Polatuzumab vedotin (combination with rituximab, cyclophosphamide, doxorubicin and prednisone; previously untreated DLBCL)

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

EXTRACT

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[1] Translation of Sections I 1 to I 5 of the dossier assessment *Polatuzumab Vedotin (Kombination mit Rituximab, Cyclophosphamid, Doxorubicin und Prednison; bisher unbehandeltes DLBCL) – Nutzenbewertung gemäß § 35a SGB V*. 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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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 Bernhard Jochheim.

IQWiG thanks the respondent and Leukämie und Lymphom SHG Ruhr-Lippe e. V for participating in the written exchange and for their assistance. The respondent and Leukämie und Lymphom SHG Ruhr-Lippe e. V were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ABC	activated B-cell
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
CD20	cluster of differentiation 20
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
FACT/GOG-NtxS	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity Subscale
FACT-LymS	Functional Assessment of Cancer Therapy - Lymphoma Subscale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCB	germinal centre B-cell
HGBL	highly malignant B-cell lymphoma
HHV8	human herpesvirus 8
IPI	International Prognostic Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
NOS	not otherwise specified
PFS	progression-free survival
PT	Preferred Term
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone
R-CHP	rituximab, cyclophosphamide, doxorubicin and prednisone
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

Abbreviation	Meaning
SMQ	Standardized MedDRA Query
SOC	System Organ Class
VAS	visual analogue scale
WHO	World Health Organization

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 polatuzumab vedotin (in combination with rituximab, cyclophosphamide, doxorubicin and prednisone [R-CHP]). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 21 December 2023.

The drug in question is a drug for the treatment of an orphan condition. The company had to submit a dossier on the added benefit versus the appropriate comparator therapy (ACT) within 3 months after the request by the G-BA, because the turnover of the drug in the statutory health insurance had exceeded 30 million euros in the previous 12 calendar months.

Research question

The aim of this report is to assess the added benefit of polatuzumab vedotin in combination with R-CHP (hereinafter referred to as polatuzumab vedotin + R-CHP) in comparison with rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (hereinafter referred to as R-CHOP) as ACT in adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

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

Table 2: Research question of the benefit assessment of polatuzumab vedotin + R-CHP

Therapeutic indication	**ACT**[a]
Adults with previously untreated DLBCL	R-CHOP[b, c]

a. Presented is the ACT specified by the G-BA.
b. According to the SPC, rituximab should be used in combination with CHOP for 8 cycles. According to the G-BA, the German health care context foresees the administration of 6 cycles as standard treatment in the therapeutic indication. Administration of 6 to 8 cycles is possible according to the generally recognized state of medical knowledge.
c. According to the G-BA, it cannot be inferred from the available evidence and the written statements of the medical associations that, in accordance with the generally recognized state of medical knowledge, the off-label use of rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (R-ACVBP) and of rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone (R-CHOEP) would, as a rule, be preferable to the R-CHOP combination therapy approved to date in the therapeutic indication or for relevant patient groups or areas of indication in the therapeutic indication. R-ACVBP and R-CHOEP are therefore not specified as ACT.

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; R-ACVBP: rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; R-CHOEP: rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; SPC: Summary of Product Characteristics

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Study pool and study design

The POLARIX study was included in the benefit assessment.

The POLARIX study is an ongoing, double-blind, multicentre RCT on the comparison of polatuzumab vedotin + R-CHP with R-CHOP. It included adult patients with previously untreated cluster of differentiation 20 (CD20)-positive DLBCL. Patients had to have one of the following diagnoses as defined by the World Health Organization (WHO) classification of lymphoid neoplasms (2016): DLBCL, not otherwise specified (NOS), including germinal centre B-cell (GCB) type, activated B-cell (ABC) type; T-cell/histiocyte-rich large B-cell lymphoma; Epstein-Barr virus (EBV)-positive DLBCL, NOS; anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma; human herpesvirus 8 (HHV8)-positive DLBCL, NOS; highly malignant B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6 rearrangements* (double-hit or triple-hit lymphoma); HGBL, NOS. Patients with grade 3B follicular lymphoma or primary mediastinal large B-cell lymphoma were excluded from participation in the study. Patients with transformed follicular lymphoma were also not included.

Patients had to be no more than 80 years old at the start of the study and had to have a life expectancy of ≥ 12 months. An Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2 and an International Prognostic Index (IPI) of 2 to 5 were also defined as inclusion criteria.

Overall, 1000 patients were included in the POLARIX study and randomly assigned in a 1:1 ratio either to treatment with polatuzumab vedotin + R-CHP or with R-CHOP.

Treatment with polatuzumab vedotin in combination with R-CHP was carried out in compliance with the recommendations of the SPC. Patients in the comparator arm received R-CHOP. Dosage of the drugs of the R-CHOP treatment regimen corresponded to the recommendations of the SPC and the generally recognized state of medical knowledge or the German health care context according to the G-BA.

Primary outcome of the POLARIX study was progression-free survival (PFS). Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

The results of the data cut-off of 15 June 2022 presented by the company (final analysis on overall survival) were used for the present benefit assessment. However, the company did not

present the planned analyses for all outcomes, which means that the available data are potentially incomplete in terms of content. This is taken into account in the assessment of the risk of bias.

Moreover, the POLARIX study has the following limitations relevant for this benefit assessment:

- According to the study design, patients with various subtypes of DLBCL and related entities were to be included. In addition to the patients with DLBCL covered by the present therapeutic indication for polatuzumab vedotin (85%), the POLARIX study also included patients who were not covered by the present therapeutic indication (HGBL: 10% of the patient population) or for whom it was unclear whether they were covered (other large B-cell lymphomas: 5% of the patient population). Since the proportion of patients with DLBCL accounts for more than 80% of the total study population, the entire study population can nevertheless be considered for the benefit assessment. However, it remains unclear whether the results for the entire study population are fully transferable to the patients with DLBCL in the present research question.
- In the POLARIX study, follow-up examinations to assess the response to therapy were carried out at very regular intervals using imaging techniques, even in the absence of symptoms. This procedure does not correspond to the recommendations in the guideline or the procedure in everyday clinical health care in Germany. In addition, no information is available on how the study proceeded in order to confirm or falsify the findings from imaging techniques. Overall, it therefore remains unclear whether the study results are fully transferable to the German health care context.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as high for the POLARIX study. This is due to the fact that results of analyses planned according to the statistical analysis plan are not reported in the study documents and the other documents submitted by the company with the dossier. The dossier provides no explanation as to why the analyses were not reported. In the present situation, the reporting is therefore potentially selective.

In addition, there are limitations regarding the transferability of the study results with regard to the included population and the follow-up examinations, which differ from everyday health care, so that the reliability of the study results for the present research question is limited.

Based on the available results from the POLARIX study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

Results

Mortality

overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

Morbidity

failure of the curative treatment approach

For the outcome of failure of the curative treatment approach, operationalized via the event rate and event-free survival (EFS), there is no statistically significant difference between the treatment groups for the event rate; for EFS, there is a statistically significant difference in favour of polatuzumab vedotin + R-CHP compared to R-CHOP. However, there is an effect modification by the characteristic of sex. For women, this results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven. For men, there is a hint of an added benefit of polatuzumab vedotin + R-CHP compared to R-CHOP.

Symptoms (recorded using EORTC QLQ-C30, FACT-LymS and FACT/GOG-NtxS)

No suitable data are available for the outcome "symptoms" (recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 [EORTC QLQ-C30], Functional Assessment of Cancer Therapy - Lymphoma Subscale [FACT-LymS] and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity Subscale [FACT/GOG-NtxS]). This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

health status (recorded with the EQ-5D VAS)

No suitable data were available for the outcome of health status (recorded with the EQ-5D visual analogue scale [VAS]). This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30)

No suitable data are available for health-related quality of life (recorded using EORTC QLQ-C30). This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe adverse events (AEs) and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Specific AEs

Peripheral neuropathy

No suitable data are available for the outcome of peripheral neuropathy. There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Infusion-related reactions

Although the dossier provides no suitable analyses for the outcome of infusion-related reactions, the events underlying the infusion-related reactions are mapped via the specific AEs. There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Infections and infestations (severe AEs)

No statistically significant difference between the treatment groups was shown for the outcome of infections and infestations (severe AE). There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Febrile neutropenia (severe AEs)

A statistically significant difference to the disadvantage of polatuzumab vedotin in comparison with R-CHOP was found for the outcome “febrile neutropenia” (severe AEs). There is a hint of greater harm from polatuzumab vedotin + R-CHP compared to R-CHOP.

Diarrhoea (severe AEs)

A statistically significant difference to the disadvantage of polatuzumab vedotin + R-CHP in comparison with R-CHOP was found for the outcome “diarrhoea” (severe AEs). However, there is an effect modification by the characteristic of IPI. There is a hint of greater harm from polatuzumab vedotin + R-CHP compared to R-CHOP for patients with IPI 3 to 5. For patients with IPI 1 to 2, there is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven for patients with IPI 1 to 2.

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

On the basis of the results presented, the probability and extent of added benefit of the drug polatuzumab vedotin + R-CHP in comparison with the ACT is assessed as follows:

Overall, there are both positive and negative effects for polatuzumab vedotin + R-CHP compared to R-CHOP. For the outcome of failure of the curative treatment approach, these are based on the planned observation period of up to 5 years after the last dose of the study medication. For the outcomes in the side effects category, however, the observed effects relate exclusively to a shortened observation period.

For men, there is a hint of minor added benefit of polatuzumab vedotin + R-CHP compared to R-CHOP for the outcome "failure of the curative treatment approach". For febrile neutropenia, there is a hint of greater harm with the extent "considerable" for the entire study population. For diarrhoea, there is a hint of greater harm with the extent "major" for patients with an IPI score from 3 to 5. In the POLARIX study, numerous patient-reported outcomes on symptoms, health status, and health-related quality of life were recorded. However, no suitable data are available for these outcomes. An adequate assessment of patient-reported symptoms, health status and health-related quality of life is not possible without suitable analyses of the outcomes recorded using the EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS and EQ-5D VAS.

In summary, the added benefit of polatuzumab vedotin + R-CHP versus the ACT R-CHOP is not proven.

Table 3 shows a summary of the probability and extent of the added benefit of polatuzumab vedotin + R-CHP.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Polatuzumab vedotin + R-CHP – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with previously untreated DLBCL	Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)[b, c]	Added benefit not proven[d]

a. Presented is the ACT specified by the G-BA.
b. According to the SPC, rituximab should be used in combination with CHOP for 8 cycles. According to the G-BA, the German health care context foresees the administration of 6 cycles as standard treatment in the therapeutic indication. Administration of 6 to 8 cycles is possible according to the generally recognized state of medical knowledge.
c. According to the G-BA, it cannot be inferred from the available evidence and the written statements of the medical associations that, in accordance with the generally recognized state of medical knowledge, the off-label use of rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (R-ACVBP) and of rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone (R-CHOEP) would, as a rule, be preferable to the R-CHOP combination therapy approved to date in the therapeutic indication or for relevant patient groups or areas of indication in the therapeutic indication. R-ACVBP and R-CHOEP are therefore not specified as ACT.
d. The POLARIX study only included patients with an ECOG PS of < 2 and an IPI ≥ 2. In addition, no patients with transformed follicular lymphoma were included in the study. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2, an IPI score of 0 or 1 or with transformed follicular lymphoma.

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group - Performance Status; G-BA: Federal Joint Committee; IPI: International Prognostic Index; R-ACVBP: rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; R-CHOEP: rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone

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.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2022. There, the G-BA had determined a non-quantifiable added benefit of polatuzumab vedotin (in combination with R-CHP). However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 2 Research question

The aim of this report is to assess the added benefit of polatuzumab vedotin in combination with R-CHP (hereinafter referred to as polatuzumab vedotin + R-CHP) in comparison with R-CHOP as ACT in adult patients with previously untreated DLBCL.

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

Table 4: Research question of the benefit assessment of polatuzumab vedotin + R-CHP

Therapeutic indication	**ACT[a]**
Adults with previously untreated DLBCL	Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)[b,c]

a. Presented is the ACT specified by the G-BA.
b. According to the Summary of Product Characteristics (SPC), rituximab should be used in combination with CHOP for 8 cycles. According to the G-BA, the German health care context foresees the administration of 6 cycles as standard treatment in the therapeutic indication. Administration of 6 to 8 cycles is possible according to the generally recognized state of medical knowledge.
c. According to the G-BA, it cannot be inferred from the available evidence and the written statements of the medical associations that, in accordance with the generally recognized state of medical knowledge, the off-label use of rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (R-ACVBP) and of rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone (R-CHOEP) would, as a rule, be preferable to the R-CHOP combination therapy approved to date in the therapeutic indication or for relevant patient groups or areas of indication in the therapeutic indication. R-ACVBP and R-CHOEP are therefore not specified as ACT.

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; R-ACVBP: rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; R-CHOEP: rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone

The company followed the G-BA's specification of the ACT.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on polatuzumab vedotin (status: 4 October 2023)
- bibliographical literature search on polatuzumab vedotin (last search on 4 October 2023)
- search in trial registries/trial results databases for studies on polatuzumab vedotin (last search on 4 October 2023)
- search on the G-BA website for polatuzumab vedotin (last search on 4 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on polatuzumab vedotin (last search on 10 January 2024); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
GO39942 (POLARIX[c])	Yes	Yes	No	Yes [3-5]	Yes [6,7]	Yes [8]

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.
c. In the tables below, the study will be referred to using this acronym.

R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: Rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial

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

I 3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
POLARIX	RCT, double-blind, parallel	Adult patients (18-80 years of age) with previously untreated CD20-positive DLBCL[b] ▪ ECOG PS 0-2 ▪ IPI 2–5	Polatuzumab vedotin + R-CHP (N = 500)[c] R-CHOP (N = 500)[c]	Screening: ≤ 28 days treatment: ▪ polatuzumab vedotin + R-CHP or R-CHOP over 6 cycles, each followed by 2 cycles of rituximab ▪ or until disease progression, unacceptable toxicity, or treatment discontinuation as decided by the investigator or the patient ▪ observation[d]: outcome-specific, at most until death, end of study, or withdrawal of consent	211 centres in Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Italy, Japan, New Zealand, Poland, Russia, South Korea, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, USA 11/2017–ongoing[e] data cut-offs: ▪ 28 June 2021f ▪ 25 February 2022[g] ▪ 15 June 2022[h]	Primary: progression-free survival secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (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 include information only on relevant available outcomes for this benefit assessment.
b. Including one of the following diagnoses according to the WHO classification (2016) of lymphoid neoplasms: DLBCL, NOS, including GCB type, ABC type; T-cell/histiocyte-rich large B-cell lymphoma; EBV-positive DLBCL, NOS; ALK-positive large B-cell lymphoma; HHV8-positive DLBCL, NOS; highly malignant B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6 rearrangements* (double-hit or triple-hit lymphoma); highly malignant B-cell lymphoma, NOS.
c. Global recruitment was planned until 875 patients had been included in the study. Recruitment was then to continue in China until a total of 150 Chinese patients had been included. According to the study design, separate analyses were planned for the Asian subpopulation of the study in addition to analyses on all patients who were included during global recruitment (global population). The latter analyses include all Asian patients in the study, regardless of whether they were enrolled during the global recruitment phase in Asia or the subsequent recruitment phase in China. In the dossier, the company presents post hoc analyses of the entire study population independent of the recruitment phase (N = 1000), which were used for the present benefit assessment.
d. Outcome-specific information is provided in Table 8.
e. Randomization o the last patient took place on 15 December 2020. According to the study plan, the study was expected to end around 65 months after the first patient was included (on 15 November 2017). At this time, all patients should have been followed up for at least 3 years.
f. Primary analysis on PFS for the global population, prespecified after the occurrence of approximately 228 PFS events and at least 24 months after inclusion of the last patient during the global recruitment phase, whichever occurred later.
g. Non-prespecified and non-regulatory required interim analysis on overall survival for the global population approximately 32 months after inclusion of the last patient (added to the statistical analysis plan with amendment 4 of 1 December 2021).
h. Final analysis on overall survival, 36 months after inclusion of the last patient during the global recruitment phase, prespecified after the occurrence of approximately 178 events in the outcome of overall survival for the global population.

ABC: activated B-cell type; AE: adverse event; ALK: anaplastic lymphoma kinase; *BCL2*: B-cell lymphoma 2; *BCL6*: B-cell lymphoma 6; CD20: cluster of differentiation 20; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GCB: germinal centre B-cell type; HHV8: human herpesvirus 8; IPI: International Prognostic Index; *MYC*: MYC proto-oncogenes; N: number of randomized patients; NOS: not otherwise specified; PFS: progression-free survival; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; WHO: World Health Organization

Table 7: Characteristics of the intervention – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study	Intervention	Comparison
POLARIX	Polatuzumab vedotin + R-CHP cycles 1-6 (21 days each)[a] ▪ day 1 ▫ polatuzumab vedotin: 1.8 mg/kg BW IV ▫ rituximab 375 mg/m2 BSA, IV ▫ cyclophosphamide 750 BSA mg/m2 IV ▫ doxorubicin 50 mg/m2 BSA, IV ▫ placebo for vincristine IV ▪ days 1–5: ▫ prednisone 100 mg/day orally cycles 7 and 8 (21 days each) ▪ day 1 ▫ rituximab 375 mg/m^2 BSA, IV	R-CHOP cycles 1-6 (21 days each)[a] ▪ day 1 ▫ placebo for polatuzumab vedotin IV ▫ rituximab 375 mg/m2 BSA, IV ▫ cyclophosphamide 750 mg/m2 BSA, IV ▫ doxorubicin 50 mg/m2 BSA, IV ▫ vincristine 1.4 mg/m^{2b} BSA, i.v. ▪ days 1–5: ▫ prednisone 100 mg/day orally cycles 7 and 8 (21 days each) ▪ day 1 ▫ rituximab 375 mg/m^2 BSA, IV
	Dose adjustments and delays: ▪ polatuzumab vedotin/placebo, cyclophosphamide, doxorubicin, vincristine/placebo: dose adjustments and delays due to AEs permitted, based on results of physical examinations, observed toxicity and laboratory results 72 hours before the administration of the study medicationc ▪ prednisone: dose adjustments and -delays due to AEs possible at the investigator's discretion ▪ rituximab: no dose adjustment allowed ▪ dosing delays due to AEs > 14 days until the start of the next planned cycle of polatuzumab vedotin + R-CHP or R-CHOP generally led to discontinuation of the study medication[c]. In the event that one or more of the study medications were discontinued, treatment could be continued with the remaining study medications.	
	Disallowed pretreatment ▪ previous treatment of DLBCL ▪ anthracyclines ▪ anti-CD20 antibodies ▪ corticosteroids > 30 mg/day prednisone or equivalent for purposes other than lymphoma symptom controld ▪ radiotherapy in the mediastinal/pericardial region ▪ organ transplantation ▪ cytotoxic drugs within 5 years before screening ▪ monoclonal antibodies within 3 months before the start of the 1st cycle ▪ live vaccines within 28 days before the start of the 1st cycle	

Table 7: Characteristics of the intervention – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study	Intervention	Comparison
	Allowed concomitant treatment ▪ required in Cycles 1-6 for neutropenia prophylaxis: G-CSF (starting 1-3 days after administration of doxorubicin, cyclophosphamide and polatuzumab vedotin) ▪ premedication before the 1st administration of polatuzumab vedotin (optional) or rituximab (required), and if infusion-related reactions have occurred during previous infusions: antihistamines and analgesics/antipyretics ▪ CNS prophylaxis with intrathecal chemotherapy according to institutional practice (with the exception of high-dose methotrexate IV) ▪ anti-infective prophylaxis against viral, fungal, bacterial or pneumocystis infections ▪ preplanned radiotherapy[e] **disallowed concomitant treatment** ▪ other cytotoxic therapies (with the exception of intrathecal CNS prophylaxis), other immunotherapies or immunosuppressive therapies and biological agents (with the exception of clinically indicated haematopoietic growth factors) for the treatment of lymphomas	

a. Order of administration: 1.) prednisone, 2.) rituximab, 3.) polatuzumab vedotin/placebo; subsequent infusions of vincristine/placebo, cyclophosphamide and doxorubicin should be administered according to the preferences of the study centre.
b. Maximum dose 2 mg.
c. The study protocol contains detailed guidelines on dose delays, dose adjustments and discontinuation of the drugs depending on the AE and its severity.
d. ≤ 30 mg/day permitted, with stable dose for at least 4 weeks before the start of the 1st cycle; also permitted to control lymphoma symptoms during screening: ≤ 30 mg/day or > 30-100 mg/day for a most 7 days.
e. If indicated, previously planned radiotherapy should be started within 8 weeks of the last dose of study medication and after completion of all end-of-treatment recordings (including PET/CT scans to assess response).

AE: adverse event; BSA: body surface area; BW: body weight; CD20: cluster of differentiation 20; CNS: central nervous system; CT: computed tomography; DLBCL: diffuse large B-cell lymphoma; G-CSF: granulocyte colony-stimulating factor; IV: intravenous; PET: positron emission tomography; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial

Study design

The POLARIX study is an ongoing, double-blind, multicentre RCT on the comparison of polatuzumab vedotin + R-CHP with R-CHOP. It included adult patients with previously untreated CD20-positive DLBCL. Patients had to have one of the following diagnoses as defined by the WHO classification of lymphoid neoplasms (2016): DLBCL, NOS, including GCB type, ABC type; T-cell/histiocyte-rich large B-cell lymphoma; EBV-positive DLBCL, NOS; ALK-positive large B-cell lymphoma; HHV8-positive DLBCL, NOS; HGBL with *MYC* and *BCL2* and/or *BCL6 rearrangements* (double-hit or triple-hit lymphoma); HGBL, NOS (see also the following text section "Suitability of the total population of the POLARIX study for the present benefit assessment"). Patients with grade 3B follicular lymphoma or primary mediastinal large B-cell

lymphoma were excluded from participation in the study. Patients with transformed follicular lymphoma were also not included.

Patients had to be no more than 80 years old at the start of the study and had to have a life expectancy of ≥ 12 months. An ECOG PS of 0 to 2 and an IPI of 2 to 5 were also defined as inclusion criteria. All patients had to have at least one two-dimensionally measurable lesion that was classified as larger than 1.5 cm in its longest dimension by an imaging technique CT or MRI).

Global recruitment was planned until 875 patients had been included in the study. Recruitment was then to continue in China until a total of 150 Chinese patients had been included. According to the study design, separate analyses were planned for the Asian subpopulation of the study in addition to analyses on all patients who were included during global recruitment (global population). The latter analyses include all Asian patients in the study, regardless of whether they were enrolled during the global recruitment phase in Asia or the subsequent recruitment phase in China. In the dossier, the company presents post hoc analyses of the entire study population independent of the recruitment phase (N = 1000), which were used for the present benefit assessment.

Overall, 1000 patients were included in the POLARIX study and randomly assigned in a 1:1 ratio either to treatment with polatuzumab vedotin + R-CHP (N = 500) or with R-CHOP (N = 500). Randomization was stratified by IPI (2 vs. 3 to 5), bulky disease defined as a lesion ≥ 7.5 cm (present vs. absent) and geographic region (USA, Western Europe, Canada and Australia vs. Asia vs. rest of the world).

Treatment with polatuzumab vedotin in combination with R-CHP was carried out in line with the SPC [9-13]. In accordance with the SPC for polatuzumab vedotin [9], polatuzumab vedotin + R-CHP was administered over 6 cycles (21 days each), followed by 2 cycles (21 days each) of rituximab as monotherapy. Patients in the comparator arm received R-CHOP. The dosing of the drugs of the R-CHOP treatment regimen corresponded to the specifications of the SPC [10-14]. The treatment consisted of 6 cycles (21 days each) of R-CHOP, followed by 2 cycles (21 days each) of rituximab as monotherapy. According to the SPC [10], rituximab should be used in combination with CHOP for 8 cycles. However, according to the G-BA, the German health care context foresees the administration of 6 cycles as standard treatment in the therapeutic indication. Thus, administration of 6 to 8 cycles is possible according to the generally recognized state of medical knowledge. Treatment in the comparator arm of the study thus corresponds to the generally recognized state of medical knowledge and the health care context in Germany according to the G-BA.

A switch from the comparator arm to the treatment of the intervention arm was not permitted. Subsequent antineoplastic therapies were allowed without restrictions in both study arms.

Primary outcome of the POLARIX study was PFS. Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Limitations of the POLARIX study

Suitability of the total population of the POLARIX study for the present benefit assessment

According to the study design, patients with various subtypes of DLBCL and related entities were to be included in the POLARIX study. In addition to the patients with DLBCL covered by the present therapeutic indication of polatuzumab vedotin, the inclusion of patients with HGBL, for example, was also planned (see Table 6), which are not covered by the present therapeutic indication according to the SPC of polatuzumab vedotin [9,15]. In fact, in addition to patients with DLBCL (85%), a certain proportion of patients with HGBL and other large B-cell lymphomas were also included in the POLARIX study (15% in total, see Table 9). The POLARIX study also includee patients who were not covered by the present therapeutic indication (HGBL: 10% of the patient population) or for whom it was unclear whether they were covered (other large B-cell lymphomas: 5% of the patient population). In the dossier for the POLARIX study, the company did not present separate analyses on patients with DLBCL, HGBL and other large B-cell lymphomas. Since the proportion of patients with DLBCL accounts for more than 80% of the total study population, the entire study population can nevertheless be considered for the benefit assessment. However, it remains unclear whether the results for the entire study population are fully transferable to the patients with DLBCL in the present research question. This issue has been taken into account in the assessment of the certainty of conclusions of the results (see Section I 4.2).

Follow-up examinations in the POLARIX study

In the POLARIX study, the response to therapy was assessed by the investigator based on clinical examinations and by means of imaging techniques (PET/CT and/or CT [with contrast agent] images) using the Lugano criteria for malignant lymphomas [16]. PET/CT and dedicated CT scans were performed at screening and 6 to 8 weeks after the last dose of study medication; an interim examination was performed after Cycle 4. In the follow-up phase, imaging procedures were performed every 6 months in the first 2 years after the last dose of study medication, then every 12 months in the following 3 years.

According to the S3 guideline on diagnostics, therapy and follow-up for adult patients with DLBCL and related entities, asymptomatic patients who have successfully completed treatment should be followed up with physical examinations, laboratory tests and a detailed history of symptoms and complaints. Based on clinical experience, it is recommended that

control examinations be carried out every 3 months in the first two years after the end of treatment and every 6 months in the following 3 years. Patients in complete metabolic remission should not undergo routine imaging [17]. These recommendations result from the fact that in studies on routine follow-up using imaging in first-line therapy, an accumulation of false-positive findings was found and no survival advantage could be shown.

In the POLARIX study, follow-up examinations were carried out at very regular intervals using imaging techniques, even in the absence of symptoms. This approach does not correspond to the recommendations in the guideline or the procedure in everyday clinical health care in Germany, as was confirmed during the oral hearing on the benefit assessment of polatuzumab vedotin as a drug for the treatment of an orphan condition [18]. In addition, no information is available on how the study proceeded in order to confirm or falsify the findings from imaging techniques. Overall, it therefore remains unclear whether the study results are fully transferable to the German health care context. This issue has been taken into account in the assessment of the certainty of conclusions of the results (see Section I 4.2).

Data cut-offs

To date, 3 data cut-offs have been performed for the ongoing POLARIX study:

- 1st data cut-off of 28 June 2021: primary analysis on PFS for the global population, prespecified after the occurrence of approximately 228 PFS events and at least 24 months after inclusion of the last patient during the global recruitment phase, whichever occurred later.
- 2nd data cut-off of 25 February 2022: non-prespecified and non-regulatory required interim analysis on overall survival for the global population approximately 32 months after inclusion of the last patient.
- 3rd data cut-off of 15 June 2022: final analysis on overall survival, 36 months after inclusion of the last patient during the global recruitment phase, prespecified after the occurrence of approximately 178 events in the outcome of overall survival for the global population.

According to the study design, the study is scheduled to end when the last patient has completed the follow-up or has discontinued the study. The study is expected to end around 65 months after the first patient has been included. At this time, all patients should have been followed up for at least 3 years.

The results of the 3rd data cut-off of 15 June 2022 (final analysis on overall survival) were used for the present assessment. However, the company did not present the planned analyses for all outcomes, which means that the available data are potentially incomplete in terms of

content. This was considered in the assessment of the risk of bias (see Section “Risk of bias across outcomes [study level]”).

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study **outcome category** **outcome**	**Planned follow-up observation**
POLARIX	
Mortality	
overall survival	Until death, end of study, or withdrawal of consent
Morbidity	
Failure of the curative treatment approach or EFS	Up to 5 years after the last dose of the study medication
Symptoms (EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS)	Up to 5 years after the last dose of the study medication
Health status (EQ-5D VAS)	Up to 5 years after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	Up to 5 years after the last dose of the study medication
Side effects	
All outcomes of the side effects category	Up to 90 days after the last dose of the study medication[a]

a. After this period, the investigator should report SAEs that are thought to be related to the study medication (with no time limit). All AEs of special interest that the investigator considers to be related to the study medication should be reported until 12 months after the last dose of study medication.

AE: adverse event; EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-NtxS: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity Subcale; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma Subscale; QLQ-C30: Quality of Life Questionnaire - Core 30; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Follow-up for the outcome "overall survival" is planned until death, end of study, or withdrawal of consent.

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 90 days). Only AEs of special interest or SAEs that the investigator considers to be related to the study medication should be reported until 12 months after the last dose of study medication or without time limit. For the outcome of failure of the curative treatment

approach or EFS as well as for the outcomes on symptoms, health status and health-related quality of life, follow-up is planned for up to 5 years after the last dose of study medication. Although the observation periods for these outcomes are thus also systematically shortened, they cover a significantly longer period than the side effect outcomes. It should also be noted as a positive aspect that the survey of patient-reported outcomes was continued after the end of treatment regardless of the occurrence of disease progression.

In order to draw a reliable conclusion on the total study period or the time to patient death, however, it would be necessary to survey all outcomes over the total period, as was done for survival.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study characteristic category	Polatuzumab vedotin + R-CHP N[a] = 500	R-CHOP N[a] = 500
POLARIX		
Age [years], mean (SD)	63 (11)	63 (12)
Sex [F/M], %	46/54	46/54
Geographical region[a], n (%)		
Western Europe/USA/Canada/Australia	302 (60)	301 (60)
Asia	141 (28)	140 (28)
Rest of the world	57 (11)	59 (12)
Disease duration: time between diagnosis and start of the study medication [years], median [Q1; Q3]	24 [14; 35]	26 [15; 39]
ECOG PS at baseline, n (%)		
0	197 (39)	195 (39)
1	222 (44)	221 (44)
2	81 (16)	82 (16)
Ann Arbor stage, n (%)		
I	2 (< 1)	11 (2)
II	51 (10)	45 (9)
III	147 (29)	136 (27)
IV	300 (60)	308 (62)
IPI (IxRS)[b]		
2	190 (38)[c]	191 (38)[c]
3–5	310 (62)[d]	309 (62)d

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study characteristic category	**Polatuzumab vedotin + R-CHP N[a] = 500**	**R-CHOP N[a] = 500**
Bulky Disease[b,e]		
Available	210 (42)	210 (42)
Not available	290 (58)	290 (58)
Number of extranodal sites, n (%)		
0-1	261 (52)	260 (52)
≥ 2	239 (48)	240 (48)
NHL histological diagnosis (eCRF), n (%)		
DLBCL NOS, ABC, GCB	430 (86)	420 (84)
HGBL, NOS, DHL/THL	44 (9)	52 (10)
Other diffuse large cell B-cell lymphoma	26 (5)	28 (6)
Cell of Origin according to central laboratory, n (%)		
ABC	131 (26)	143 (29)
GCB	193 (39)	187 (37)
Not classified	53 (11)	60 (12)
Unknown	123 (25)	110 (22)
Double-expressor lymphoma according to central laboratory, n (%)		
Yes	150 (30)	163 (33)
No	253 (51)	244 (49)
Unknown	97 (19)	93 (19)
Treatment discontinuation, n (%)[f]	57 (11)	69 (14)
Study discontinuation, n (%)[g]	88 (18)	100 (20)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Stratification factor of the randomization.
c. According to the eCRF, 1 patient in the intervention arm had an IPI of 1 and 8 patients in the intervention arm and 7 patients in the comparator arm had an IPI of 3-5, which deviates from the data of the IXRS.
d. According to the eCRF, 6 patients in the intervention arm and 3 patients in the comparator arm had an IPI of 2, which deviates from the data of the IXRS.
e. Defined as a lesion ≥ 7.5 cm.
f. Common reasons for treatment discontinuation in the intervention vs. comparator arm were: AE (12 vs. 19), disease progression (12 vs. 18), decision by the investigator (12 vs. 15).
g. Common reasons for study discontinuation in the intervention vs. the comparator arm were: death (68 vs. 79), withdrawal of consent by the patient (12 vs. 14).

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study characteristic category	Polatuzumab vedotin + R-CHP N[a] = 500	R-CHOP N[a] = 500
ABC: activated B-cell type; AE: adverse event; DHL: double-hit lymphoma; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; f: female; GCB: germinal centre B-cell type; HGBL: high-grade B-cell lymphoma; IPI: International Prognostic Index; IXRS: interactive voice/web response system; m: male; n: number of patients in the category; N: number of randomized patients; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; Q1: 1st quartile; Q3: 3rd quartile; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; SD: standard deviation; THL: triple-hit lymphoma		

The demographic and clinical characteristics of the patients are sufficiently comparable between the treatment arms of the POLARIX study. The mean age of the patients was 63 years, and about 46% of the patient population were female. 60% of the patients came from Western Europe, the USA, Canada and Australia, while around 30% of the patients came from Asia. The majority of patients had an ECOG PS of 0 (39%) or 1 (44%) and stage IV according to Ann Arbor (61%). 62% of patients were at high intermediate to high risk according to IPI. At the time the study medication was started, a median of 24 and 26 days (intervention and comparator arm) had elapsed since the diagnosis. Bulky disease, defined as a lesion ≥ 7.5 cm, was present in 42% of patients. The majority of patients (85%) had a histological diagnosis of DLBCL, NOS, ABC type or GCB type. 10% of the patients had HGBL, NOS, double-hit or triple-hit lymphoma, 5% had other large B-cell lymphomas (see text section "Suitability of the total population of the POLARIX study for the present benefit assessment").

Information on the course of the study

Table 10 shows the mean and median treatment duration of the patients and (if available) the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study **duration of the study phase** **outcome category**	**Polatuzumab vedotin + R-CHP** **N = 500[a]**		**R-CHOP** **N = 500[a]**	
POLARIX				
Treatment duration [months][b]				
Median [Q1; Q3]	Polatuzumab Vedotin:	3.5 [3.4; 3.6]	Vincristine:	3.5 [3.4; 3.5]
	Rituximab:	4.9 [4.9; 5.1]	Rituximab:	4.9 [4.9; 5.1]
	Cyclophosphamide:	3.5 [3.5; 3.6]	Cyclophosphamide:	3.5 [3.4; 3.5]
	Doxorubicin:	3.5 [3.5; 3.6]	Doxorubicin:	3.5 [3.4; 3.5]
	Prednisone:	3.6 [3.6; 3.7]	Prednisone:	3.6 [3.6; 3.7]
Mean (SD)	Polatuzumab Vedotin:	3.4 (0.6)	Vincristine:	3.4 (0.7)
	Rituximab:	4.8 (0.9)	Rituximab:	4.6 (1.2)
	Cyclophosphamide:	3.5 (0.6)	Cyclophosphamide:	3.4 (0.7)
	Doxorubicin:	3.5 (0.6)	Doxorubicin:	3.4 (0.7)
	Prednisone:	3.6 (0.6)	Prednisone:	3.5 (0.7)
Observation period [months]				
Overall survival[c]				
Median [Q1; Q3]	39.2 [36.3; 42.6]		38.7 [36.2; 42.6]	
Mean (SD)	ND		ND	
Failure of the curative treatment approach or EFS				
Median [Q1; Q3]	ND		ND	
Mean (SD)	ND		ND	
Symptoms (EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS)				
Median [Q1; Q3]	30 [13.3; 31.7]		29.1 [9.2; 31.0]	
Mean (SD)	ND		ND	
Health status (EQ-5D VAS)				
Median [Q1; Q3]	30 [13.3; 31.7]		29.1 [9.2; 31.0]	
Mean (SD)	ND		ND	
Health-related quality of life (EORTC QLQ-C30)				
Median [Q1; Q3]	30 [13.3; 31.7]		29.1 [9.2; 31.0]	
Mean (SD)	ND		ND	
Side effects				
Median [Q1; Q3]	ND[d]		ND[d]	
Mean (SD)	ND[d]		ND[d]	

Table 10: Information on the course of the study – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study duration of the study phase outcome category	Polatuzumab vedotin + R-CHP N = 500[a]	R-CHOP N = 500[a]
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. Information on median [Q1; Q3] and mean (SD) is only available for the individual drugs. c. 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 categorised as an event at the end of the observation period. d. The data provided by the company are unsuitable. These are based on the reverse Kaplan-Meier method, which is not an adequate method for calculating the observation period for the outcomes on side effects. EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-NtxS: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity Subcale; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma Subscale; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire - Core 30; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

The median and mean treatment duration is comparable between the study arms. The median duration of observation for the outcomes of overall survival and for the outcomes on symptoms, health status and health-related quality of life are also comparable between the study arms. There is no information on the mean observation period for these outcomes.

No information is available on the observation duration for the outcome of failure of the curative treatment approach or for EFS and the outcomes on side effects. Since the duration of observation is linked to the duration of treatment (up to 5 years or 90 days after the last dose) and treatment or study discontinuations did not occur frequently overall and to a comparable extent in the intervention and the comparator arm (see Table 9), it can be assumed in the present data situation that the duration of observation - as well as the duration of treatment - is comparable between the study arms. Based on the available data, conclusions on the outcomes in the side effects category can only be made for the period up to 90 days after the end of treatment due to the shortened observation period.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study drug class drug	Patients with subsequent therapy n (%)	
	polatuzumab vedotin + R-CHP N = 500	R-CHOP N = 500
POLARIX		
≥ 1 new anti-lymphoma therapy[a]	128 (25.6)	170 (34.0)
≥ 1 radiotherapy	49 (9.8)	67 (13.4)
Pre-planned treatment	13 (2.6)	19 (3.8)
Unplanned treatment	36 (7.2)	48 (9.6)
≥ 1 systemic therapy	98 (19.6)	135 (27.0)
Stem cell transplantation	20 (4.0)	34 (6.8)
Autologous transplantation	20 (4.0)	31 (6.2)
Allogeneic transplantation	0 (0)	3 (0.6)
CAR-T cell therapy	11 (2.2)	18 (3.6)
Platinum-based therapy[b]	45 (9.0)	69 (13.8)

a. Including pre-planned radiotherapy.
b. Platinum-based therapy refers to regimens typically intended for consolidating transplantation or cellular therapies (including R-GDP, R-ICE, R-DHAP, R-ESHAP or similar).

CAR: chimeric antigen receptor; n: number of patients with subsequent therapy; N: number of analysed patients; PFS: progression-free survival; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: Rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; R-DHAP: rituximab in combination with dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP: rituximab in combination with etoposide, methylprednisolone, high-dose cytarabine and cisplatin; R-GDP: rituximab in combination with gemcitabine, dexamethasone and cisplatin; R-ICE: rituximab in combination with ifosfamide, carboplatin and etoposide

In the POLARIX study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. Overall, 26% of patients in the intervention arm and 34% of patients in the comparator arm received at least 1 new anti-lymphoma therapy. Assuming that all patients who experienced an EFS event other than death (150 patients in the intervention arm vs. 178 patients in the comparator arm, see Table 15) received follow-up therapy, this would mean that 85% of these patients in the intervention arm and 96% in the comparator arm received at least 1 new anti-lymphoma therapy (including preplanned radiotherapy). Systemic therapy was given to 20% of patients in the intervention arm (65% in relation to an EFS event other than death) and 27% of patients in the comparator arm (76% in relation to an EFS event other than death). The most frequently administered treatment in both study arms was platinum-based therapy, whereby according to the information in the dossier, this refers to regimens that are typically intended to be followed by consolidating transplantation or cellular therapies. The available data on stem cell transplantations and CAR-T cell therapies, which were documented as follow-up therapy during the observation period

of the study, show that a proportion of patients in both study arms received such systemic therapies (stem cell transplantation: 4% vs. 7%, in relation to an EFS event other than death 13% vs. 19%; CAR-T cell therapies: 2% vs. 4%, in relation to an EFS event other than death 7% vs. 10%). Based on the guideline recommendations available at the time of the assessment [17], it can be assumed that CAR-T cell therapies in particular are used more frequently in the current health care context, but in the present data situation with little difference in the proportion of patients with systemic follow-up therapy between the study arms, this is of no consequence for the benefit assessment.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
POLARIX	Yes	Yes	Yes	Yes	No[a]	Yes	High

a. According to the statistical analysis plan, analyses for the POLARIX study were planned explicitly for HTA, which were to be reported separately from the clinical study report (for a detailed explanation, see the following text section). However, according to the study design, the analyses are neither included in the study documents nor in the other documents submitted by the company with the dossier. In the present situation, the reporting is therefore potentially results-driven.

HTA: health technology assessment; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial

According to the statistical analysis plan, analyses for the POLARIX study were explicitly planned for HTA, which were to be reported separately from the clinical study report (CSR). These are analyses on exploratory efficacy outcomes or exploratory patient-reported outcomes such as complete response (CR) at Month 24 after randomization or additional analyses on B-symptoms. However, analyses on these outcomes are neither included in the study documents nor in the other documents submitted by the company with the dossier. The dossier provides no explanation as to why the analyses were not reported. In the present situation, the reporting is therefore potentially results-driven. Therefore, the risk of bias across outcomes was rated as high for the POLARIX study.

Transferability of the study results to the German health care context

The company stated that the results of the POLARIX study were transferable to the German health care context. A slightly higher proportion of patients in the POLARIX study were male (polatuzumab vedotin + R-CHP: 53.6%; R-CHOP: 54%). The German guidelines also report a slight predominance in men [19]. The median age of the study population was 65 years, which is in line with the literature for the German health care context [19]. Over 60% of the study patients came from countries with a predominantly Caucasian population. It can therefore be assumed that the study results are transferable.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also the text section on "Follow-up examinations in the POLARIX study".

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - failure of the curative treatment approach
  - symptoms
    - recorded using the EORTC QLQ-C30
    - recorded using the FACT-LymS
    - recorded using the FACT/GOG-NtxS
  - 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
  - peripheral neuropathy
  - infusion-related reactions
  - infections and infestations (severe AEs)
  - other specific AEs, if any

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

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study	Outcomes											
	Overall survival	Failure of the curative treatment approach[a]	Symptoms (EORTC QLQ-C30, FACT-LymS[b], FACT/GOG-NtxS[c])	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[d]	Discontinuation due to AEs	Peripheral neuropathy	Infusion-related reactions	Infections and infestations (SOC, severe AEs[d])	Further specific Aes,[d,e]
POLARIX	Yes	Yes	No[f]	No[f]	No[f]	Yes	Yes	Yes	No[f]	No[g]	Yes	Yes

a. Operationalized via the event rate and EFS; includes the events of death, progression/recurrence, no achievement of a CR at the end of treatment, whichever occurs first; for explanation see the following text section.
b. The lymphoma-specific subscale FACT-LymS is part of the FACT-LYM. Only the subscale was recorded in the study.
c. The neurotoxicity subscale FACT/GOG-NtxS is part of the FACT/GOG-Ntx. Only the subscale was recorded in the study.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. The following events (MedDRA coding) are considered: “febrile neutropenia (PT, severe AEs)”, "diarrhoea (PT, severe AEs)".
f. No suitable data available; for reasons, see the following text section.
g. Although the dossier provides no suitable analyses for the outcome of infusion-related reactions, the events underlying the outcome are mapped via the specific AEs; for reasons, see the following text section.

AE: adverse event; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity; NtxS: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity Subscale; FACT-LYM: Functional Assessment of Cancer Therapy - Lymphoma; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma Subscale; MedDRA: Medical Dictionary of Drug Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire - Core 30; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on included outcomes

Failure of the curative treatment approach

In the present therapeutic indication, curative therapy is possible in principle. Failure to achieve remission or occurrence of relapse after achieving remission means that the curative treatment approach in this line of therapy has failed. In the present treatment situation,

failure of the curative treatment approach in the current line of therapy is a patient-relevant event because, albeit possible in principle, cure is less likely to achieve in a subsequent line of therapy. Failure of the curative treatment approach is therefore considered a patient-relevant outcome in this assessment. Alternatively, in the present data situation with a sufficiently long observation period (see Table 10; most relapses in previously untreated DLBCL occur within the first 2 years [17]), the counter-event, i.e. cure, could also be considered as outcome. Analyses to map the proportion of patients with a cure at the time point of 24 months after randomization (CR at Month 24) were explicitly planned for the study, but results were not reported (for a detailed explanation and consequences for the risk of bias, see the text section "Risk of bias across outcomes (study level)" in Section I 3.2).

In the POLARIX study, failure of the curative treatment approach was not directly recorded as an outcome. As an approximation, the present assessment considers the events that were recorded as part of the composite outcome of EFS as operationalization for the outcome. The proportion of patients with event (referred to below as “event rate”) and also the time to the occurrence of an event (EFS) were used for the assessment of the outcome “failure of the curative treatment approach”. According to the study design, the following operationalizations were pre-specified for the EFS:

- EFS_{eff},defined as the time from randomization to the first occurrence of one of the following events: death, progression/relapse, initiation of new anti-lymphoma therapy for efficacy reasons (but not due to progression or relapse), and positive residual disease on biopsy after end of treatment, regardless of whether new anti-lymphoma therapy was started or not
- EFS_{all}, defined as the time from randomization to the first occurrence of one of the following events: death, progression/relapse, initiation of new anti-lymphoma therapy

In Module 4 A, the company presented results on EFS_{eff}. It also presents the results on a further post-hoc operationalization of the EFS (EFS-EOT). EFS-EOT was defined as time from randomization to the first occurrence of one of the following events:

- death from any cause
- progression or recurrence
- failure to achieve a CR at the end of treatment

The operationalization of the EFS-EOT was used for the present benefit assessment, as it is suitable for depicting the failure of the curative treatment approach. A possible disease relapse after achieving a CR (via the events of relapse and death) as well as disease progression and failure to achieve a CR with the therapy were recorded. Irrespective of the fact that the operationalization EFS-EOT is relevant for the outcome for the present benefit assessment,

comparable results were shown for the operationalization EFS_{eff}, which was pre-specified according to the study design.

In the POLARIX study, the response to therapy was assessed by the investigator based on clinical examinations and by means of imaging techniques (PET/CT and/or CT [with contrast agent] images) using the Lugano criteria for malignant lymphomas [16]. As described above, it remains unclear whether the study results are fully transferable to the German health care context (see text section "Follow-up examinations in the POLARIX study" in Section I 3.2) due to the follow-up examinations in the POLARIX study, which differ from everyday healthcare practice. This issue has been taken into account in the assessment of the certainty of conclusions of the results (see Section I 4.2).

Patient-reported outcomes on symptoms, health status and health-related quality of life

The company's dossier provides analyses on symptoms recorded using the EORTC QLQ-C30, FACT-LymS and FACT/GOG-NtxS, on health status recorded using the EQ-5D VAS, and on health-related quality of life recorded using the EORTC QLQ-C30.

In the POLARIX study, EORTC QLQ-C30, FACT-LymS and EQ-5D VAS were recorded on the first day of Cycle 1 (baseline), Cycle 2, Cycle 3 and Cycle 5, at the end of treatment and in the follow-up phase every 6 months in the first 2 years after the last dose of the study medication, then every 12 months in the subsequent 3 years. The FACT/GOG-NtxS was also recorded in Cycle 4 as well as in Cycles 6 to 8 (each on Day 1).

Module 4 A of the dossier provides responder analyses and analyses using a mixed-effects model with repeated measures (MMRM) for patient-reported outcomes on symptoms (EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30) at different time points during the course of the study. For the responder analyses, the company considered the analysis date at the end of treatment on the one hand, and the analysis date at Month 24 after the end of treatment on the other. For the MMRM analyses, the company presented analyses for all individual time points of recording up to and including Month 48 after the end of treatment. The responder analyses and analyses using MMRM presented by the company are unsuitable for the present benefit assessment, however. This is explained below.

In the POLARIX study, surveys of patient-reported outcomes were planned for up to 5 years after the last dose of study medication. At Month 24 after the end of treatment, however, the response rates are clearly below 70% - even taking into account the deaths that occurred during the course of the study. Therefore, the responder analyses at the analysis time point "Week 24 after the end of treatment" are not suitable for the benefit assessment. In view of the responses, an analysis using MMRM, in which all patient observations over the entire course of the study or up to Month 24 after the end of treatment are taken into account,

would generally be suitable. MMRM analyses containing information on the number of patients with a value at baseline and at the respective time point are available in Module 4 A of the dossier. However, there is no information on the total number of patients included in the respective MMRM for each stated effect estimate. It is therefore not comprehensible whether and for which of the specified analysis time points the proportion of patients included in the analyses is above 70%. Furthermore, it is unclear whether the effect estimates are to be interpreted as a statement at one point in time or as a statement about the entire course up to this point in time. The MMRM analyses presented by the company are therefore unsuitable for the benefit assessment.

For the present assessment, MMRM analyses would be necessary in which all observations are taken into account, indicating the total number of patients included in the analysis. An effect estimate that maps the entire course up to a point in time (to be interpreted as an average over all points in time) is preferable - in contrast to an effect estimate that explicitly refers only to a single point in time. In addition, in the event of premature discontinuation of the study medication, it should be noted that the time points at Months 6, 12, 18, 24, 36 and 48 of the follow-up refer to the observation period after the last dose. In such cases, the values must be transparently assigned to the corresponding time points from randomization (i.e. the corresponding visits) in a comprehensible manner.

Side effects

Operationalization of specific AEs in the POLARIX study

In Module 4 A of the dossier, the company presents analyses on AEs of special interest (AESI) and selected AEs, including peripheral neuropathy, (febrile) neutropenia, and infections. It can be inferred from the study protocol that analyses on these AESIs and selected AEs listed in Module 4 A were pre-specified for the POLARIX study according to the study design. However, it is unclear on which operationalization the AESI and selected AEs reported by the company in Module 4 A are based. However, the CSR does not report results on AESI and selected AEs, but on "Adverse Events of Particular Interest" (AEPI). Some AEs among the AEPI are named analogously to AESI or selected AE (e.g. peripheral neuropathy, [febrile] neutropenia, and infections). However, the AEPI also comprise additional AEs that are not listed under the AESI and selected AEs according to the study protocol (e.g. infusion-related reactions), while some AESI and selected AEs are not listed under the AEPI. Thus, the analyses presented in the CSR and the analyses planned according to the study protocol are not congruent. Thus, neither the analyses of the AESI and selected AEs presented by the company in Module 4 A of the dossier nor the analyses of the AEPI from the CSR are suitable for the benefit assessment.

Peripheral neuropathy

For peripheral neuropathy, the company’s dossier provides analyses within the scope of AESI and selected AEs or AEPI. However, as described above, these analyses are not suitable for

the benefit assessment. In principle, a recording of all patient-relevant events, for example from the Standardized MedDRA Query (SMQ) [broad] on peripheral neuropathy would be desirable for the benefit assessment. However, based on the common AEs at System Organ Class (SOC) and Preferred Term (PT) level that occurred in the study, it cannot be assumed overall that there are relevant differences between the treatment arms for the outcome (see I Appendix C).

The symptoms of peripheral neuropathy were also recorded in the POLARIX study, using FACT/GOG-NtxS. However, no suitable data for the benefit assessment are available for this outcome either (for details, see text section "Patient-reported outcomes on symptoms, health status and health-related quality of life").

Infusion-related reactions

The company's dossier provides analyses of infusion-related reactions within the framework of AEPI. However, as described above, these analyses are not suitable for the benefit assessment. In addition to the uncertainties mentioned above regarding the AEPI, there is the additional limitation that it is unclear to what extent specific criteria were specified in the POLARIX study for the investigators' assessment of whether an AE is to be classified as an infusion-related AE (e.g. a predefined list with PTs).

According to the study design, no analyses of infusion-related reactions were planned for the POLARIX study, but the recording of "infusion-related reactions" was predefined. For AEs that occurred during or within 24 hours of infusion of the study medication, the underlying individual symptoms (e.g. dyspnoea, hypotension) are to be documented instead of the diagnosis of an allergic reaction or infusion reaction. Although no suitable summarizing analyses of all events are available for infusion-related reactions, it is assumed on the basis of the available information on the recording of "infusion-related reactions" and the common AEs that occurred in the study (see I Appendix C) that symptoms that occurred as infusion-related reactions in the POLARIX study were also included in the analyses on AEs. The events underlying the outcome are therefore mapped via the other specific AEs.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study		Outcomes											
	Study level	Overall survival	Failure of the curative treatment approach[a]	Symptoms (EORTC QLQ-C30, FACT-LymS[b], FACT/GOG-NtxS[c])	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[d]	Discontinuation due to AEs	Peripheral neuropathy	Infusion-related reactions	Infections and infestations (SOC, severe AEsd)	Further specific AEs,[d, e]
POLARIX	H	H[f]	H[f]	–[g]	–[g]	–[g]	H[f]	H[f]	H[f]	–[g]	–[h]	H[f]	H[f]

a. Operationalized via the event rate and EFS; includes the events of death, progression/recurrence, no achievement of a CR at the end of treatment, whichever occurs first; for explanation see Section I 4.1.
b. The lymphoma-specific subscale FACT-LymS is part of the FACT-LYM. Only the subscale was recorded in the study.
c. The neurotoxicity subscale FACT/GOG-NtxS is part of the FACT/GOG-Ntx. Only the subscale was recorded in the study.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. The following events (MedDRA coding) are considered: “febrile neutropenia (PT, severe AEs)”, "diarrhoea (PT, severe AEs)".
f. High risk of bias across outcomes.
g. No suitable data available; see Section I 4.1 for the reasoning.
h. Although the dossier provides no suitable analyses for the outcome of infusion-related reactions, the events underlying the outcome are mapped via the specific AEs; for reasons, see Section I 4.1.

AE: adverse event; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity; FACT/GOG-Ntxs: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity Subscale; FACT-LYM: Functional Assessment of Cancer Therapy - Lymphoma; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma Subscale; MedDRA: Medical Dictionary of Drug Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire - Core 30; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results on all outcomes is rated as high due to the high risk of bias across outcomes (see Table 12). This is due to the fact that reporting is potentially selective (for a detailed explanation, see the text section "Risk of bias across outcomes (study level)" in Section I 3.2).

Summary assessment of the certainty of conclusions

In addition to patients covered by the present research question, the POLARIX study includes a subpopulation of patients with HGBL, which are not comprised in the present therapeutic indication. Since the proportion of patients with DLBCL accounts for more than 80% of the total study population, the entire study population can nevertheless be considered for the benefit assessment. However, it remains unclear whether the results for the entire study population are fully transferable to the patients with DLBCL in the present research question (see text section on "Suitability of the overall population of the POLARIX study for the present benefit assessment" in Section I 3.2). In addition, there is further uncertainty regarding the transferability of the study results due to follow-up examinations that differ from everyday health care (see text section "Follow-up examinations in the POLARIX study" in Section I 3.2). Irrespective of this, the risk of bias across outcomes is rated as high for the POLARIX study, as the reporting is potentially selective (analyses explicitly planned for HTA were not reported; for a detailed explanation, see the text section "Risk of bias across outcomes (study level)" in Section I 3.2). Overall, the certainty of conclusions of the study results for the present research question is limited. Based on the available results from the POLARIX study, at most hints, e.g. of an added benefit, can be determined for all outcomes.

I 4.3 Results

Table 15 summarizes the results on the comparison of polatuzumab vedotin + R-CHP with R-CHOP in adult patients with previously untreated DLBCL. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

The Kaplan-Meier curves on the time-to-event analyses 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 can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study outcome category outcome	Polatuzumab vedotin + R-CHP N	Polatuzumab vedotin + R-CHP median time to event in months [95% CI] patients with event n (%)	R-CHOP N	R-CHOP median time to event in months [95% CI] patients with event n (%)	Polatuzumab vedotin + R-CHP vs. R-CHOP RR [95% CI]; p-value[a]
POLARIX					
Mortality					
Overall survival	500	NA 69 (13.8)	500	NA 77 (15.4)	HR: 0.88 [0.64; 1.22]; 0.450[b]
Morbidity					
Failure of the curative treatment approach					
Event rate[c]	500	– 169 (33.8)	500	– 199 (39.8)	0.85 [0.72; 1.00]; 0.051
Death	500	– 19 (3.8)	500	– 21 (4.2)	–[d]
Progression/recurrence	500	– 95 (19.0)	500	– 123 (24.6)	–[d]
No achievement of CR at the end of treatment	500	– 55 (11.0)	500	– 55 (11.0)	–[d]
Event-free survival (EFS)	500	NR 169 (33.8)	500	NR 199 (39.8)	HR: 0.80 [0.65; 0.98]; 0.030[b]
Symptoms (EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS)				No suitable data[e]	
Health status (EQ-5D VAS)				No suitable data[e]	
Health-related quality of life					
EORTC QLQ-C30				No suitable data[e]	
Side effects[f]					
AEs (supplementary information)	495	– 485 (98.0)	498	– 491 (98.6)	–
SAEs	495	– 170 (34.3)	498	– 155 (31.1)	1.10 [0.92; 1.32]; 0.292
Severe AEs[g]	495	– 310 (62.6)	498	– 302 (60.6)	1.03 [0.94; 1.14]; 0.542
Discontinuation due to AEs	495	– 30 (6.1)	498	– 30 (6.0)	1.01 [0.62; 1.64]; > 0.999
Peripheral neuropathy				No suitable data[e]	

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study outcome category outcome	Polatuzumab vedotin + R-CHP N	 median time to event in months [95% CI] patients with event n (%)	R-CHOP N	 median time to event in months [95% CI] patients with event n (%)	Polatuzumab vedotin + R-CHP vs. R-CHOP RR [95% CI]; p-value[a]
Infusion-related reactions				Analysis unsuitable[h]	
Infections and infestations (SOC, severe AEs[g])	495	– 76 (15.4)	498	– 66 (13.3)	1.16 [0.85; 1.57]; 0.530
Other specific AEs					
Febrile neutropenia (PT, severe AEs[g])	495	– 64 (12.9)	498	– 38 (7.6)	1.69 [1.16; 2.48]; 0.006
Diarrhoea (PT, severe AEs[g])	495	– 18 (3.6)	498	– 8 (1.6)	2.26 [0.99; 5.16]; 0.047

a. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [20]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
b. HR and CI: Cox regression model, stratified by IPI (2 vs. 3-5), bulky disease (present vs. absent) and geographical region (USA, Western Europe, Canada and Australia vs. Asia vs. rest of the world). p-value from log-rank test.
c. Proportion of patients with a qualifying event for "EFS". The individual components are presented in the lines below.
d. As only the qualifying events for the EFS are specified for the individual components, the effect estimates for the individual components are not shown.
e. See Section I 4.1 for reasons.
f. Events occurring in the period from the 1st dose of study medication until 90 days after the last dose of any study medication or until the start of new anti-lymphoma therapy, whichever is earlier.
g. Operationalized as CTCAE grade ≥ 3.
h. Although the dossier provides no suitable analyses for the outcome of infusion-related reactions, the events underlying the outcome are mapped via the specific AEs; for reasons, see Section I 4.1.

AE: adverse event; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntxs: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity Subscale; FACT-LymS: Functional Assessment of Cancer Therapy – Lymphoma Subscale; HR: hazard ratio; IPI: International Prognositc Index; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire - Core 30; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

Morbidity

Failure of the curative treatment approach

For the outcome of failure of the curative treatment approach, operationalized via the event rate and EFS, there is no statistically significant difference between the treatment groups for the event rate; for EFS, there is a statistically significant difference in favour of polatuzumab vedotin + R-CHP compared to R-CHOP. However, there is an effect modification by the characteristic of sex. For women, this results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven. For men, there is a hint of an added benefit of polatuzumab vedotin + R-CHP compared to R-CHOP (see Section I 4.4).

Symptoms (recorded using EORTC QLQ-C30, FACT-LymS and FACT/GOG-NtxS)

There were no usable data for the outcome “symptoms” (recorded with the EORTC QLQ-C30, FACT-LymS und FACT/GOG-NtxS) (for reasons, see Section I 4.1). This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

Health status (recorded with the EQ-5D VAS)

There were no suitable data for the outcome “health status” (recorded with the EQ-5D VAS) (for reasons, see Section I 4.1). This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30)

No usable data are available for health-related quality of life (recorded using the EORTC QLQ-C30) (for reasons, see Section I 4.1). This results in no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; 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 from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Severe AEs

No statistically significant difference between treatment groups was found for the outcome of severe AEs. There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Specific AEs

Peripheral neuropathy

No suitable data are available for the outcome of peripheral neuropathy (see Section I 4.1 for reasons). There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Infusion-related reactions

Although the dossier provides no suitable analyses for the outcome of infusion-related reactions (see Section I 4.1 for reasons), the events underlying the infusion-related reactions are mapped via the specific AEs. There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Infections and infestations (severe AEs)

No statistically significant difference between the treatment groups was shown for the outcome of infections and infestations (severe AE). There is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison with R-CHOP; greater or lesser harm is therefore not proven.

Febrile neutropenia (severe AEs)

A statistically significant difference to the disadvantage of polatuzumab vedotin in comparison with R-CHOP was found for the outcome “febrile neutropenia” (severe AEs). There is a hint of greater harm from polatuzumab vedotin + R-CHP compared to R-CHOP.

Diarrhoea (severe AEs)

A statistically significant difference to the disadvantage of polatuzumab vedotin + R-CHP in comparison with R-CHOP was found for the outcome “diarrhoea” (severe AEs). However, there is an effect modification by the characteristic of IPI. There is a hint of greater harm from polatuzumab vedotin + R-CHP compared to R-CHOP for patients with IPI 3 to 5. For patients with IPI 1 to 2, there is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in

comparison with R-CHOP; greater or lesser harm is therefore not proven for patients with IPI 1 to 2 (see Section I 4.4).

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (≤ 60 versus > 60 years)
- Sex (female versus male)
- IPI (1 to 2 vs. 3 to 5)

No categories were pre-specified in the POLARIX study for the subgroup analyses on the characteristic of age. The study documents contain results of subgroup analyses for this characteristic based on 2 different cut-off values of 60 years and 65 years. In Module 4 A of the dossier the company presents results for the age categories ≤ 60 vs. > 60 years. This classification is considered to be meaningful in the present indication, as an age of 60 years corresponds to the prognostically relevant age limit according to the IPI [17].

Categories for the subgroup analyses on the characteristic “IPI” were also not pre-specified in the POLARIX study. The study documents contain the results of subgroup analyses for this characteristic based on 2 different classifications: On the one hand, the categories IPI 1 to 2 vs. IPI 3 vs. IPI 4 to 5 were analysed based on the data collected in the eCRF; on the other hand, the categories IPI 2 vs. IPI 3 to 5 were analysed based on the data collected according to the interactive voice/web response system (IxRS). The classification IPI 2 vs. IPI 3 to 5 according to IxRS, which differentiates patients with low/low-intermediate risk from patients with high-intermediate/high risk, was also a prespecified stratification factor according to the study design. This categorisation is considered to be meaningful in the present indication and is therefore considered in the present benefit assessment. In Module 4 A of the dossier, the company only presented subgroup analyses on IPI 1 to 2 vs. IPI 3 vs. IPI 4 to 5 according to the eCRF. However, based on the available subgroup analyses on the IPI according to the eCRF from Module 4 A, Institute's calculation can be performed and considered as an approximation for the benefit assessment. For this purpose, the categories for the IPI according to eCRF (1 to 2 vs. 3 vs. 4 to 5) were summarized for the individual outcomes to IPI 1 to 2 vs. 3 to 5 analogous to the categories by stratification factor.

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 one 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 presented only if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 16. The Kaplan-Meier curves on the event time analyses are presented in I Appendix B.2 of the full dossier assessment. Forest plots for the Institute's calculations of subgroup analyses that meet the criteria mentioned for the presentation of the benefit assessment can be found in I Appendix D.

Table 16: Subgroups (morbidity, side effects) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study outcome characteristic subgroup	Polatuzumab vedotin + R-CHP N	Polatuzumab vedotin + R-CHP median time to event in months [95% CI] patients with event n (%)	R-CHOP N	R-CHOP median time to event in months [95% CI] patients with event n (%)	Polatuzumab vedotin + R-CHP vs. R-CHOP RR [95% CI][a]	Polatuzumab vedotin + R-CHP vs. R-CHOP p-value[a]
POLARIX						
Morbidity						
Failure of the curative treatment approach						
Event rate						
Sex						
Female	232	– 78 (33.6)	230	– 74 (32.2)	1.04 [0.81; 1.36]	0.804
Male	268	– 91 (34.0)	270	– 125 (46.3)	0.73 [0.59; 0.91]	0.004
Total					Interaction:	0.038[b]
Event-free survival (EFS)						
Sex						
Female	232	NA 78 (33.6)	230	NA 74 (32.2)	HR: 1.05 [0.76; 1.44][c]	0.784[c]
Male	268	NA [42.6; NC] 91 (34.0)	270	33.4 [25.3; NC] 125 (46.3)	HR: 0.68 [0.52; 0.89][c];	0.005[c]
Total					Interaction:	0.041[d]

Table 16: Subgroups (morbidity, side effects) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study outcome characteristic subgroup	Polatuzumab vedotin + R-CHP N	Polatuzumab vedotin + R-CHP median time to event in months [95% CI] patients with event n (%)	R-CHOP N	R-CHOP median time to event in months [95% CI] patients with event n (%)	Polatuzumab vedotin + R-CHP vs. R-CHOP RR [95% CI][a]	Polatuzumab vedotin + R-CHP vs. R-CHOP p-value[a]
Side effects						
Diarrhoea (PT, severe AEs[e])						
IPI						
1–2	187	– 1 (0.5)	187	– 4 (2.1)	0.25 [0.03; 2.22]	0.246
3-5[f]	308[g]	- 17 (5.5)[g]	311[g]	- 4 (1.3)[g]	4.29 [1.46; 12.61]	0.004
Total					Interaction:	0.022[h]

d. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [20]).
b. Institute's calculation, Cochran's Q test.
c. HR and CI: Cox regression model; p-value: log-rank test; each unstratified.
d. p-value from likelihood ratio test.
e. Operationalized as CTCAE grade ≥ 3.
f. Summary of the IPI 3 and IPI 4-5 subgroups
g. Institute's calculation.
h. Institute's calculation, Cochran's Q-test, related to the 2 subgroups IPI 1-2 vs. IPI 3-5

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EFS: event-free survival; HR: hazard ratio; IPI: International Prognostic Index; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomized controlled trial; RR: relative risk

Morbidity

Failure of the curative treatment approach

There is a statistically significant effect modification for the characteristic sex for the outcome of failure of the curative treatment approach. For women, there was no statistically significant difference between the treatment groups for both the event rate and EFS. There is no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP for women; an added benefit is therefore not proven. For men, however, there was a statistically significant difference in favour of polatuzumab vedotin + R-CHP compared to R-CHOP in both the event rate and the EFS. For men, there is a hint of an added benefit of polatuzumab vedotin + R-CHP compared to R-CHOP. The results of the operationalizations of event rate and EFS for men differ in their extent, however. In the present data situation, taking into account the

differences in the proportions of patients with event and the time courses (see I Appendix B.2), the overall extent of the added benefit is rated as “minor” (see Section I 5).

Side effects

Diarrhoea (severe AEs)

For the outcome of diarrhoea (severe AEs), there is a statistically significant effect modification by the characteristic IPI. A statistically significant difference to the disadvantage of polatuzumab vedotin + R-CHP compared to R-CHOP is shown for patients with IPI 3 to 5. There is a hint of greater harm from polatuzumab vedotin + R-CHP compared to R-CHOP for patients with IPI 3 to 5. For patients with IPI 1-2, in contrast, there was no statistically significant difference between the treatment groups. For this subgroup, there is no hint of greater or lesser harm from polatuzumab vedotin + R-CHP in comparison R-CHOP; greater or lesser harm is therefore not proven for this outcome for patients with IPI 1 to 2.

I 5 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 IQWiG *General Methods* [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 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for the outcome of failure of curative treatment

It cannot be inferred from the dossier whether the following outcome of failure of curative treatment is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

The outcome of failure of curative treatment is deemed to be serious/severe. On the one hand, recurrence of the cancer can be life-threatening, and an event in the outcome shows that the attempt to cure a potentially life-threatening disease with the curative treatment approach has not been successful. On the other hand, the event of death from any cause is a component of the outcome of failure of curative treatment.

Table 17: Extent of added benefit at outcome level: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Polatuzumab vedotin + R-CHP vs. R-CHOP** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA months HR: 0.88 [0.64; 1.22] p = 0.450	Lesser/added benefit not proven
Outcomes observed over 5 months		
Morbidity		
Failure of the curative treatment approach		
Sex		
Female		Lesser/added benefit not proven
Event rate	33.6% vs. 32.2% RR: 1.04 [0.81; 1.36] p = 0.804	
Event-free survival (EFS)	NA vs. NA months HR: 1.05 [0.76; 1.44] p = 0.784	
Male		Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit; extent: “minor”
Event rate	34.0% vs. 46.3% RR: 0.73 [0.59; 0.91] p = 0.004 probability: “hint”	
Event-free survival (EFS)	NA vs. 33.4 months HR: 0.68 [0.52; 0.89] p = 0.005 probability: “hint”	
Symptoms (EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS)	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[c]	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Polatuzumab vedotin + R-CHP vs. R-CHOP** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with shortened observation period		
Side effects		
SAEs	34.3% vs. 31.1% RR: 1.10 [0.92; 1.32] p = 0.292	Greater/lesser harm not proven
Severe AEs	62.6% vs. 60.6% RR: 1.03 [0.94; 1.14] p = 0.542	Greater/lesser harm not proven
Discontinuation due to AEs	6.1% vs. 6.0% RR: 1.01 [0.62; 1.64] p > 0.999	Greater/lesser harm not proven
Peripheral neuropathy	No suitable data[c]	Greater/lesser harm not proven
Infusion-related reactions	Analysis unsuitable[d]	Greater/lesser harm not proven
Infections and infestations (severe AEs)	15.4% vs. 13.3% RR: 1.16 [0.85; 1.57] p = 0.530	Greater/lesser harm not proven
Febrile neutropenia (severe AEs)	12.9% vs. 7.6% RR: 1.69 [1.16; 2.48] RR: 0.59 [0.40; 0.86][e] p = 0.006 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Diarrhoea (severe AEs) IPI 1–2	0.5% vs. 2.1% RR: 0.25 [0.03; 2.22] p = 0.246	Lesser/added benefit not proven
3–5	5.5% vs. 1.3% RR: 4.29 [1.46; 12.61] RR: 0.23 [0.08; 0.68][e] p = 0.004 probability: “hint”	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% greater harm, extent: “major”

Table 17: Extent of added benefit at outcome level: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Polatuzumab vedotin + R-CHP vs. R-CHOP** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
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. See Section I 4.1 for reasons. d. Although the dossier provides no suitable analyses for the outcome of infusion-related reactions, the events underlying the outcome are mapped via the specific AEs; for reasons, see Section I 4.1. e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-NtxS: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity Subcale; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma Subscale; HR: hazard ratio; IPI: International Prognostic Index; NA: not achieved; QLQ-C30: Quality of Life Questionnaire - Core 30; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of polatuzumab vedotin + R-CHP compared with R-CHOP

Positive effects	**Negative effects**
Outcomes observed over 5 months	
Morbidity ▪ failure of the curative treatment approach ▫ sex, male: hint of an added benefit – extent: “minor”	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ febrile neutropenia: hint of greater harm – extent: "considerable" ▪ diarrhoea ▫ IPI 3–5: hint of greater harm – extent: "major"
No suitable data are available for outcomes of symptoms, health status and health-related quality of life.	
IPI: International Prognostic Index; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone	

Overall, there are both positive and negative effects for polatuzumab vedotin + R-CHP compared to R-CHOP. For the outcome of failure of the curative treatment approach, these are based on the planned observation period of up to 5 years after the last dose of the study medication (see Table 8). For the outcomes in the side effects category, however, the observed effects relate exclusively to a shortened observation period.

For men, there is a hint of minor added benefit of polatuzumab vedotin + R-CHP compared to R-CHOP for the outcome “failure of the curative treatment approach”. For febrile neutropenia, there is a hint of greater harm with the extent “considerable” for the entire study population. For diarrhoea, there is a hint of greater harm with the extent “major” for patients with an IPI score from 3 to 5. In the POLARIX study, numerous patient-reported outcomes on symptoms, health status, and health-related quality of life were recorded. However, no suitable data are available for these outcomes (see Section I 4.1). An adequate assessment of patient-reported symptoms, health status and health-related quality of life is not possible without suitable analyses of the outcomes recorded using the EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS and EQ-5D VAS.

In summary, the added benefit of polatuzumab vedotin + R-CHP versus the ACT R-CHOP is not proven.

Table 19 summarizes the result of the assessment of the added benefit of polatuzumab vedotin + R-CHP in comparison with the ACT.

Table 19: Polatuzumab vedotin + R-CHP – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with previously untreated DLBCL	Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)[b, c]	Added benefit not proven[d]

a. Presented is the ACT specified by the G-BA.
b. According to the SPC, rituximab should be used in combination with CHOP for 8 cycles. According to the G-BA, the German health care context foresees the administration of 6 cycles as standard treatment in the therapeutic indication. Administration of 6 to 8 cycles is possible according to the generally recognized state of medical knowledge.
c. According to the G-BA, it cannot be inferred from the available evidence and the written statements of the medical associations that, in accordance with the generally recognized state of medical knowledge, the off-label use of rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (R-ACVBP) and of rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone (R-CHOEP) would, as a rule, be preferable to the R-CHOP combination therapy approved to date in the therapeutic indication or for relevant patient groups or areas of indication in the therapeutic indication. R-ACVBP and R-CHOEP are therefore not specified as ACT.
d. The POLARIX study only included patients with an ECOG PS of < 2 and an IPI ≥ 2. In addition, no patients with transformed follicular lymphoma were included in the study. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2, an IPI score of 0 or 1 or with follicular lymphoma.

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group - Performance Status; G-BA: Federal Joint Committee; IPI: International Prognostic Index; R-ACVBP: rituximab in combination with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; R-CHOEP: rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: rituximab in combination with cyclophosphamide, doxorubicin and prednisone

The above assessment deviates from the assessment by the company, which derived an indication of considerable added benefit of polatuzumab vedotin + R-CHP versus R-CHOP.

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.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2022. There, the G-BA had determined a non-quantifiable added benefit of polatuzumab vedotin (in combination with R-CHP). However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

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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