Pirtobrutinib (chronic lymphocytic leukaemia)

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

EXTRACT

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange and for their support. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of tables[2]

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

I List of abbreviations

Abbreviation	Meaning
17p deletion	deletion in the short arm of chromosome 17
ACT	appropriate comparator therapy
AE	adverse event
BCL2	B-cell lymphoma 2
BSA	body surface area
BTK	Bruton's tyrosine kinase inhibitor
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRO	patient-reported outcome
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small lymphocytic lymphoma
SmPC	summary of product characteristics
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pirtobrutinib. 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 11 April 2025.

Research question

The aim of this report is to assess the added benefit of pirtobrutinib in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTK).

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of pirtobrutinib

Research question	Therapeutic indication[a]	ACT[b]
1	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor	venetoclax + rituximab
2	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor	Individualized treatment[c, d, e] with a choice of: ▪ idelalisib + rituximab ▪ venetoclax + rituximab ▪ bendamustine + rituximab

a. It is assumed for the therapeutic indication in question that the patients require treatment (e.g. Binet stage C).
b. Presented is the respective ACT specified by the G-BA.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).
e. The treatment decision in particular takes into account prior therapy, response, genetic risk factors and duration of remission following prior therapies, and the patient's general condition. According to the current state of medical knowledge, the presence of a 17p deletion/TP53 mutation as well as an unmutated IGHV status and complex karyotype are considered genetic risk factors.

17p deletion: deletion of the short arm of chromosome 17; BCL2: B-cell lymphoma 2; BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; EU: European Union; G-BA: Federal Joint Committee; HTA: Health Technology Assessment; IGHV: immunoglobulin heavy-chain variable region; TP53: tumour suppressor protein 53

The G-BA's most recent adjustment to the research questions and the ACT was on 23 April 2025, as shown in Table 2. However, in its dossier, the company referred to the research questions and the ACT defined by the G-BA in 2021.

The population for research question 1 specified by the company were patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor, but without the restriction specified in the current ACT by the G-BA that they have not yet been treated with a BCL2 inhibitor. For research question 2, the company cited patient-specific therapy with a choice of idelalisib + rituximab, bendamustine + rituximab, chlorambucil + rituximab and best supportive care as the ACT. On the one hand, the individualized treatment options listed by the company did not include the option venetoclax + rituximab mentioned by the G-BA; on the other hand, the company continued to name the options chlorambucil + rituximab and best supportive care mentioned in the outdated ACT.

This benefit assessment was conducted in comparison with the ACT specified by the G-BA on 23 April 2025, as shown in Table 2. 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 to derive the added benefit. This concurred with the company's inclusion criteria.

Research question 1: adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor

Results

The review of the information retrieval did not identify any RCTs for the direct comparison of pirtobrutinib with the ACT. There were therefore no suitable data.

Results on added benefit

No data were available to assess the added benefit of pirtobrutinib in comparison with the ACT in adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor. There is no hint of an added benefit of pirtobrutinib in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor

Study pool and study design

The BRUIN CLL-321 study was included in the benefit assessment.

The BRUIN CLL-321 study is an open-label, ongoing RCT comparing pirtobrutinib with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

The study included adult patients with CLL or small lymphocytic lymphoma (SLL) with an indication for treatment, who had been previously treated with a BTK inhibitor.

A total of 119 patients were randomized to the intervention arm and 119 to the comparator arm. For the benefit assessment, the company presented a subpopulation of those patients who had been previously treated with a BCL2 inhibitor in addition to one BTK inhibitor. These were 60 patients in the intervention arm and 62 in the comparator arm.

Treatment with pirtobrutinib in the intervention arm was carried out in compliance with the summary of product characteristics (SmPC). Treatment with bendamustine + rituximab in the comparator arm was given for a maximum of 6 cycles (28 days each). The use in the BRUIN CLL-321 study corresponds to the approach in the studies conducted on the combination of bendamustine and rituximab in the therapeutic indication. In the comparator arm, idelalisib + rituximab was also administered for 6 cycles, after which idelalisib was continued until disease progression or the occurrence of unacceptable toxicity. The use in the BRUIN CLL-321 study corresponds to the approach in the studies conducted on the combination of idelalisib and rituximab in the therapeutic indication.

According to the SmPC, premedication with an analgesic/antipyretic and an antihistamine should always be given before administering rituximab. It was unclear whether all patients in the BRUIN CLL-321 study were given adequate premedication.

After disease progression, it was allowed to switch from the comparator arm to treatment with pirtobrutinib.

The primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

The prespecified data cut-off of 29 August 2024 is used for the benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for the BRUIN CLL-321 study.

The results on overall survival had a high risk of bias because a high proportion of patients (37%) switched from the control arm to treatment with pirtobrutinib. No information was available regarding the time points at which the patients switched treatment. The risk of bias for the time-to-event analyses of the side effects outcomes was rated as high. This was due to incomplete observations for potentially informative reasons with different observation periods, and, for non-severe/non-serious AEs, to lack of blinding in subjective recording of outcomes.

Results

Mortality

Overall survival

No statistically significant difference between the study arms was shown for the outcome of overall survival. There is no hint of an added benefit of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30) and health status (EQ-5D VAS)

No suitable data were available for the outcomes of symptoms recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and health status recorded with the EQ-5D visual analogue scale (VAS). There is no hint of an added benefit of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data were available for the outcome of health-related quality of life recorded with the EORTC QLQ-C30. There is no hint of an added benefit of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was shown for the outcome of SAEs. There is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcome severe AEs (CTCAE grade ≥ 3).

There was an effect modification for the characteristic of Rai stage, however. For patients with Rai stage 0–II, there was a statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or

bendamustine + rituximab. There is a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

No statistically significant difference between the treatment groups was shown for patients with Rai stage III–IV. There is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcome discontinuation due to AEs. There is a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

Infections and infestations (AEs) and cardiac disorders (AEs)

No statistically significant difference between the treatment groups was shown for either of the outcomes infections and infestations (AEs) and cardiac disorders (AEs). In each case, there is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Haemorrhages (severe AEs, AEs)

No suitable data were available for the outcomes haemorrhages (severe AEs and AEs). In each case, there is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Bronchitis (AEs), pyrexia (AEs)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcomes bronchitis (AEs) and pyrexia (AEs). In each case, there is therefore a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

Injury, poisoning and procedural complications (SAEs), renal and urinary disorders (SAEs), diarrhoea (SAEs)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcomes injury, poisoning and procedural complications (SAEs), renal and urinary

disorders (SAEs) and diarrhoea (SAEs). In each case, there is therefore a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

Investigations (severe AEs), skin and subcutaneous tissue disorders (severe AEs), metabolism and nutrition disorders (severe AEs), hepatobiliary disorders (severe AEs), vascular disorders (severe AEs)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcomes investigations (severe AEs), skin and subcutaneous tissue disorders (severe AEs), metabolism and nutrition disorders (severe AEs), hepatobiliary disorders (severe AEs) and vascular disorders (severe AEs). In each case, there is therefore a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Overall, there are only positive effects of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

In the outcome category of side effects, there are hints of lesser harm with an extent of up to major for various specific SAEs, severe AEs and non-serious/non-severe AEs as well as for the outcome of discontinuation due to AEs. These results refer exclusively to the shortened period up to 28 days after discontinuation of treatment. Furthermore, it was unclear whether all patients in the comparator arm were given adequate premedication. The interpretation of these results was therefore limited.

The interpretation of the results for overall survival was also limited due to the treatment switching of patients from the comparator arm to treatment with pirtobrutinib. However, there were more deaths in the pirtobrutinib arm than in the comparator arm. A negative effect could not therefore be ruled out with sufficient certainty. In addition, there were no suitable data for the outcome categories of morbidity and health-related quality of life. In summary,

[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].

the positive effects, which were shown exclusively for side effects outcomes, were not sufficient to derive an added benefit of pirtobrutinib.

The added benefit of pirtobrutinib in comparison with the ACT is not proven for adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor and for whom idelalisib + rituximab or bendamustine + rituximab is a suitable individualized treatment.

No data were available for adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor and for whom venetoclax + rituximab is the suitable individualized treatment. Also for these patients, the added benefit of pirtobrutinib versus the ACT is not proven.

Table 3 presents a summary of the probability and extent of the added benefit of pirtobrutinib.

Table 3: Pirtobrutinib – probability and extent of added benefit

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor	venetoclax + rituximab	Added benefit not proven
2	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and with a BCL2 inhibitor	Individualized treatment[c, d, e] with a choice of: ▪ idelalisib in combination with rituximab, ▪ venetoclax in combination with rituximab, ▪ bendamustine in combination with rituximab	Added benefit not proven

a. It is assumed for the therapeutic indication in question that the patients require treatment (e.g. Binet stage C).
b. Presented is the respective ACT specified by the G-BA.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).
e. The treatment decision in particular takes into account prior therapy, response, genetic risk factors and duration of remission following prior therapies, and the patient's general condition. According to the current state of medical knowledge, the presence of a 17p deletion/TP53 mutation as well as an unmutated IGHV status and complex karyotype are considered genetic risk factors.

17p deletion: deletion of the short arm of chromosome 17; BCL2: B-cell lymphoma 2; BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; EU: European Union; G-BA: Federal Joint Committee; HTA: Health Technology Assessment; IGHV: immunoglobulin heavy-chain variable region; TP53: tumour suppressor protein 53

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

I 2 Research question

The aim of this report is to assess the added benefit of pirtobrutinib in comparison with the ACT in adult patients with relapsed or refractory CLL who have been previously treated with a BTK.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of pirtobrutinib

Research question	Therapeutic indication[a]	ACT[b]
1	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor	venetoclax + rituximab
2	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor	Individualized treatment[c, d, e] with a choice of: ▪ idelalisib + rituximab ▪ venetoclax + rituximab ▪ bendamustine + rituximab

a. It is assumed for the therapeutic indication in question that the patients require treatment (e.g. Binet stage C).
b. Presented is the respective ACT specified by the G-BA.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).
e. The treatment decision in particular takes into account prior therapy, response, genetic risk factors and duration of remission following prior therapies, and the patient's general condition. According to the current state of medical knowledge, the presence of a 17p deletion/TP53 mutation as well as an unmutated IGHV status and complex karyotype are considered genetic risk factors.

17p deletion: deletion of the short arm of chromosome 17; BCL2: B-cell lymphoma 2; BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; EU: European Union; G-BA: Federal Joint Committee; HTA: Health Technology Assessment; IGHV: immunoglobulin heavy-chain variable region; TP53: tumour suppressor protein 53

The G-BA's most recent adjustment to the research questions and the ACT was on 23 April 2025, as shown in Table 4. However, in its dossier, the company referred to the research questions and the ACT defined by the G-BA in 2021.

The population for research question 1 specified by the company were patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor, but without the restriction specified in the current ACT by the G-BA that they have not yet been treated with a B-cell lymphoma 2 (BCL2) inhibitor. For research question 2, the company cited patient-specific therapy with a choice of idelalisib + rituximab, bendamustine + rituximab,

chlorambucil + rituximab and best supportive care as the ACT. On the one hand, the individualized treatment options listed by the company did not include the option venetoclax + rituximab mentioned by the G-BA; on the other hand, the company continued to name the options chlorambucil + rituximab and best supportive care mentioned in the outdated ACT.

This benefit assessment was conducted in comparison with the ACT specified by the G-BA on 23 April 2025, as shown in Table 4. 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 to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Research question 1: adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor

I 3.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on pirtobrutinib (status: 12 March 2025)
- Bibliographical literature search on pirtobrutinib (last search on 12 March 2025)
- Search of trial registries/trial results databases for studies on pirtobrutinib (last search on 12 March 2025)
- Search on the G-BA website for pirtobrutinib (last search on 12 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on pirtobrutinib (last search on 25 April 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, a review of the completeness of the study pool did not identify any RCTs on the direct comparison of pirtobrutinib versus the ACT.

I 3.2 Results

No data were available to assess the added benefit of pirtobrutinib in comparison with the ACT in adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor. There is no hint of an added benefit of pirtobrutinib in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

As the company did not present any data for the assessment of the added benefit of pirtobrutinib in adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor, an added benefit is not proven.

The assessment described above concurs with that by the company.

I 4 Research question 2: adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor

I 4.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on pirtobrutinib (status: 12 March 2025)
- Bibliographical literature search on pirtobrutinib (last search on 12 March 2025)
- Search of trial registries/trial results databases for studies on pirtobrutinib (last search on 12 March 2025)
- Search on the G-BA website for pirtobrutinib (last search on 12 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on pirtobrutinib (last search on 25 April 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 4.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
BRUIN CLL-321	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

CSR: clinical study report; RCT: randomized controlled trial

The BRUIN CLL-321 study was used for the benefit assessment. The study pool was consistent with that selected by the company. The study is described in the following section.

I 4.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BRUIN CLL-321	RCT, open-label, parallel	Adult patients with CLL/SLL with an indication for treatment[b], with known 17p deletion status[c] and ▪ previously treated with a covalent BTK inhibitor, either alone or in combination with other drugs ▪ ECOG PS: 0–2	pirtobrutinib (N = 119) Individualized treatment (N = 119), of which: ▪ idelalisib + rituximab (N = 82) ▪ bendamustine + rituximab (N = 37) Relevant subpopulation thereof[d]: pirtobrutinib (n = 60) Individualized treatment (n = 62), of which: ▪ idelalisib + rituximab (N = 48) ▪ bendamustine + rituximab (N = 14)	Screening: up to 28 days Treatment: ▪ Until disease progression[e, f], unacceptable toxicity, physician decision to discontinue treatment, or withdrawal of consent; bendamustine + rituximab: maximum of 6 cycles Observation: ▪ Outcome-specific[g], at most until death, withdrawal of consent, or end of study	235 centres in Australia, Austria, Belgium, Canada, China, Croatia, Czech Republic, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Poland, Russia, Singapore, South Korea, Spain, Switzerland, Taiwan, Turkey, United Kingdom, United States 3/2021–ongoing Data cut-offs: ▪ 29 August 2023[h] ▪ 29 August 2024[i]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. Indication for treatment as defined by the international iwCLL working group 2018 criteria [8]. c. Wild type for 17p locus or positive for 17p deletion. d. Patients with prior therapy with at least one BTK inhibitor and one BCL2 inhibitor e. Patients in the control arm had the option of switching to the intervention arm in the event of disease progression according to iwCLL 2018 criteria. f. Patients were allowed to continue treatment after disease progression if, in the opinion of the investigator, they were deriving clinical benefit from continuing treatment. g. Outcome-specific information is provided in Table 8. h. Prespecified analysis of the primary outcome. i. Prespecified data cut-off for the final analysis of overall survival. 17p deletion: deletion of the short arm of chromosome 17; AE: adverse event; BCL2: B-cell lymphoma 2; BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; n.: number of patients in the relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma					

Table 7: Characteristics of the intervention – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study	Intervention	Comparison
BRUIN CLL-321	pirtobrutinib 200 mg orally daily[a]	▪ idelalisib + rituximab: ▫ idelalisib 150 mg orally twice daily + ▫ rituximab 375 mg/m² BSA IV on Day 1 of Cycle 1[b], then 500 mg/m² BSA IV on Day 1 of Cycle 1 and on Day 1 and 15 of Cycle 2 500 mg/m² BSA IV on Day 1 of Cycles 3–6 or ▪ bendamustine + rituximab: ▫ bendamustine 70 mg/m² BSA IV on Day 1 und 2 for 6 cycles + ▫ rituximab 375 mg/m² BSA IV on Day 1 of Cycle 1[b] and 500 mg/m² BSA IV on Day 1 of Cycles 2–6 Duration of cycle: 28 days
	Dose modification: ▪ Up to 2 dose reductions (to 100 mg, then to 50 mg)[c] permitted in case of toxicity, then treatment discontinuation	▪ idelalisib/bendamustine: Dose modifications permitted as per local SmPC and at investigator discretion in case of toxicity ▪ rituximab: no dose modifications allowed[d] ▪ If one treatment component was discontinued, the other component could be continued (taking into account the maximum cycle duration for rituximab)
	Treatment interruption due to toxicity permitted for up to 28 days[e]	

Table 7: Characteristics of the intervention – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study	Intervention	Comparison
	Required pretreatment ▪ 1 covalent BTK inhibitor, either alone or in combination with other drugs **Disallowed prior treatment** ▪ Non-covalent BTK inhibitors ▪ Allogeneic or autologous stem cell transplantation or CAR-T cell therapy ≤ 60 days before baseline ▪ Major surgery ≤ 4 weeks before starting the study medication **Concomitant treatment** <u>Premedication required before rituximab</u> ▪ paracetamol, antihistamine and/or steroids as per local practice <u>Allowed</u> <u>Any concomitant treatment required, such as</u> ▪ Haematopoietic growth factors to treat neutropenia, anaemia or thrombocytopenia ▪ Red blood cells and platelet transfusions ▪ Glucocorticoids (≤ 20 mg per day prednisone or equivalent) for ≤ 14 days ▪ Palliative radiation therapy (e.g. for symptomatic nodal disease) <u>Disallowed</u> ▪ Live vaccines ▪ CYP inhibitors or inducers	

a. Until disease progression, unacceptable toxicity or end of study.
b. Patients at high risk for infusion-related reactions could, at the investigator's discretion, receive the initial dose of rituximab split over 2 consecutive days.
c. The dose did not need to be re-escalated; however, re-escalation was possible if the reduced dose was well tolerated for ≥ 2 weeks, at the discretion of the investigator.
d. Exception: to manage infusion-related reactions.
e. In the control arm, in exceptional cases, also possible for longer after consultation with the sponsor.

BSA: body surface area; BTK: Bruton's tyrosine kinase; CAR: chimeric antigen receptor; CYP: cytochrome P; IV: intravenous; RCT: randomized controlled trial

The BRUIN CLL-321 study is an open-label, ongoing RCT comparing pirtobrutinib with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab. The study included adult patients with CLL or SLL with an indication for treatment, who had been previously treated with a BTK inhibitor. The indication for treatment was determined based on the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria [8]. Patients had to have a general condition that concurred with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2.

Patients were randomized in a 1:1 ratio, stratified by deletion in the short arm of chromosome 17 (17p deletion) and prior therapy with venetoclax. Before randomization, patients were allocated to possible treatment with idelalisib + rituximab or bendamustine + rituximab in the comparator arm. A total of 119 patients were randomized to the intervention arm and 119 to the comparator arm. For the benefit assessment, the company presented a subpopulation of those patients who had been previously treated with a BCL2 inhibitor in addition to one BTK inhibitor. These were 60 patients in the intervention arm and 62 in the comparator arm.

Treatment with pirtobrutinib in the intervention arm was carried out in compliance with the SmPC [9]. Treatment with pirtobrutinib was planned until disease progression or the occurrence of unacceptable toxicity.

Treatment with bendamustine + rituximab in the comparator arm was given for a maximum of 6 cycles (28 days each). Treatment with rituximab was in compliance with the SmPC [10]. The patients received bendamustine intravenously at a dose of 70 mg/m² body surface area (BSA). However, according to the SmPC, bendamustine should be administered at 100 mg/m^2 [11]. The SmPCs contain no specific dosage recommendations for the use of bendamustine in combination therapy with rituximab. The SmPC for rituximab, for example, refers to combination therapy with chemotherapy generally and not explicitly to the combination with bendamustine [10,11]. However, its use in the BRUIN CLL-321 study corresponds to the approach in the studies conducted on the combination of bendamustine and rituximab in the therapeutic indication [12-14].

In the comparator arm, idelalisib + rituximab was also administered for 6 cycles, after which idelalisib was continued until disease progression or the occurrence of unacceptable toxicity. Treatment with idelalisib in the BRUIN CLL-321 study was carried out in compliance with the SmPC [15]. Deviating from the SmPC, rituximab in combination with idelalisib was administered every 14 days in the first 2 cycles rather than only at the beginning of each 28-day cycle [10]. However, the use in the BRUIN CLL-321 study corresponds to the approach in the studies conducted on the combination of idelalisib and rituximab in the therapeutic indication [16,17].

Overall, the uncertainties described regarding treatment with bendamustine + rituximab or idelalisib + rituximab were of no consequence for this benefit assessment.

According to the study protocol, patients in the study were to receive premedication with paracetamol, antihistamines and/or steroids as per local practice before treatment with rituximab. However, according to the SmPC, premedication with an analgesic/antipyretic and an antihistamine should always be given before administering rituximab [10]. Precise information on the premedication administered was not available in the company's dossier.

However, the information on concomitant medication showed that in the subpopulation presented by the company, only approximately 68% of patients in the comparator arm received treatment with analgesics and approximately 57% received treatment with antihistamines. It was therefore unclear whether all patients received the required premedication before receiving rituximab. In addition, prophylaxis with adequate hydration and administration of uricostatics before treatment with rituximab is recommended for CLL patients [10]. There was no information in the study documents as to whether such prophylaxis was conducted.

After disease progression, patients from the comparator arm were allowed to switch to treatment with pirtobrutinib.

Patients in both study arms were allowed to continue study treatment after disease progression if, in the opinion of the investigator, they were deriving clinical benefit from continuing treatment.

The primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Data cuts

A total of 3 data cut-offs have been conducted for the BRUIN CLL-321 study to date:

- 29 August 2023: prespecified final data cut-off for the outcome PFS after about 88 events
- 9 February 2024: according to the company, data cut submitted as part of the marketing authorization process
- 29 August 2024: After availability of the 1st data cut in version 3 of the statistical analysis plan dated 6 September 2023, prespecified final data cut-off for the outcome overall survival after about 70 events about 1 year after the 1st data cut-off

In its dossier, the company presented results for the subpopulation at the 29 August 2024 data cut-off.

Uncertainties of the BRUIN CLL-321 study

Not all of the options specified by the G-BA for individualized treatment were available in the BRUIN CLL-321 study

For research question 2, the G-BA specified individualized treatment with a choice of idelalisib + rituximab, bendamustine + rituximab or venetoclax + rituximab as the ACT. In the BRUIN CLL-321 study, idelalisib + rituximab and bendamustine + rituximab were available to

the investigators, but not venetoclax + rituximab. In the subpopulation presented by the company, all but 2 patients had already received treatment with venetoclax.

According to current guidelines, renewed treatment with venetoclax may be an option for patients with relapse, especially after a longer remission period (of 2 to 3 years) [18-20].

The company's dossier did not provide any information on how much time had passed since the patients in the subpopulation had been treated with venetoclax or whether and for how long the patients had been in remission. It was therefore unclear whether treatment with venetoclax + rituximab would have been a relevant option for these patients. However, it was assumed that this only affected a small number of patients. However, conclusions can only be drawn from the results of the study for those patients for whom treatment with idelalisib + rituximab or bendamustine + rituximab was indicated.

Treatment with rituximab

As explained above, it is questionable whether patients in the comparator arm received adequate premedication prior to treatment with rituximab. This was taken into account when interpreting the results, particularly those of adverse events (AEs).

Treatment switching

At the data cut-off on 29 August 2024, approximately 37% (23) of patients from the comparator arm of the subpopulation had switched to treatment with pirtobrutinib. This treatment switching was taken into account in the assessment of the risk of bias at outcome level.

Uncertainties do not lead to study exclusion

Overall, the uncertainties described did not lead to the exclusion of the study from the benefit assessment. However, the aspects described were considered in the assessment of the certainty of conclusions of the results (see Section I 4.2).

In summary, the results of the subpopulation of the BRUIN CLL-321 study presented by the company, on the basis of the data cut-off on 29 August 2024, were used for the benefit assessment.

Planned duration of follow-up

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

Table 8: Planned duration of follow-up – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Study **Outcome category** **Outcome**	**Planned follow-up**
BRUIN CLL-321	
Mortality	
Overall survival	Until death or study end
Morbidity	
Symptoms (EORTC QLQ-C30)	28 days after the last dose of study medication
Health status (EQ-5D VAS)	
Health-related quality of life	
EORTC QLQ-C30	28 days after the last dose of study medication
Side effects	
All outcomes of the side effects category, except secondary malignancies	28 days after the last dose of study medication
Secondary malignancies	5 years after starting the study medication[a]
a. Patients from the control arm who switched to pirtobrutinib after disease progression were followed up for secondary malignancies for 5 years after the start of pirtobrutinib therapy.	
EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes morbidity, health-related quality of life, and side effects (except secondary malignancies) were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 28 days). However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the relevant subpopulation as well as discontinuation of the study/treatment – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study **Characteristic** **Category**	**Pirtobrutinib** **N[b] = 60**	**Individualized treatment[a]** **N[b] = 62**
CLL-321		
Age [years], mean (SD)	67 (9)	67 (9)
Sex [F/M], %	30/70	35/65
Family origin n (%)		
White/Caucasian	54 (90)	52 (84)
Asian	2 (3)	3 (5)
Black or African American	1 (2)	3 (5)
Unknown	3 (5)[c]	4 (6)[c]
Region, n (%)		
North America	13 (22)	21 (34)
Europe	40 (67)	36 (58)
Asia	2 (3)	3 (5)
Australia	5 (8)	2 (3)
Histology, n (%)		
CLL	56 (93)	58 (94)
SLL	4 (7)	4 (6)
ECOG PS, n (%)		
0	24 (40)	25 (40)
1	33 (55)	35 (56)
2	3 (5)	2 (3)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	141.2 (67.2)	134.7 (53.8)
Rai stage, n (%)		
0	0 (0)	3 (5)
I	8 (13)	11 (18)
II	14 (23)	15 (24)
III	4 (7)	11 (18)
IV	30 (50)	20 (32)
Unknown	4 (7)	2 (3)

Table 9: Characteristics of the relevant subpopulation as well as discontinuation of the study/treatment – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study Characteristic **Category**	**Pirtobrutinib** **N[b] = 60**	**Individualized treatment[a]** **N[b] = 62**
Chromosome anomaly del(17p), n (%)		
Yes	20 (33)	27 (44)
No	36 (60)	32 (52)
Unknown	4 (7)	3 (5)
IGHV status, n (%)		
Mutant	2 (3)	8 (13)
Unmutated	51 (85)	42 (68)
Unknown	7 (12)	12 (19)
TP53 mutation, n (%)		
Mutant	22 (37)	15 (24)
Unmutated	31 (52)	38 (61)
Unknown	7 (12)	9 (15)
Complex karyotype, n (%)		
Yes	28 (47)	28 (45)
No	12 (20)	14 (23)
Unknown	20 (33)	20 (32)
Number of prior systemic therapies, n (%)		
1	1 (2)	2 (3)
2	10 (17)	10 (16)
3	17 (28)	7 (11)
≥ 4	32 (53)	43 (69)
Prior therapies		
Systemic therapy, n (%)	60 (100)	62 (100)
BTKi, n (%)	60 (100)	62 (100)
BCL2i, n (%)	60 (100)	62 (100)
Chemotherapy, n (%)	45 (75)	53 (85)
Anti-CD20 antibodies, n (%)	53 (88)	53 (85)
PI3K, n (%)	8 (13)	9 (15)
Treatment discontinuation, n (%)[d]	41 (68)[c]	60 (97)[c]
Study discontinuation, n (%)[e]	33 (55)	32 (52)

Table 9: Characteristics of the relevant subpopulation as well as discontinuation of the study/treatment – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study Characteristic Category	Pirtobrutinib N[b] = 60	Individualized treatment[a] N[b] = 62

a. Individualized treatment with a choice of idelalisib + rituximab and bendamustine + rituximab.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation.
d. This includes 2 vs. 6 patients who never started therapy. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): disease progression (43.3% vs. 40.3%), AE (15% vs. 16.1%), investigator decision (0% vs. 11.3%), death (1.7% vs. 8.1%).
e. A common reason for study discontinuation in the intervention vs. comparator arm was (percentages refer to randomized patients): withdrawal of consent (10% vs. 19.4%). The data additionally include patients who died during the course of the study (intervention arm: 43.3% vs. control arm: 30.6%).

BCL2i: B-cell lymphoma 2 inhibitor; BTK(i): Burton's tyrosine kinase (inhibitor); CD: cluster of differentiation; CLL: chronic lymphocytic leukaemia; del: deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IGHV: immunoglobulin heavy-chain variable region; M: male; n: number of patients in the category; N: number of randomized patients; PI3K: phosphatidylinositol-3-kinase; RCT: randomized controlled trial; SD: standard deviation; SLL: small lymphocytic lymphoma; TP53: tumour suppressor protein 53

The patient characteristics of the relevant subpopulation were largely comparable between the 2 treatment arms. The mean age of the patients was 67 years. At 2 thirds, the majority of the subpopulation in both treatment arms were men. The majority (approx. 96%) of patients had an ECOG PS of 0 or 1. Approximately 53% of patients were in Rai stage III–IV at baseline. The patients in both study arms had been diagnosed with the disease for an average of over 11 years, and about 61% had received ≥ 4 lines of systemic treatment prior to enrolment in the BRUIN CLL-321 study.

More patients in the comparator arm (97%) than in the intervention arm (68%) discontinued treatment. This difference was due in particular to the higher proportion of deaths (2% vs. 8%) and treatment discontinuations due to the investigator's decision in the comparator arm (0% vs. 11%).

Information on the course of the study

Table 10 shows the patients' mean/median treatment duration and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Study	**pirtobrutinib**	**Individualized treatment**			
Duration of the study phase	**N = 58**	**N = 56**			
Outcome category/outcome					
		idelalisib + rituximab (N = 44)		**bendamustine + rituximab (N = 12)**	
		idelalisib	**rituximab**	**bendamustine**	**rituximab**
BRUIN CLL-321					
Treatment duration [months]					
Median [Q1; Q3]	13.5 [4.2; 19.6]	7.1 [2.2; 10.1]	5.0 [2.6; 5.5]	1.5 [1.0; 4.7]	2.4 [0.9; 4.7]
Mean (SD)	12.9 (8.0)	7.4 (6.3)	4.2 (1.8)	2.7 (2.2)	2.8 (2.2)
	N = 60	**N = 62**			
Observation period [months][a]					
Overall survival[b]					
Median [Q1; Q3]	19.8 [15.4; 24.2]	19.2 [14.2; 25.1]			
Symptoms, health-related quality of life (EORTC QLQ-C30)					
Median [Q1; Q3]	11.0 [3.3; 16.6]	2.8 [0.0; 8.2]			
Health status (EQ-5D VAS)					
Median [Q1; Q3]	8.5 [3.7; 16.5]	3.0 [0.0; 8.3]			
Side effects					
Median [Q1; Q3]	13.9 [5.4; 19.7]	5.3 [2.6; 10.0]			

a. No information on mean values.
b. The observation period is calculated using a Kaplan-Meier curve in which deceased patients are censored at the time of death, while non-deceased patients are categorized as an event at the end of the observation period.

EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The overall treatment duration in the pirtobrutinib arm was notably longer than the duration with individualized treatment. In the comparator arm, patients who received idelalisib + rituximab were treated for longer than those who received bendamustine + rituximab. The observation periods for overall survival were comparable between the intervention arm and the comparator arm. In all other outcome categories, the observation period was notably longer in the intervention arm than in the comparator arm. The reason for this was that the observation period was linked to the treatment period (see Table 8).

The differences in observation periods were taken into account when deriving the outcome-specific risk of bias of the outcomes in the category of side effects.

Information on subsequent therapies

In Module 4 A, the company provided contradictory information on subsequent therapies (all subsequent therapies, 1st subsequent therapy) and on the proportion of patients who switched from the comparator arm to treatment with pirtobrutinib during the course of the study. The table for the overview of subsequent therapies shows that 4 patients (7%) in the comparator arm received pirtobrutinib as their first subsequent therapy (and a total of 5 [approx. 9%] as subsequent therapy). Elsewhere, however, the company stated that 23 (approx. 37%) switched to treatment with pirtobrutinib. The company's information on subsequent therapies can therefore not be interpreted and is not presented. Switching treatment from the comparator arm to pirtobrutinib was taken into account in the assessment of the risk of bias at outcome level.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
BRUIN CLL-321	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low. Limitations resulting from the open-label study design are described in Section I 4.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company described that the demographic and disease-specific characteristics of the patients in the BRUIN CLL-321 study corresponded to the target population of CLL patients in Germany and that the patients came almost exclusively from Western countries with similar health care standards for CLL to Germany and had received guideline-compliant prior treatment. The company stated that the patients in the BRUIN CLL-321 study had a poor prognosis and had already undergone several prior treatments. According to the current state of the therapeutic landscape, there is no standard therapy available for these patients, nor is there any effective therapy in general, the company added. It considered the results of the BRUIN CLL-321 study to be transferable to the German health care context.

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

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Symptoms recorded with the EORTC QLQ-C30
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Infections and infestations (System Organ Class [SOC], AEs)
  - Severe haemorrhages (Standardized Medical Dictionary for Regulatory Activities Query [SMQ], severe AEs)
  - Haemorrhages (SMQ, AEs)
  - Cardiac disorders (SOC, AEs)

- Other specific AEs, if any

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

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

Table 12: Matrix of outcomes – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infections and infestations (SOC, AEs)	Severe haemorrhages (SMQ[b], severe AEs[a])	Haemorrhages (SMQ[b], AEs)	Cardiac disorders (SOC, AEs)	Further specific AEs[a, c]
BRUINCLL-321	Yes	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Without events based on laboratory values.
c. The following events are considered (coded according to MedDRA): bronchitis (PT, AEs), pyrexia (PT, AEs), injury, poisoning and procedural complications (SOC, SAEs), renal and urinary disorders (SOC, SAEs), diarrhoea (PT, SAEs), investigations (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), vascular disorders (SOC, severe AEs).
d. No suitable data available (see running text below for reasons).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Results on patient-reported outcomes not usable

For the patient-reported outcomes (PROs) on morbidity and health-related quality of life, the company presented responder analyses of the time to first deterioration. It presented the EORTC QLQ-C30 for the recording of symptoms and health-related quality of life, and the EQ-5D VAS for health status. For health status, the company also presented analyses of the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGIS), although the wording of the corresponding items was not included in the dossier. Furthermore, the company presented 2 symptom scales (CLL/SLL symptom score and fatigue score) based on the EORTC Item Library. The validity of these 2 symptom scales was not verified, as the results presented by the company for the PROs could not be used for the assessment. This is justified below.

In the BRUIN CLL-321 study, the observation period for the PROs was linked to the treatment duration and thus, on the one hand, systematically and very notably shorter compared with overall survival and, on the other, notably different between the treatment arms (see Table 8 and Table 10). The response rates for all questionnaires declined early on, particularly in the control arm, and varied greatly between the study arms. This resulted in clear discrepancies in response rates between the study arms as early as Week 13 (on average just about 30%). As only a few events occurred at the early time points of recording, this means that it was overall not possible to interpret the results of the PROs.

Severe haemorrhages and haemorrhages

For haemorrhages, the company presented results from a selection of PTs. This selection was not prespecified in the study documents and the results were therefore not used for the benefit assessment. Analyses for AEs and severe AEs based on the SMQ haemorrhages are required.

I 4.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Study	Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infections and infestations (SOC, AEs)	Severe haemorrhages (SMQ[b], severe AEs[a])	Haemorrhages (SMQ[b], AEs)	Cardiac disorders (SOC, AEs)	Further specific AEs[a, c]
BRUIN CLL-321	L	H[d]	–[e]	–[e]	–[e]	H[f]	H[f]	H[g]	H[f, g]	–[e]	–[e]	H[f, g]	H[f, h]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Without events based on laboratory values.
c. The following events are considered (coded according to MedDRA): bronchitis (PT, AEs), pyrexia (PT, AEs), injury, poisoning and procedural complications (SOC, SAEs), renal and urinary disorders (SOC, SAEs), diarrhoea (PT, SAEs), investigations (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), vascular disorders (SOC, severe AEs).
d. High proportion of patients who switched from the control arm to treatment with pirtobrutinib (37%).
e. No suitable data available; for reasoning, see Section I 4.2.1 of this dossier assessment.
f. Incomplete observations for potentially informative reasons with different follow-up periods.
g. Lack of blinding in the presence of subjective recording of outcomes.
h. For non-serious/non-severe AEs: lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The results on overall survival had a high risk of bias because a high proportion of patients (37%) switched from the control arm to treatment with pirtobrutinib. No information was available regarding the time points at which the patients switched treatment. In Module 4, the company presented a sensitivity analysis for the outcome overall survival, in which patients with treatment switching were censored at the time of treatment switching. This approach was inadequate as it may lead to potentially biased effect estimates due to informative censoring. The primary analysis, in which the intention-to-treat principle was implemented and which included the longest possible follow-up period, was used for the benefit assessment.

No suitable data were available for the outcomes on symptoms, health status, health-related quality of life and the specific AEs severe haemorrhages and haemorrhages (see Section I 4.2.1), so the risk of bias of the results for these outcomes was not assessed.

The risk of bias for the time-to-event analyses of the side effects outcomes was rated as high. This was due to incomplete observations for potentially informative reasons with different observation periods. As described in Section I 4.1.2, the discontinuation of observation for these outcomes was linked to the end of treatment with the study medication. The observation period was thus determined by the reasons for treatment discontinuation, which differed between the treatment arms (investigator decision: 0% in the intervention arm and 11% in the comparator arm; death: 2% in the intervention arm and 8% in the comparator arm; patient decision: 2% in the intervention arm and 5% in the control arm). For these outcomes, this additionally resulted in notable differences in the median observation periods between the treatment groups (13.9 months versus 5.3 months). The risk of bias of the results for the outcome discontinuation due to AEs and for the non-severe/non-serious specific AEs infections and infestations (SOC, AEs) and cardiac disorders (SOC, AEs) and the other non-severe/non-serious specific AEs was also assessed as high due to the lack of blinding.

Summary assessment of the certainty of conclusions

The open-label RCT BRUIN CLL-321 was available for the assessment. The risk of bias was rated as high for the results of overall survival and side effects.

As described in Section I 4.1.2, it remained unclear whether treatment with venetoclax + rituximab would have been a relevant option for the patients in the comparator arm of the study, but was not available. Furthermore, it was unclear whether all patients in the comparator arm received adequate premedication before being treated with rituximab.

Thus, only hints, e.g. of an added benefit, can be derived on the basis of the available information from the BRUIN CLL-321 study.

I 4.2.3 Results

Table 14 summarizes the results from the comparison of pirtobrutinib with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab in patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the included outcomes are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs in I Appendix C of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study Outcome category Outcome	Pirtobrutinib		Individualized treatment[a]		Pirtobrutinib vs. individualized treatment[a]
	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[b]
BRUIN CLL-321					
Mortality					
Overall survival	60	26.3 [16.0; 29.7] 26 (43.3)	62	NC [28.0; NA] 19 (30.6)	1.39 [0.77; 2.52]; 0.279
Morbidity					
Symptoms (EORTC QLQ-C30)	No suitable data[c]				
Health status (EQ-5D VAS)	No suitable data[c]				
Health-related quality of life					
EORTC QLQ-C30	No suitable data[c]				
Side effects					
AEs (supplementary information)	58	0.6 [0.3; 1.2] 53 (91.4)	56	0.3 [0.1; 0.5] 55 (98.2)	–
SAEs	58	13.5 [6.9; 18.9] 32 (55.2)	56	6.8 [3.0; NA] 28 (50.0)	0.72 [0.42; 1.22]; 0.213
Severe AEs[d]	58	5.1 [2.8; NA] 34 (58.6)	56	2.3 [1.8; 3.3] 43 (76.8)	0.49 [0.31; 0.78]; 0.003
Discontinuation due to AEs[e]	58	29.4 [NA; NA] 10 (17.2)	56	13.0 [8.8; NA] 18 (32.1)	0.31 [0.14; 0.71]; 0.004
Infections and infestations (SOC, AEs[d])	58	NA [15.2; NA] 20 (34.5)	56	24.5 [NA; NA] 12 (21.4)	1.17 [0.56; 2.43]; 0.683
Severe haemorrhages (SMQ, severe AEs[d])	No suitable data[c]				
Haemorrhages (SMQ, AEs)	No suitable data[c]				
Cardiac disorders (SOC, AEs)	58	NA 5 (8.6)	56	24.5 [24.5; NA] 8 (14.3)	0.46 [0.15; 1.43]; 0.172
Bronchitis (PT, AEs)	58	NA 1 (1.7)	56	NA 8 (14.3)	0.09 [0.01; 0.70]; 0.004
Pyrexia (PT, AEs)	58	NA 8 (13.8)	56	NA [7.8; NA] 15 (26.8)	0.28 [0.11; 0.73]; 0.006

Table 14: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Study Outcome category Outcome	Pirtobrutinib		Individualized treatment[a]		Pirtobrutinib vs. individualized treatment[a]
	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[b]
Injury, poisoning and procedural complications (SOC, SAEs)	58	NA 0 (0.0)	56	NA 5 (8.9)	NC; 0.018
Renal and urinary disorders (SOC, SAEs)	58	NA 0 (0.0)	56	NA [13.0; NA] 3 (5.4)	NC; 0.039
Diarrhoea (PT, SAEs)	58	NA 0 (0.0)	56	NA 3 (5.4)	NC; < 0.001
Investigations (SOC, severe AEs[d])	58	NA 5 (8.6)	56	NA 9 (16.1)	0.32 [0.10; 1.00]; 0.040
Skin and subcutaneous tissue disorders (SOC, severe AEs[d])	58	NA 2 (3.4)	56	NA 7 (12.5)	0.19 [0.04; 0.96]; 0.027
Metabolism and nutrition disorders (SOC, severe AEs[d])	58	NA 1 (1.7)	56	NA 4 (7.1)	0.09 [0.01; 1.12]; 0.035
Hepatobiliary disorders (SOC, severe AEs[d])	58	NA 0 (0.0)	56	NA 3 (5.4)	NC; 0.031
Vascular disorders (SOC, severe AEs[d])	58	NA 0 (0.0)	56	NA 4 (7.1)	NC; 0.043

a. Individualized treatment with a choice of idelalisib + rituximab and bendamustine + rituximab.
b. HR from Cox regression model, p-value from log-rank test, each stratified according to the presence of the chromosomal anomaly del(17p) (yes, no)
c. See Section I 4.2.1 for details.
d. Operationalized as CTCAE grade ≥ 3.
e. Discontinuation of at least one drug component.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized Medical Dictionary for Regulatory Activities Query; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

No statistically significant difference between the study arms was shown for the outcome of overall survival. There is no hint of an added benefit of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30) and health status (EQ-5D VAS)

No suitable data were available for the outcomes of symptoms recorded with the EORTC QLQ-C30 and health status recorded with the EQ-5D VAS. There is no hint of an added benefit of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data were available for the outcome of health-related quality of life recorded with the EORTC QLQ-C30. There is no hint of an added benefit of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was shown for the outcome of SAEs. There is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcome severe AEs (CTCAE grade ≥ 3).

There was an effect modification for the characteristic of Rai stage, however (see Section I 4.2.4). For patients with Rai stage 0–II, there is a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

For patients with Rai stage III–IV, there is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcome discontinuation due to AEs. There is a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

Infections and infestations (AEs) and cardiac disorders (AEs)

No statistically significant difference between the treatment groups was shown for either of the outcomes infections and infestations (AEs) and cardiac disorders (AEs). In each case, there is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Haemorrhages (severe AEs, AEs)

No suitable data were available for the outcomes haemorrhages (severe AEs and AEs). In each case, there is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

Bronchitis (AEs), pyrexia (AEs)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcomes bronchitis (AEs) and pyrexia (AEs). In each case, there is therefore a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

Injury, poisoning and procedural complications (SAEs), renal and urinary disorders (SAEs), diarrhoea (SAEs)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcomes injury, poisoning and procedural complications (SAEs), renal and urinary disorders (SAEs) and diarrhoea (SAEs). In each case, there is therefore a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

Investigations (severe AEs), skin and subcutaneous tissue disorders (severe AEs), metabolism and nutrition disorders (severe AEs), hepatobiliary disorders (severe AEs), vascular disorders (severe AEs)

A statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab was shown for the outcomes investigations (severe AEs), skin and subcutaneous tissue disorders (severe AEs), metabolism and nutrition disorders (severe AEs), hepatobiliary disorders (severe AEs) and vascular disorders (severe AEs). In each case, there is therefore a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

I 4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered relevant and taken into account for this benefit assessment:

- Sex (men/women)
- Age (< 65 / ≥ 65 years)
- Rai stage (stage 0–II / stage III–IV)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 15 summarizes the subgroup results from the comparison of pirtobrutinib with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab in patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix B.3 of the full dossier assessment.

Table 15: Subgroups (side effects) – RCT, direct comparison: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Study Outcome	Pirtobrutinib		Individualized treatment[a]		Pirtobrutinib vs. individualized treatment[a]	
Characteristic Subgroup	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][b]	p-value[c]
BRUIN CLL-321						
Severe AEs[d]						
Rai stage						
0–II	22	NA [5.8; NA] 8 (36.4)	26	2.3 [1.4; 2.8] 21 (80.8)	0.22 [0.09; 0.52]	< 0.001
III–IV	32	3.1 [1.8; 4.8] 24 (75.0)	29	2.8 [0.6; 5.7] 22 (75.9)	0.83 [0.46; 1.51]	0.559
Total					Interaction:	0.009[e]

a. Individualized treatment with a choice of idelalisib + rituximab and bendamustine + rituximab.
b. HR and CI from Cox regression model, unclear whether unstratified or stratified by presence of chromosomal abnormality del(17p) (yes, no) (discrepant data in Module 4).
c. p-value from log-rank test, unclear whether unstratified or stratified by presence of chromosomal abnormality del(17p) (yes, no) (discrepant data in Module 4).
d. Operationalized as CTCAE grade ≥ 3.
e. p-value from interaction term of subgroup characteristic and treatment from Cox regression model.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial

Side effects

Severe AEs (CTCAE grade ≥ 3)

There was an effect modification by the characteristic Rai stage for the outcome severe AEs (CTCAE grade ≥ 3). For patients with Rai stage 0–II at enrolment, there was a statistically significant difference in favour of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab. There is a hint of lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

No difference between the treatment groups was shown for patients with Rai stage III–IV. There is no hint of greater or lesser harm of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab; greater or lesser harm is therefore not proven.

I 4.3 Probability and extent of added benefit

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

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

I 4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 4.2 (see Table 16).

Determination of the outcome category for the outcomes on side effects

It was not clear from the dossier whether the following outcome was serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Discontinuation due to AE

For the outcome discontinuation due to AEs, insufficient severity data were available for a classification as serious/severe. The outcome discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Observation period **Outcome category** **Outcome**	**Pirtobrutinib vs. individualized treatment** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	26.3 vs. NA months HR: 1.39 [0.77; 2.52]; p = 0.279	Lesser benefit not proven/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC-QLQ C30)	No suitable data	Lesser benefit not proven/added benefit not proven
Health status (EQ-5D VAS)	No suitable data	Lesser benefit not proven/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data	Lesser benefit not proven/added benefit not proven
Side effects		
SAEs	13.5 vs. 6.8 months HR: 0.72 [0.42; 1.22]; p = 0.213	Greater/lesser harm not proven
Severe AEs Rai stage 0–II	NA vs. 2.3 months HR: 0.22 [0.09; 0.52]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: major
III–IV	3.1 vs. 2.8 months HR: 0.83 [0.46; 1.51]; p = 0.559	Greater/lesser harm not proven
Discontinuation due to AEs	29.4 vs. 13.0 months HR: 0.31 [0.14; 0.71]; p = 0.004 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable
Infections and infestations (AEs)	NA vs. 24.5 months HR: 1.17 [0.56; 2.43]; p = 0.683	Greater/lesser harm not proven
Severe haemorrhages (severe AEs)	No suitable data	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Observation period **Outcome category** **Outcome**	**Pirtobrutinib vs. individualized treatment** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Haemorrhages (AEs)	No suitable data	Greater/lesser harm not proven
Cardiac disorders (AEs)	NA vs. 24.5 months HR: 0.46 [0.15; 1.43]; p = 0.172	Greater/lesser harm not proven
Bronchitis (AEs)	NA vs. NA HR: 0.09 [0.01; 0.70]; p = 0.004 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable
Pyrexia (AEs)	NA vs. NA HR: 0.28 [0.11; 0.73]; p = 0.006 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable
Injury, poisoning and procedural complications (SAEs)	NA vs. NA HR: NC; p = 0.018 Probability: hint	Outcome category: serious/severe side effects Lesser harm, extent: non-quantifiable
Renal and urinary disorders (SAEs)	NA vs. NA HR: NC; p = 0.039 Probability: hint	Outcome category: serious/severe side effects Lesser harm, extent: non-quantifiable
Diarrhoea (SAEs)	NA vs. NA HR: NC; p = < 0.001 Probability: hint	Outcome category: serious/severe side effects Lesser harm, extent: non-quantifiable
Investigations (severe AEs)	NA vs. NA HR: 0.32 [0.10; 1.00]; p = 0.040 Probability: hint	Outcome category: serious/severe side effects Lesser harm[c]; extent: minor[d]
Skin and subcutaneous tissue disorders (severe AEs)	NA vs. NA HR: 0.19 [0.04; 0.96]; p = 0.027 Probability: hint	Outcome category: serious/severe side effects CI_u < 1.00 Lesser harm, extent: minor
Metabolism and nutrition disorders (severe AEs)	NA vs. NA HR: 0.09 [0.01; 1.12]; p = 0.035 Probability: hint	Outcome category: serious/severe side effects Lesser harm[c]; extent: minor[d]

Table 16: Extent of added benefit at outcome level: pirtobrutinib vs. individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab (multipage table)

Observation period **Outcome category** **Outcome**	**Pirtobrutinib vs. individualized treatment** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Hepatobiliary disorders (severe AEs)	NA vs. NA HR: NC; p = 0.031 Probability: hint	Outcome category: serious/severe side effects Lesser harm, extent: non-quantifiable
Vascular disorders (severe AEs)	NA vs. NA HR: NC; p = 0.043 Probability: hint	Outcome category: serious/severe side effects Lesser harm, extent: non-quantifiable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. The result of the statistical test is decisive for the derivation of the added benefit.
d. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale

I 4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
Serious/severe side effects ▪ SAEs: ▫ Injury, poisoning and procedural complications; renal and urinary disorders; diarrhoea: in each case hint of lesser harm – extent: non-quantifiable ▪ Severe AEs: patients with Rai stage 0–II: hint of lesser harm – extent: major ▪ Severe AEs: ▫ Investigations; skin and subcutaneous tissue disorders; metabolism and nutrition disorders: in each case hint of lesser harm – extent: minor ▫ Hepatobiliary disorders; vascular disorders: in each case hint of lesser harm – extent: non-quantifiable	–
Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of lesser harm – extent: considerable ▪ Bronchitis; pyrexia: hint of lesser harm – extent: considerable	–
No suitable data are available for the outcomes of symptoms, health status and health-related quality of life.	
AE: adverse event; SAE: serious adverse event	

Overall, there are only positive effects of pirtobrutinib in comparison with individualized treatment with a choice of idelalisib + rituximab or bendamustine + rituximab.

In the outcome category of side effects, there are hints of lesser harm with an extent of up to major for various specific SAEs, severe AEs and non-serious/non-severe AEs as well as for the outcome of discontinuation due to AEs. These results refer exclusively to the shortened period up to 28 days after discontinuation of treatment. Furthermore, it was unclear whether all patients in the comparator arm were given adequate premedication. The interpretation of these results was therefore limited.

The interpretation of the results for overall survival was also limited due to the treatment switching of patients from the comparator arm to treatment with pirtobrutinib. However, there were more deaths in the pirtobrutinib arm than in the comparator arm. A negative effect could not therefore be ruled out with sufficient certainty. In addition, there were no suitable data for the outcome categories of morbidity and health-related quality of life. In summary,

the positive effects, which were shown exclusively for side effects outcomes, were not sufficient to derive an added benefit of pirtobrutinib.

The added benefit of pirtobrutinib in comparison with the ACT is not proven for adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor and for whom idelalisib + rituximab or bendamustine + rituximab is a suitable individualized treatment.

No data were available for adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and a BCL2 inhibitor and for whom venetoclax + rituximab is the suitable individualized treatment. For these patients, the added benefit of pirtobrutinib versus the ACT is not proven.

The assessment described above deviates from that of the company, which claimed an indication of major added benefit.

I 5 Probability and extent of added benefit – summary

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

Table 18: Pirtobrutinib – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and not with a BCL2 inhibitor	venetoclax + rituximab	Added benefit not proven
2	Adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor and with a BCL2 inhibitor	Individualized treatment[c, d, e] with a choice of: ▪ idelalisib in combination with rituximab, ▪ venetoclax in combination with rituximab, ▪ bendamustine in combination with rituximab	Added benefit not proven

a. It is assumed for the therapeutic indication in question that the patients require treatment (e.g. Binet stage C).
b. Presented is the respective ACT specified by the G-BA.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).
e The treatment decision in particular takes into account prior therapy, response, genetic risk factors and duration of remission following prior therapies, and the patient's general condition. According to the current state of medical knowledge, the presence of a 17p deletion/TP53 mutation as well as an unmutated IGHV status and complex karyotype are considered genetic risk factors.

17p deletion: deletion of the short arm of chromosome 17; BCL2: B-cell lymphoma 2; BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; EU: European Union; G-BA: Federal Joint Committee; HTA: Health Technology Assessment; IGHV: immunoglobulin heavy-chain variable region; TP53: tumour suppressor protein 53

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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