Polatuzumab vedotin (combination with rituximab, cyclophosphamide, doxorubicin and prednisone; previously untreated DLBCL 1)

Addendum to Project A23-141 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AEPI	AEs of particular interest
AESI	AEs of special interest
CR	complete response
DLBCL	diffuse large B-cell lymphoma
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)
HTA	Health Technology Assessment
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
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
SGB	Sozialgesetzbuch (Social Code Book)
SMD	Standardized mean difference
SMQ	Standardized MedDRA Query
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 7 May 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-141 (Polatuzumab vedotin [combination with rituximab, cyclophosphamide, doxorubicin and prednisone; previously untreated DLBCL)]– Benefit assessment according to § 35a Social Code Book V) {Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2024 #22}.

The commission comprises the assessment of the following analyses presented by the pharmaceutical company (hereinafter referred to as “the company”) in the commenting procedure [1,2], taking into account the information provided in the dossier [3]:

- Follow-up time for "failure of the curative treatment approach" (event-free survival at the end of treatment EFS-EOT] and EFS_{eff})
- Recurrences (disease-free survival at the end of treatment [DFS-EOT])
- Patient-reported outcomes: mixed-effects model with repeated measures (MMRM) analyses including patient numbers and standardized mean differences (SMD)
- Analyses on adverse events of special interest (AESI)/selected adverse events (AEs)/adverse events of particular interest (AEPI)
- Analyses on EFS_{all} at Month 24 after randomization, complete response (CR) at Month 24 after randomization and B symptoms

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) POLARIX was included for the benefit assessment of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (hereinafter referred to as polatuzumab vedotin + R-CHP) in comparison with the appropriate comparator therapy rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (hereafter referred to as R-CHOP) in adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL). A detailed description of the study can be found in dossier assessment A23-141.

Based on the information provided in the company's dossier, no suitable data were available for dossier assessment A23-141 for the outcomes "symptoms", "health status" and "health-related quality of life". In addition, the company's dossier lacked information on the duration of observation for the outcome of failure of the curative treatment approach or EFS and the outcomes on side effects. Furthermore, results of analyses on exploratory efficacy outcomes or exploratory patient-reported outcomes planned according to the statistical analysis plan for Health Technology Assessment (HTA) were not reported. These were analyses of EFS_{all} at Month 24 after randomization, CR at Month 24 after randomization and additional analyses on B-symptoms. In addition, there were uncertainties in the analyses of specific AEs presented in the company's dossier ("AESI", "selected AEs", "AEPI").

As part of the commenting procedure, the company subsequently submitted information on the analyses of the patient-reported outcomes on symptoms, health status, health-related quality of life and on the duration of observation for the outcomes of failure of the curative treatment approach or EFS as well as the outcomes on side effects. Moreover, with its statement it presented evaluations of the analyses planned for HTA on EFS_{all} at Month 24 after randomization, CR at Month 24 after randomization and B symptoms. The company subsequently submitted information on the operationalization on specific AEs and conducted additional analyses.

In accordance with the commission, the analyses and data subsequently submitted by the company in the commenting procedure are assessed below, taking into account the information in the dossier.

2.1 Subsequently submitted information on the course of the study

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 for dossier assessment A23-141. The information on the course of the study subsequently submitted by the company with the comments shows that the median duration of observation for these outcomes is comparable between the study arms (see Table 1). 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. There are no consequences for the benefit assessment from the subsequently submitted data on the course of the study.

Table 1: Information on the course of the study subsequently submitted by the company with its comments – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study **duration of the study phase** **outcome category**	**Polatuzumab vedotin + R-CHP** **N = 500[a]**	**R-CHOP** **N = 500[a]**
POLARIX		
Observation period [months]		
Failure of the curative treatment approach or EFS[b]		
Median [Q1; Q3]	30.7 [29.6; 41.3]	30.7 [29.8; 41.0]
Mean (SD)	ND	ND
Side effects		
Median [Q1; Q3]	7.8 [7.8; 8.0][c]	7.8 [7.7; 7.9][c]
Mean (SD)	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b. The observation duration for the EFS-EOT operationalization used in the benefit assessment (see dossier assessment A23-141) based on the reverse Kaplan-Meier method is shown. The median observation period for the operationalization EFF_{eff} pre-specified according to the study design was 30.7 [29.3; 41.3] vs. 30.6 [29.7; 40.1] months [Q1; Q3].
c. Defined as the time from treatment initiation to the earliest of the following events: data cut-off, death, lost to follow-up, withdrawal of consent, last dose of study medication + 90 days, initiation of subsequent anti-cancer therapy.

CR: complete response; eCRF: electronic case report form; EFS: event-free survival; EOT: end of treatment; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third 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

2.2 Recurrences (DFS-EOT)

For the outcome "recurrence", the company presented analyses on the post hoc defined operationalization DFS-EOT on disease-free survival in its dossier. DFS-EOT was defined as the time from a documented CR at the end of treatment until the occurrence of recurrence or death from any cause. Only patients in the intervention or comparator arm who achieved a CR at the end of treatment were included in the company's analysis. These were 381 out of 500 (76%) patients in the intervention arm vs. 364 out of 500 (73%) patients in the comparator arm. This means that not all randomized patients were included in the analysis. Since achieving a CR is a progression parameter, it cannot be assumed that the structural equality between the intervention and comparator arm achieved at the start of the study through randomization will continue to exist in the patients included in the analysis. A randomized

comparison is therefore no longer be feasible. The operationalization DFS-EOT was not relevant for the present benefit assessment. The occurrence of recurrences is mapped via the operationalization EFS-EOT for the outcome of failure of the curative treatment approach (see dossier assessment A23-141).

2.3 MMRM analyses on patient-reported outcomes

The company's dossier provides analyses on the following patient-reported outcomes for the POLARIX study:

- on "symptoms", recorded using the European Organisation for Research and Treatment of Cancer – Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Lymphoma Subscale (FACT-LymS) and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity Subcale (FACT/GOG-NtxS)
- on health status recorded using the EQ-5D visual analogue scale (VAS)
- on health-related quality of life recorded using EORTC QLQ-C30

As explained in dossier assessment A23-141, an analysis using an MMRM, in which all patient observations over the entire course of the study or up to Month 24 after the end of treatment are considered, would generally be suitable for these patient-reported outcomes in view of the responses. Although MMRM analyses are available in Module 4 A of the dossier, it was unclear how many patients in total were included in the respective MMRM for each stated effect estimate. It was therefore not comprehensible whether and for which of the specified analysis time points the proportion of patients included in the analyses was above 70%. In its comments, the company explained that the number of patients with a baseline value and a value at the respective visit was stated in the company's results tables. In the oral hearing [4], the company furthermore stated that all patients for whom both a baseline value and at least one further value after the start of the study were available were included in the analysis. Based on this statement and the number of patients with a baseline value and a value at the respective visit, it can be concluded that the proportion of patients included in the analysis is at least 88% for the analysis time point "Month 24" after the end of treatment for each individual patient-reported outcome.

Furthermore, as described in dossier assessment A23-141, 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 company did not provide specific comments on this in the commenting procedure. It is assumed that the effect estimates are to be interpreted as a statement at a point in time.

As described in dossier assessment A23-141, in the event of premature discontinuation of study medication, it must be taken into account that the time point at Month 24 of follow-up

refers to the observation period after the last dose of study medication. 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. The company provided no such analyses. Since only 57 (11%) patients in the intervention arm vs. 69 (14%) patients in the comparator arm discontinued treatment with the study medication prematurely, the existing analyses were used in the present data situation.

The MMRM analyses presented by the company on the outcomes recorded using the EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS and EQ-5D VAS are used for the benefit assessment.

2.4 Analyses on AESI, selected AEs and AEPI

In Module 4 A of the dossier, the company presents analyses on AESI and selected AEs. The study protocol indicates that, according to the study design, analyses of these AESI and selected AEs were pre-specified for the POLARIX study, but the specific operationalization was unclear (see dossier assessment A23-141). However, the clinical study report does not report results on AESI and selected AEs, but on AEPI). These analyses presented in the CSR (AEPI) and the analyses planned according to the study protocol (AESI, selected AEs) 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 dossier assessment A23-141.

Within the framework of the commenting procedure, the company clarified on which operationalization the analyses of AESI, selected AE and AEPI were based. According to the company, the AESI and selected AEs presented in Module 4 A of the dossier refer to the events pre-specified in the study protocol according to the module template. With regard to the AEPI, the company stated in its comments that further analyses beyond the AESI/selected AE had been conducted at the time the study report was prepared. According to the company, all AESI/selected AEs are included in this more comprehensive AEPI. For the AEPI - if not already presented as AESI or selected AE in the dossier - the company subsequently submitted analyses for the total population of the POLARIX study with its comments. It should be noted that the unjustified deviation from the analyses specified in the study protocol in the study report is not appropriate.

In dossier assessment A23-141, no suitable data or no suitable analyses were available for the specific AEs peripheral neuropathy and infusion-related reactions relevant for the benefit assessment. The analyses and information presented by the company in the commenting procedure are therefore assessed below for these outcomes, taking into account the information in the dossier.

Peripheral neuropathy

The company's comments show that the analysis on peripheral neuropathy presented by the company is based on the Standardized MedDRA Query (SMQ) [broad], but the Preferred Terms (PTs) of muscular weakness and gait disorder were not taken into account by the company. This approach is not appropriate. The analyses on peripheral neuropathy presented by the company are therefore still unsuitable. However, this remains without consequence, since - as already described in dossier assessment A23-141 - based on the common AEs at System Organ Class (SOC) and PT level that occurred in the study, it can overall not be assumed that there are relevant differences between the treatment arms for the outcome.

Infusion-related reactions

In its dossier, the company provided analyses of infusion-related reactions within the framework of AEPI. In addition to the uncertainties mentioned above regarding the AEPI, there was the additional limitation that it was unclear to what extent specific criteria were specified in the POLARIX study for the investigators' assessment of whether an AE was to be classified as an infusion-related AE (e.g. a predefined list with PTs). The company did not comment on this in the course of the commenting procedure, so that the ambiguity remains. The analyses on infusion-related reactions presented by the company in the context of the AEPI are still unsuitable for the benefit assessment. However, this is of no consequence, since - as already described in dossier assessment A23-141 - the events underlying the outcome are mapped via the other specific AEs.

2.5 Subsequently submitted data for analyses planned for HTA

With its comments, the company subsequently submitted the analyses on EFS_{all} at Month 24 after randomization planned for HTA, on CR at Month 24 after randomization and on B symptoms based on the FACT-LymS or the eCRF, but these do not meet the requirements described in the dossier templates provided by the G-BA (see the G-BA's Code of Procedure [5]). For example, subgroup analyses on these outcomes are lacking. This approach is not appropriate. Irrespective of this, the analyses presented by the company in the commenting procedure are assessed below, taking into account the information in the dossier as commissioned by the G-BA.

2.5.1 EFS_{all} at Month 24 after randomization

The operationalization EFS_{all} pre-specified according to the study design was defined as the time from randomization to the first occurrence of one of the following events: death, progression/recurrence (assessed by the investigator) or initiation of a new anti-lymphoma therapy. The component "initiation of a new anti-lymphoma therapy" does not reflect the failure of the curative treatment approach with sufficient certainty. To assess the failure of the curative treatment approach, the operationalization EFS-EOT (death of any cause,

progression or recurrence, failure to achieve CR at the end of treatment) already used in dossier assessment A23-141 is considered relevant over the entire observation period. The operationalisation EFS_{all} (at Month 24 after randomization) is therefore not relevant for the present benefit assessment.

2.5.2 CR at Month 24 after randomization

In dossier assessment A23-141, failure of the curative treatment approach was mapped via the operationalization EFS-EOT (see previous text section). Alternatively, in the present data situation with a sufficiently long observation period (see Table 10 in dossier assessmentA23-141), most relapses in previously untreated DLBCL occur within the first 2 years [6]), the counter-event, i.e. cure, could also be considered as outcome. The prespecified analysis on the proportion of patients with a cure at 24 months after randomization was presented by the company as part of the commenting procedure (CR at Month 24 after randomization). Curation was determined by the investigator at the visit within a time window of 3 months before or after 24 months after randomization. The information provided by the company in the oral hearing shows that the analysis on the CR at Month 24 after randomization potentially includes patients as events who received 1 or more subsequent therapies and only achieved CR under the subsequent therapies. It remains unclear how many patients this affects. However, in order to depict the counter-event (curation by polatuzumab vedotin + R-CHP or R-CHOP) to the failure of the curative treatment approach in this therapy line, it would be necessary to include only patients with CR achieved under the initial study therapy and persisting at Month 24 as an event in the analysis. The company did not present such analyses. In the present therapeutic indication, it is certainly relevant how many patients achieve a cure across all therapy lines. However, this requires a longer observation period than the one for CR at 24 months after randomization in order to map the high-risk period for recurrence in the further course of treatment. Irrespective of the limitation described above, there is no statistically significant difference between the treatment groups for the proportion of patients with CR at Month 24 after randomization in the total population of the POLARIX study (see Table 7 in Appendix B). This confirms the relevant result of the event rate for the total population for the outcome failure of the curative treatment approach (see Table 15 in dossier assessment A23-141).

2.5.3 B symptoms

Within the framework of the commenting procedure, the company subsequently submitted analyses on B symptoms based on the FACT-LymS or the eCRF. FACT-LymS was used to determine the extent (scale from 0 ["not at all"] to 4 ["very strongly"]) to which the patient had been affected by B symptoms (fever, night sweats, weight loss) during the last 7 days. These B symptoms, which were assessed via 3 items, were included in the total score of the FACT-LymS (15 items), which was already taken into account in the benefit assessment (see

Section 2.3). The B symptoms recorded via the eCRF correspond to the criteria specified in the guideline [6] for a history of B symptoms: unexplainable pyrexia > 38°C, night sweats with change of bedding/pyjamas and unexplained weight loss > 10% in the last 6 months. In the POLARIX study, B symptoms were recorded at screening, during treatment with the study medication (on Day 1 of Cycles 2 to 8), at the end of treatment, and after the end of treatment every 6 months up to 5 years after the last dose of study medication or until disease progression. The company did not provide any information on the actual observation duration in the intervention and the comparator arm for the outcome of B symptoms.

The outcome of B symptoms was classified as patient-relevant and the analyses based on the eCRF were used for the benefit assessment. The company presented the following operationalizations for this purpose:

- Time to the first occurrence or first recurrence of at least one B symptom
- Time to absence of all B symptoms

The analysis of the time to the first occurrence or first recurrence of at least one B symptom includes both patients without B symptoms at baseline and patients with B symptoms at baseline. In the intervention vs. the comparator arm, 335 (67%) vs. 346 (69%) patients had no B symptoms at baseline and were at risk for the event of interest from baseline. 165 (33%) vs. 154 (31%) patients in the intervention vs. the comparator arm had at least one B symptom at baseline. At first, these patients had to be free of symptoms during the course of the study to be at risk for the event of interest. The analysis of the time to absence of all B symptoms presented by the company provides information on how long the period to the first documented absence of B symptoms was. This shows that the median time to the absence of all B symptoms was 0.8 months and was comparable between the treatment arms. The analyses Time to first occurrence or first recurrence of at least one B symptom are therefore suitable and are used for the benefit assessment.

2.6 Risk of bias and certainty of conclusions

In dossier assessment A23-141, the risk of bias across outcomes due to potentially selective reporting was rated as high. Although the company presented analyses on missing outcomes as part of the commenting procedure, these are still incomplete (see Section 2.5). This means that the points of criticism outlined in dossier assessment A23-141 have not been fully resolved. Irrespective of the high risk of bias, there are still limitations regarding the transferability of the study results with regard to the included population and the follow-up examinations that deviates from everyday health care (see dossier assessment A23-141). 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.

2.7 Results

The following Table 2 presents the results for the outcome of symptoms (recorded using EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS), health status (recorded using the EQ-5D VAS) and health-related quality of life (recorded using the EORTC QLQ-C30) from the POLARIX study.

The results for the outcome "B symptoms" from the POLARIX study are shown in Table 3 below. The Kaplan-Meier curves on time-to-event analysis are presented in Appendix A of the full dossier assessment.

Table 2: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study outcome category outcome	Polatuzumab vedotin + R-CHP			Polatuzumab vedotin + R-CHP vs. R-CHOP			Polatuzumab vedotin + R-CHP vs. R-CHOP
	N[a]	values at baseline mean (SD)	change at FU month 24 mean[b] (SE)	N[a]	values at baseline mean (SD)	change at month 24 mean[b] (SE)	MD[b] [95% CI]; p-value
POLARIX							
Morbidity							
Symptoms (EORTC QLQ-C30)							
Fatigue	ND	35.70 (27.24)	-14.78 (1.13)	ND	33.79 (26.47)	-14.82 (1.18)	0.05 [-2.97; 3.07]; 0.976
Nausea and vomiting	ND	7.95 (17.78)	-3.66 (0.54)	ND	5.85 (14.25)	-4.78 (0.57)	1.12 [-0.35; 2.59]; 0.135
Pain	ND	29.38 (30.36)	-12.35 (1.27)	ND	27.66 (30.41)	-16.07 (1.32)	3.71 [0.27; 7.15]; 0.034 SMD: 0.19 [0.01; 0.36]
Dyspnoea	ND	17.93 (27.03)	-5.34 (1.15)	ND	15.71 (25.27)	-2.82 (1.21)	-2.53 [-5.65; 0.59]; 0.112
Insomnia	ND	34.67 (33.48)	-17.64 (1.46)	ND	34.90 (33.37)	-16.82 (1.53)	-0.82 [-4.78; 3.14]; 0.686
Appetite loss	ND	25.00 (32.99)	-16.93 (0.84)	ND	23.62 (32.10)	-17.08 (0.89)	0.15 [-2.14; 2.44]; 0.898
Constipation	ND	19.79 (29.50)	-9.68 (1.13)	ND	20.55 (28.64)	-12.53 (1.18)	2.84 [-0.22; 5.91]; 0.069
Diarrhoea	ND	9.53 (20.63)	-2.11 (1.00)	ND	8.51 (18.84)	-0.40 (1.06)	-1.71 [-4.48; 1.06]; 0.225
Symptoms (FACT-LymS[d])	ND	45.24 (9.94)	7.42 (0.39)	ND	45.56 (9.85)	7.29 (0.40)	0.14 [-0.90; 1.18]; 0.796
Symptoms (FACT/GOG-NtxS[e])	ND	39.93 (4.46)	-1.45 (0.33)	ND	39.63 (4.89)	-1.31 (0.35)	-0.14 [-1.06; 0.77]; 0.759
Health status (EQ-5D VAS)[f]	ND	69.40 (21.53)	10.91 (0.86)	ND	70.60 (19.40)	12.21 (0.87)	-1.30 [-3.55; 0.95]; 0.258

Table 2: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP (multipage table)

Study outcome category outcome	Polatuzumab vedotin + R-CHP			Polatuzumab vedotin + R-CHP vs. R-CHOP			Polatuzumab vedotin + R-CHP vs. R-CHOP
	N[a]	values at baseline mean (SD)	change at FU month 24 mean[b] (SE)	N[a]	values at baseline mean (SD)	change at month 24 mean[b] (SE)	MD[b] [95% CI]; p-value
Health-related quality of life							
EORTC QLQ-C30[f]							
Global health status	ND	60.13 (24.54)	15.45 (1.07)	ND	62.09 (23.97)	15.31 (1.13)	0.15 [-2.76; 3.06]; 0.920
Physical functioning	ND	80.39 (21.96)	5.14 (0.90)	ND	80.68 (22.50)	6.31 (0.93)	-1.18 [-3.56; 1.20]; 0.332
Role functioning	ND	70.98 (33.22)	15.60 (1.21)	ND	72.06 (31.61)	15.85 (1.26)	-0.26 [-3.50; 2.98]; 0.876
Emotional functioning	ND	76.81 (21.56)	10.35 (0.95)	ND	74.92 (21.84)	12.45 (1.00)	-2.10 [-4.67; 0.47]; 0.110
Cognitive functioning	ND	85.34 (20.04)	0.50 (0.95)	ND	86.80 (17.67)	1.75 (1.00)	-1.25 [-3.84; 1.34]; 0.345
Social functioning	ND	74.58 (28.63)	14.07 (1.10)	ND	74.30 (27.70)	16.43 (1.16)	-2.35 [-5.30; 0.59]; 0.117

a. At least 441 (88.2%) patients in the intervention vs. 442 (88.4%) comparator arm were included in the effect estimate; the values at baseline are based on other patient numbers.
b. MMRM analysis of the ITT population adjusted for the value at baseline and the stratification factors (IPI [2 vs. 3-5], bulky disease [present vs. absent] and geographic region [USA, Western Europe, Canada and Australia vs. Asia vs. rest of the world].
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparator) indicate an advantage for the intervention (scale range of 0 to 100).
d. According to the company, higher (increasing) values indicate improved symptoms; positive effects (intervention minus comparator) indicate an advantage for the intervention (scale range 0 to 60).
e. According to the company, lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparator) indicate an advantage for the intervention (scale range of 0 to 44).
f. Higher (increasing) values indicate better health status/better health-related quality of life; positive effects (intervention minus comparator) indicate an advantage for the intervention (scale range 0 to 100).

CI: confidence interval; ITT: intention to treat; 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; FU: follow-up; IPI: International Prognostic Index; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; 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; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

Table 3. Results (morbidity, time to event) health-related quality of life, continuous) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study outcome category outcome	Polatuzumab vedotin + R-CHP		R-CHOP		Polatuzumab vedotin + R-CHP vs. R-CHOP
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
POLARIX					
Morbidity					
B symptoms[b]	485	NA 68 (14.0)	490	NA 59 (12.0)	1.15 [0.81; 1.63]; 0.432

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.

b. Operationalized as the time until first occurrence or first recurrence of at least one B symptom (symptoms recorded via eCRF: unexplainable pyrexia > 38°C, night sweats with change of bedding/pyjamas, unexplainable weight loss > 10% in the last 6 months); no information is available on the proportions of symptoms were included.

CI: confidence interval; eCRF: electronic case report form; HR: hazard ratio; IPI: International Prognostic Index; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; 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

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.6).

Morbidity

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

For the outcomes of fatigue, nausea and vomiting, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea (recorded using the EORTC QLQ-C30) and for the FACT-LymS and FACT/GOG-NtxS, the analyses showed no statistically significant difference between the treatment groups on the basis of mean differences. In each case, there is no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

On the basis of mean differences, the analysis showed a statistically significant difference between treatment groups for the outcome of pain recorded with the EORTC QLQ-C30). The SMD was analysed to examine the relevance of the result. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. There is 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)

On the basis of mean differences, no statistically significant difference between treatment groups was found for "health status" (recorded using the EQ-5D VAS). There is 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)

For "health-related quality of life", no statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning (recorded using the EORTC QLQ-C30). In each case, there is no hint of an added benefit of polatuzumab vedotin + R-CHP in comparison with R-CHOP; an added benefit is therefore not proven.

B symptoms

No statistically significant difference between the treatment groups was shown for the outcome of B symptoms. 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

Peripheral neuropathy

No suitable data are available for the outcome of peripheral neuropathy (see Section 2.4 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 2.4 for reasons), the events underlying the infusion-related reactions are mapped via the specific AEs, as described in dossier assessment A23-141. 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.

2.8 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment (see also dossier assessment A23-141):

- Age (≤ 60 years versus > 60 years)
- Sex (female versus male)
- International Prognostic Index (IPI) (1 to 2 vs. 3 to 5)

The methods described in Section I 4.4 of dossier assessment A23-141 are used.

In its dossier and as part of the commenting procedure, the company did not present any subgroup analyses for the MMRM analyses on the outcomes recorded using the EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS and EQ-5D VAS. Subgroup analyses for the B symptoms outcome are also lacking - as well as for the other analyses planned for HTA. It is therefore not possible to assess potential effect modifications for these outcomes.

2.9 Probability and extent of added benefit

The extent of the respective added benefit at outcome level was estimated from the results presented in dossier assessment A23-141 and the previous sections (see Table 4).

Table 4: 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 event rate (%) or mean change at follow-up month 24** **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)		
Fatigue	-14.78 vs. -14.82 MD: 0.05 [-2.97; 3.07]; p = 0.976	Lesser/added benefit not proven
Nausea and vomiting	-3.66 vs. -4.78 MD: 1.12 [-0.35; 2.59]; p = 0.135	Lesser/added benefit not proven

Table 4: 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 event rate (%) or mean change at follow-up month 24** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Pain	-12.35 vs. -16.07 MD: 3.71 [0.27; 7.15]; p = 0.034 SMD: 0.19 [0.01; 0.36][c]	Lesser/added benefit not proven
Dyspnoea	-5.34 vs. -2.82 MD: -2.53 [-5.65; 0.59]; p = 0.112	Lesser/added benefit not proven
Insomnia	-17.64 vs. -16.82 MD: -0.82 [-4.78; 3.14]; p = 0.686	Lesser/added benefit not proven
Appetite loss	-16.93 vs. -17.08 MD: 0.15 [-2.14; 2.44]; p = 0.898	Lesser/added benefit not proven
Constipation	-9.68 vs. -12.53 MD: 2.84 [-0.22; 5.91]; p = 0.069	Lesser/added benefit not proven
Diarrhoea	-2.11 vs. -0.40 MD: -1.71 [-4.48; 1.06]; p = 0.225	Lesser/added benefit not proven
Symptoms (FACT-LymS)	7.42 vs. 7.29 MD: 0.14 [-0.90; 1.18]; p = 0.796	Lesser/added benefit not proven
Symptoms (FACT/GOG-NtxS)	-1.45 vs. -1.31 MD: -0.14 [-1.06; 0.77]; p = 0.759	Lesser/added benefit not proven
Health status (EQ-5D VAS)	10.91 vs. 12.21 MD: -1.30 [-3.55; 0.95]; p = 0.258	Lesser/added benefit not proven
B symptoms	NA vs. NA months HR: 1.15 [0.81; 1.63]; p = 0.432	Lesser/added benefit not proven

Table 4: 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 event rate (%) or mean change at follow-up month 24** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30		
Global health status	15.45 vs. 15.31 MD: 0.15 [-2.76; 3.06]; p = 0.920	Lesser/added benefit not proven
Physical functioning	5.14 vs. 6.31 MD: -1.18 [-3.56; 1.20]; p = 0.332	Lesser/added benefit not proven
Role functioning	15.60 vs. 15.85 MD: -0.26 [-3.50; 2.98]; p = 0.876	Lesser/added benefit not proven
Emotional functioning	10.35 vs. 12.45 MD: -2.10 [-4.67; 0.47]; p = 0.110	Lesser/added benefit not proven
Cognitive functioning	0.50 vs. 1.75 MD: -1.25 [-3.84; 1.34]; p = 0.345	Lesser/added benefit not proven
Social functioning	14.07 vs. 16.43 MD: -2.35 [-5.30; 0.59]; p = 0.117	Lesser/added benefit not proven
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[d]	Greater/lesser harm not proven
Infusion-related reactions	Analysis unsuitable[e]	Greater/lesser harm not proven

Table 4: 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 event rate (%) or mean change at follow-up month 24** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
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][f]; 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][f]; p = 0.004 probability: "hint"	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"

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. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. See Section 2.4. for reasons.
e. Although there are 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 2.4.
f. Institute's calculation; reversed 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; FU: follow-up: HR: hazard ratio; IPI: International Prognostic Index; MD: mean difference; 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; SMD: standardized mean difference; VAS: visual analogue scale

Table 5 presents the results of dossier assessment A23-141 and the present addendum A24-60, both of which were factored into the overall conclusion on the extent of added benefit. The data assessed in this addendum revealed no further positive or negative effects compared to dossier assessment A23-141.

Table 5: 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"
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	

2.10 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of Polatuzumab vedotin + R-CHP from dossier assessment A23-141.

Table 6 below shows the result of the benefit assessment of polatuzumab vedotin + R-CHP, taking into account dossier assessment A23-141 and the present addendum.

Table 6: 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 in combination with CHOP should be used 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.

3 References

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

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Appendix A Kaplan-Meier curves on B symptoms

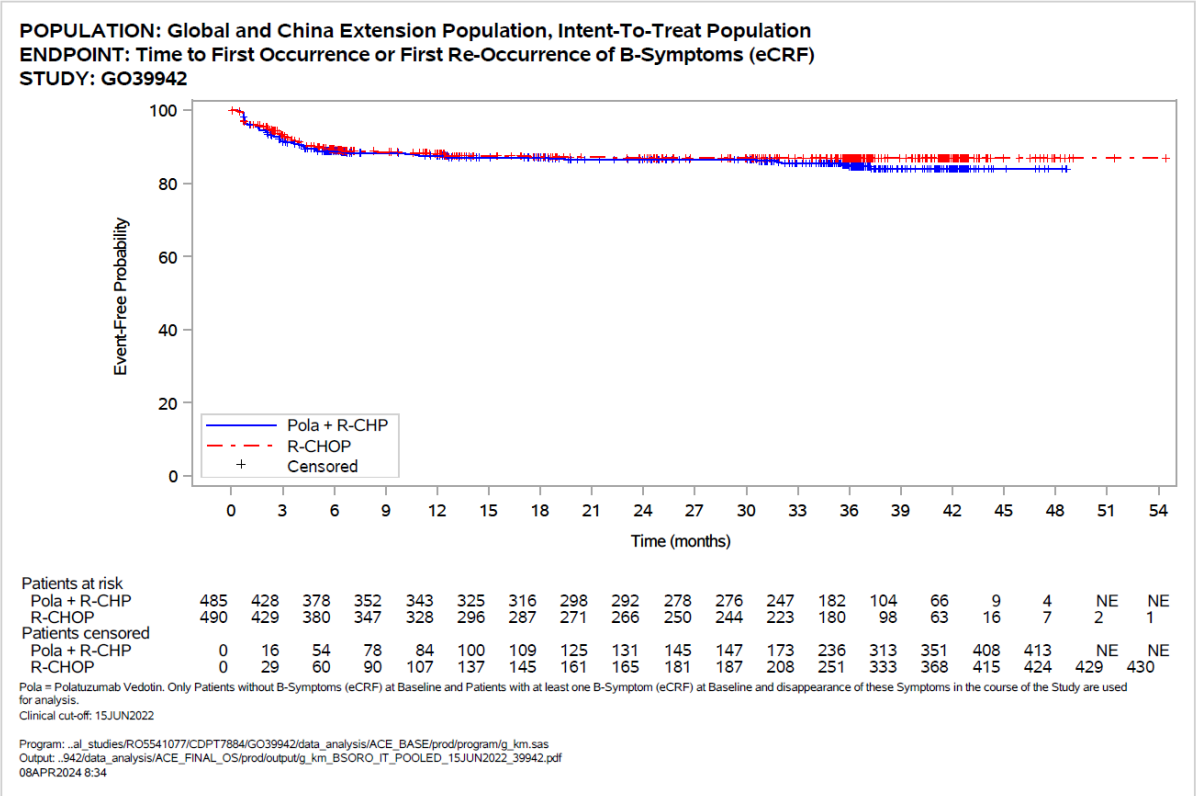

Figure 1: Kaplan-Meier curves for B symptoms in the POLARIX study, 3rd data cut-off (15 June 2022), total population

Appendix B Supplementary presentation of the CR at Month 24 after randomization

Table 7: Results: (morbidity, dichotomous) – RCT, direct comparison: polatuzumab vedotin + R-CHP versus R-CHOP

Study outcome category outcome	Polatuzumab vedotin + R-CHP		R-CHOP		Polatuzumab vedotin + R-CHP vs. R-CHOP
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
POLARIX					
Morbidity					
CR at Month 24 after randomization	500	252 (50.4)	500	225 (45.0)	1.12 [0.98; 1.28]; 0.097

a. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [7]).

CR: complete response; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP: Rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT: randomised controlled trial; RR: relative risk