all drug components of a treatment group is available.
AE: adverse event; BR: bendamustine + rituximab; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACIT: Functional Assessment of Chronic Illness Therapy; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Mortality

A statistically significant difference in favour of ibrutinib + BR in comparison with placebo + BR was shown for the outcome "overall survival". This resulted in an indication of an added benefit of ibrutinib + BR in comparison with placebo + BR. Despite the high risk of bias caused by treatment switching from the control to the intervention group, in this concrete situation, the survival advantage of ibrutinib would only be challenged by several extreme assumptions (including, for example, the assumption of an increased mortality risk from ibrutinib after the treatment switching). The certainty of conclusions of the result ("indication") is therefore not compromised.

The assessment concurs with that of the company.

Morbidity

Symptoms

Outcomes on symptoms were recorded with the symptom scales of the EORTC QLQ-C30 and with the FACIT-Fatigue scale. The time to deterioration or improvement by at least 10 points (EORTC QLQ C30) and 3 points (FACIT-Fatigue) was considered. No statistically significant result was shown for any of the outcomes. Hence there was no hint of an added benefit of ibrutinib + BR in comparison with placebo + BR for the outcome "symptoms"; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Health status

The outcome "health status" was recorded with the EQ-5D-5L VAS. The time to improvement or deterioration by 7 and 10 mm was considered in each case. No statistically significant result was shown for any of these outcomes. Hence there was no hint of an added benefit of ibrutinib + BR in comparison with placebo + BR for the outcome "health status"; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for recording global health status of the instrument EORTC-QLQ-C30. The time to deterioration or improvement by at least 10 points was considered in each case.

A statistically significant difference between the treatment groups in favour of ibrutinib + BR was only shown for the item of social functioning, and only for the operationalization "time to deterioration". There was no statistically significant difference between the treatment groups for the operationalization "time to improvement of social functioning".

In the overall consideration of all domains of health-related quality of life and the respective operationalization as time to deterioration and time to improvement as well as of the data on symptoms and health status, the result on deterioration of social functioning was an isolated finding. Important information for the BR subpopulation, such as time course curves (including information on the area under the curve), were missing for the interpretation of this result. In the overall consideration, no added benefit of ibrutinib + BR can therefore be derived for the outcome "social functioning".

This assessment deviates from that of the company, which derived an indication of an added benefit for this outcome.

Side effects

Serious adverse events, discontinuation due to adverse events and severe adverse events (CTCAE grade ≥ 3)

Only incomplete data were available for the outcome "discontinuation due to AEs" (see Section 2.7.2.4.3 of the full dossier assessment). No statistically significant differences between the treatment groups were shown for the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3).

The large proportion of patients with treatment switching from the control to the intervention group resulted in a high risk of bias for the outcomes mentioned. In the present data situation, the results are interpretable despite the high risk of bias. In the HELIOS study, treatment switching after progression of the disease was mandated. The available data for PFS in Module 4 A (Section 4.3.1.3.1.2) show that few progressions occurred in both treatment

groups in the first 3 months of the study. Hence the events for SAEs or severe AEs (CTCAE grade ≥ 3) observed in the first 3 months of the study can be assigned to the medications allocated in the randomization (see Figure 2 and Figure 3 in Appendix A of the full dossier assessment).

No statistically significant differences between the treatment groups were shown for the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3). There were only incomplete data for the outcome "discontinuation due to AEs".

The large proportion of patients with treatment switching from the control to the intervention group resulted in a high risk of bias for the outcomes mentioned. The Kaplan-Meier curve for severe AEs shows that a large proportion of the events were already observed in the first 3 months and therefore before progression. It is not plausible that an elimination of the potential bias by treatment switching after progression would have resulted in a statistically significant disadvantage in severe AEs (CTCAE grade ≥ 3).

The Kaplan Meier curve for SAEs shows that the majority of the events occurred after 3 months. Hence this outcome is potentially biased due to the treatment switching from the control to the intervention group. Despite this potential high bias, in this concrete situation, a statistically significant disadvantage of ibrutinib + BR in SAEs would only result under several extreme assumptions.

Overall, there was no hint of greater or lesser harm from ibrutinib + BR in comparison with placebo + BR; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The subgroup analyses are not described in the present benefit assessment. All outcomes have a high risk of bias for different reasons (e.g. due to different observation periods, informative censoring and the large proportion of patients who switched treatment [see Section 2.4.2 and Section 2.7.2.4.2 of the full dossier assessment]). The magnitude of the bias can be different in the subgroups so that this bias alone can lead to statistically significant results from interaction tests. In addition, the subgroup analyses on the BR population were based on calculations with small sample sizes. Overall, the informative value of the subgroup analyses is severely limited. Irrespective of this, the consideration of the subgroup results shows no pattern regarding the occurrence of certain effect modifiers across several outcomes.

The company presented the subgroup analyses on all outcomes, but did not use the results for the derivation of an added benefit of ibrutinib + BR in comparison with placebo + BR.

2.5 Extent and probability of added benefit

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

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

2.5.1 Assessment of added benefit at outcome level

The evidence presented by the company for patients with at least 1 prior therapy for whom chemotherapy is indicated is presented in Section 2.4.

The assessment of the added benefit refers to the subpopulation of patients with CLL who have received at least 2 prior therapies and for whom BR is an individually optimized chemotherapy in combination with rituximab. For this subpopulation, there was an indication of an added benefit for the outcome “overall survival”.

The company presented no usable data for further patients of the target population (patients with 1 prior therapy and patients for whom other treatments than BR are the individually optimized treatment).

The extent of the respective added benefit at outcome level was estimated from this result (see Table 14).

Table 14: Extent of added benefit at outcome level for the BR population: ibrutinib + BR vs. placebo + BR

Outcome category	**Ibrutinib + BR vs. placebo + BR** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: NA vs. NA HR: 0.43 [0.21; 0.89]; 0.022 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms		
EORTC QLQ-C30 symptom scales – time to improvement of symptoms		
Fatigue	Median: NA vs. NA HR: 1.0 [0.57; 1.73]; 0.987	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: NA vs. NA HR: 1.93 [0.72; 5.23]; 0.194	Lesser benefit/added benefit not proven
Pain	Median: NA vs. NA HR: 0.97 [0.53; 1.79]; 0.921	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 0.93 [0.48; 1.83]; 0.841	Lesser benefit/added benefit not proven
Insomnia	Median: 19.6 vs. 4.0 HR: 0.97 [0.57; 1.65]; 0.902	Lesser benefit/added benefit not proven
Appetite loss	Median: NA vs. NA HR: 0.87 [0.43; 1.76]; 0.687	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. NA HR: 0.63 [0.27; 1.46]; 0.283	Lesser benefit/added benefit not proven
Diarrhoea	Median: NA vs. NA HR: 2.09 [0.72; 6.13]; 0.177	Lesser benefit/added benefit not proven
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms		
Fatigue	Median: 6.5 vs. 7.1 HR: 1.19 [0.72; 1.97]; 0.498	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 11.4 vs. NA HR: 1.56 [0.87; 2.82]; 0.140	Lesser benefit/added benefit not proven
Pain	Median: NA vs. 13.9 HR: 0.81 [0.46; 1.44]; 0.474	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 1.57 [0.81; 3.05]; 0.180	Lesser benefit/added benefit not proven
Insomnia	Median: NA vs. NA HR: 1.44 [0.68; 3.04]; 0.341	Lesser benefit/added benefit not proven
Appetite loss	Median: NA vs. NA HR: 1.11 [0.56; 2.20]; 0.767	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. NA HR: 1.68 [0.76; 3.71]; 0.197	Lesser benefit/added benefit not proven

(continued)

Table 14: Extent of added benefit at outcome level for the BR population: ibrutinib + BR vs. placebo + BR (continued)

Outcome category	**Ibrutinib + BR vs. placebo + BR** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Diarrhoea	Median: NA vs. NA HR: 0.78 [0.40; 1.54]; 0.473	Lesser benefit/added benefit not proven
FACIT-Fatigue		
Time to deterioration	Median: 14.5 vs. NA HR: 1.23 [0.71; 2.12]; 0.456	Lesser benefit/added benefit not proven
Time to improvement	Median: 6.5 vs. 2.9 HR: 0.96 [0.60; 1.55]; 0.869	Lesser benefit/added benefit not proven
Health status (EQ-5D-5L VAS)		
Time to deterioration		
MID 7 mm	Median: NA vs. 9.0 HR: 0.80 [0.47; 1.38]; 0.428	Lesser benefit/added benefit not proven
MID 10 mm	Median: NA vs. 12 HR: 0.72 [0.41; 1.28]; 0.264	Lesser benefit/added benefit not proven
Time to improvement		
MID 7 mm	Median: 5.8 vs. 6.5 HR: 1.18 [0.72; 1.95]; 0.508	Lesser benefit/added benefit not proven
MID 10 mm	Median: 11.1 vs. 14.6 HR: 1.10 [0.65; 1.86]; 0.715	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to improvement of health-related quality of life[c]		
Global health status	Median: 8.3 vs. 14.7 HR: 1.13 [0.67; 1.92]; 0.654	Lesser benefit/added benefit not proven
Role functioning	Median: NA vs. NA HR: 1.0 [0.56; 1.78]; > 0.999	Lesser benefit/added benefit not proven
Emotional functioning	Median: NA vs. NA HR: 1.22 [0.66; 2.26]; 0.521	Lesser benefit/added benefit not proven
Physical functioning	Median: NA vs. NA HR: 0.91 [0.49; 1.66]; 0.746	Lesser benefit/added benefit not proven
Cognitive functioning	Median: NA vs. NA HR: 1.06 [0.56; 2.01]; 0.867	Lesser benefit/added benefit not proven
Social functioning	Median: NA vs. NA HR: 1.22 [0.68; 2.19]; 0.508	Lesser benefit/added benefit not proven
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life		
Global health status	Median: NA vs. NA HR: 0.89 [0.46; 1.72]; 0.737	Lesser benefit/added benefit not proven
Role functioning	Median: 8.5 vs. NA HR: 1.46 [0.84; 2.55]; 0.179	Lesser benefit/added benefit not proven

(continued)

Table 14: Extent of added benefit at outcome level for the BR population: ibrutinib + BR vs. placebo + BR (continued)

Outcome category	Ibrutinib + BR vs. placebo + BR Median time to event Effect estimate [95% CI]; p-value Probability[a]	Derivation of extent[b]
Emotional functioning	Median: NA vs. NA HR: 0.97 [0.49; 1.92]; 0.931	Lesser benefit/added benefit not proven
Physical functioning	Median: NA vs. NA HR: 0.85 [0.47; 1.53]; 0.595	Lesser benefit/added benefit not proven
Cognitive functioning	Median: NA vs. NA HR: 1.09 [0.61; 1.94]; 0.771	Lesser benefit/added benefit not proven
Social functioning	Median: NA vs. 7.1 HR: 0.54 [0.29; 0.996]; 0.049 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"[c]
Side effects		
SAEs	Median: 13.4 vs. 11.4 HR: 0.96 [0.57; 1.62]; 0.874	Lesser benefit/added benefit not proven
Discontinuation due to AEs	Data incomplete	Lesser benefit/added benefit not proven
Severe AEs (CTCAE ≥ 3)	Median: 2.3 vs. 1.6 HR: 0.67 [0.44; 1.02]; 0.064	Lesser benefit/added benefit not proven

a: Probability provided if statistically significant results are present.
b: Estimation of effect size is made depending on the outcome category with different limits based on the CI_u.
c: Due to the missing time course data, the relevance of the result cannot be estimated. In the overall consideration, an added benefit for the outcome "social functioning" is not proven.

AE: adverse event; BR: bendamustine + rituximab; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACIT: Functional Assessment of Chronic Illness Therapy; HR: hazard ratio; MID: minimally important difference; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of ibrutinib + BR in comparison with placebo + BR

Positive effects	Negative effects
▪ Mortality[a] ▫ overall survival: indication of an added benefit – extent: "considerable"	–
a: Information refers to the subpopulation of patients with CLL who have received at least 2 prior therapies and for whom BR is an individually optimized chemotherapy in combination with rituximab. ACT: appropriate comparator therapy; BR: bendamustine + rituximab; CLL: chronic lymphocytic leukaemia	

Usable data for the assessment of the added benefit were only available for the subpopulation of patients with CLL who have received at least 2 prior therapies and for whom BR is an individually optimized chemotherapy in combination with rituximab.

For this patient population, an indication of considerable added benefit resulted in a positive effect for the outcome "overall survival". The positive effect on overall survival is not accompanied by a negative effect.

Overall, there is therefore an indication of considerable added benefit versus of ibrutinib + BR versus BR, one treatment option within the ACT, for this patient population.

The company presented no usable data for further patients of the target population (patients with 1 prior therapy and patients for whom other treatments than BR are the individually optimized treatment). The added benefit is not proven for this patient population.

The result of the assessment of the added benefit of ibrutinib + BR in comparison with the ACT is summarized in Table 16.

Table 16: Ibrutinib + BR – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Patients with CLL who have received at least one prior therapy and for whom chemotherapy indicated is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	*Patients with at least 2 prior therapies and for whom BR is an individually optimized chemotherapy in combination with rituximab:* indication of considerable added benefit *Further patients of the target population[b]:* added benefit not proven
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: Patients with only 1 prior therapy and patients for whom other treatments than BR are the individually optimized treatment. ACT: appropriate comparator therapy; BR: bendamustine + rituximab; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee		

This does not concur with the company's assessment. The company also derived an indication of considerable added benefit, but for the total target population.

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

2.6 List of included studies

HELIOS-Studie

Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol 2016; 17(2): 200-211.

Janssen Research & Development. Randomized, double-blind, placebo-controlled phase 3 study of ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, in combination with bendamustine and rituximab (BR) in subjects with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma; study PCI-32765CLL3001; clinical study report [unpublished]. 2015.

Janssen Research & Development. A study of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chroniclymphocytic leukemia or small lymphocytic lymphoma: full text view [online]. In: ClinicalTrials.gov. 30.09.2016 [Accessed: 27.10.2016]. URL: https://ClinicalTrials.gov/show/NCT01611090.

Janssen Research & Development. Randomized, double-blind, placebo-controlled phase 3 study of ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, in combination with bendamustine and rituximab (BR) in subjects with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma; study PCI-32765CLL3001; Zusatzanalysen [unpublished]. 2016.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-60-ibrutinib-chronic-lymphocytic-leukaemia-benefit-assessment-according-to-35a-social-code-book-v.7705.html.