Epcoritamab
(diffuse large B-cell lymphoma, DLBCL)

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

EXTRACT

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Bernhard Jochheim.

IQWiG thanks the respondent and the Leukämie und Lymphom SHG Ruhr-Lippe e. V. for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent and the 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
ACT	appropriate comparator therapy
CAR	chimeric antigen receptor
DLBCL	diffuse large B-cell lymphoma
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug epcoritamab. 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 01 November 2024.

Research question

The aim of the present report is to assess the added benefit of epcoritamab in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 of systemic therapy.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of epcoritamab

Research question	Therapeutic indication	ACT[a]
1	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[b, c]	Treatment of physician's choice, taking into account ▪ tisagenlecleucel ▪ axicabtagene ciloleucel ▪ lisocabtagene maraleucel ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with autologous stem cell transplantation if there is a response to induction therapy ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with allogeneic stem cell transplantation if there is a response to induction therapy
2	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[d]	Treatment of physician's choice, taking into account ▪ polatuzumab vedotin + bendamustine + rituximab ▪ tafasitamab + lenalidomide ▪ radiation

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, treatment with curative intent is assumed to be an option for the patients.
c. According to the G-BA, among patients who have not yet been treated with autologous stem cell transplantation, allogeneic stem cell transplantation is an option for those who are at very high risk of relapse or for whom it was not possible to obtain sufficient stem cells for autologous stem cell transplantation.
d. According to the G-BA, treatment with curative intent is not assumed to be an option for the patients.

ACT: appropriate comparator therapy; CAR: chimeric antigen receptor; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin or carboplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide

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

For patients in research question 1 (for whom chimeric antigen receptor [CAR]-T cell therapy or stem cell therapy is an option), the company only specified allogeneic stem cell transplantation in addition to CAR-T cell therapy with tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleucel, and not autologous stem cell transplantation as a treatment option according to physician's choice. Furthermore, the company provided no information on induction and high-dose therapy for stem cell transplantation.

The company divides the population of research question 2 (patients for whom CAR-T cell therapy and stem cell therapy are not an option) into 2 subpopulations based on the criterion

of prior therapy with CAR-T cells. It describes a separate ACT for each of these. For patients who have not yet received CAR-T cell therapy, the company names the drugs glofitamab and loncastuximab tesirine in addition to the options named by the G-BA for research question 2. In the company's view, radiotherapy does not represent an independent ACT. For patients who have already received CAR-T cell therapy in their prior treatment, the company specified glofitamab as the comparator therapy.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the G-BA's ACT remains without consequence, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by it nor compared with the ACT specified by the G-BA.

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

Results

The check of the information retrieval did not identify a relevant randomized controlled trial (RCT) for the direct comparison of epcoritamab with the ACT for either of the two research questions.

As the company itself did not identify any RCT for the direct comparison of epcoritamab versus the ACT, it conducted an information retrieval for further investigations on epcoritamab. In this information retrieval, the company identified the single-arm GCT3013-01 study and used this study to assess the added benefit.

The GCT3013-01 study included by the company is an ongoing single-arm study on the treatment of adult patients with epcoritamab. The study is not suitable for the benefit assessment because it does not allow a comparison of epcoritamab with the ACT for either of the two research questions. There are therefore no suitable data available for either question.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of epcoritamab in comparison with the ACT; an added benefit is therefore not proven. This applies to both research questions.

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

Table 3 shows a summary of probability and extent of the added benefit of epcoritamab.

[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

Table 3: Epcoritamab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[b, c]	Treatment of physician's choice, taking into account ▪ tisagenlecleucel ▪ axicabtagene ciloleucel ▪ lisocabtagene maraleucel ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with autologous stem cell transplantation if there is a response to induction therapy ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with allogeneic stem cell transplantation if there is a response to induction therapy	Added benefit not proven
2	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[d]	Treatment of physician's choice, taking into account ▪ polatuzumab vedotin + bendamustine + rituximab ▪ tafasitamab + lenalidomide ▪ radiation	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, treatment with curative intent is assumed to be an option for the patients.
c. According to the G-BA, among patients who have not yet been treated with autologous stem cell transplantation, allogeneic stem cell transplantation is an option for those who are at very high risk of relapse or for whom it was not possible to obtain sufficient stem cells for autologous stem cell transplantation.
d. According to the G-BA, treatment with curative intent is not assumed to be an option for the patients.

ACT: appropriate comparator therapy; CAR: chimeric antigen receptor; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin or carboplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide

The G-BA decides on the added benefit.

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].

I 2 Research question

The aim of the present report is to assess the added benefit of epcoritamab in comparison with the ACT in adult patients with relapsed or refractory DLBCL after at least 2 of systemic therapy.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of epcoritamab

Research question	Therapeutic indication	ACT[a]
1	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[b, c]	Treatment of physician's choice, taking into account ▪ tisagenlecleucel ▪ axicabtagene ciloleucel ▪ lisocabtagene maraleucel ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with autologous stem cell transplantation if there is a response to induction therapy ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with allogeneic stem cell transplantation if there is a response to induction therapy
2	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[d]	Treatment of physician's choice, taking into account ▪ polatuzumab vedotin + bendamustine + rituximab ▪ tafasitamab + lenalidomide ▪ radiation

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, treatment with curative intent is assumed to be an option for the patients.
c. According to the G-BA, among patients who have not yet been treated with autologous stem cell transplantation, allogeneic stem cell transplantation is an option for those who are at very high risk of relapse or for whom it was not possible to obtain sufficient stem cells for autologous stem cell transplantation.
d. According to the G-BA, treatment with curative intent is not assumed to be an option for the patients.

ACT: appropriate comparator therapy; CAR: chimeric antigen receptor; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin or carboplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide

The company deviated from the G-BA's specification of the ACT. These deviations are presented below.

For patients in research question 1 (for whom CAR-T cell therapy or stem cell therapy is an option), the company only specified allogeneic stem cell transplantation in addition to CAR-T cell therapy with tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleucel, and not autologous stem cell transplantation as a treatment option according to physician's choice. Furthermore, the company provided no information on induction and high-dose therapy for stem cell transplantation.

The company divides the population of research question 2 (patients for whom CAR-T cell therapy and stem cell therapy are not an option) into 2 subpopulations based on the criterion of prior therapy with CAR-T cells. It describes a separate ACT for each of these. For patients who have not yet received CAR-T cell therapy, the company names the drugs glofitamab and loncastuximab tesirine in addition to the options named by the G-BA for research question 2. In the company's view, radiotherapy does not represent an independent ACT. For patients who have already received CAR-T cell therapy in their prior treatment, the company specified glofitamab as the comparator therapy.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the G-BA's ACT remains without consequence, as the company did not present any suitable data for the benefit assessment – neither versus a comparator therapy designated by it nor versus the ACT specified by the G-BA (see Chapter I 3). Since suitable data are not available for either of the 2 research questions, both research questions are assessed below in joint sections of the report.

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

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 lists on epcoritamab (status: 10 October 2024)
- bibliographical literature searches on epcoritamab (last search on 10 October 2024)
- search in trial registries/trial results databases for studies on epcoritamab (last search on 10 October 2024)
- search on the G-BA website for epcoritamab (last search on 10 October 2024)

To check the completeness of the study pool:

- search in trial registries for studies on epcoritamab (last search on 20 November 2024); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

Concurring with the company's assessment, the check did not identify any relevant RCTs for the direct comparison of epcoritamab versus the ACT specified by the G-BA.

Further investigations

As the company itself did not identify any RCT for the direct comparison of epcoritamab versus the ACT, it conducted an information retrieval for further investigations on epcoritamab. In doing so, it identified the single-arm study GCT3013-01 [3], on the basis of which epcoritamab was approved, and used the study to assess the added benefit. The company conducted no information retrieval on further studies with the ACT.

The completeness of the study pool presented by the company for further investigations was not checked. The study presented by the company among other trials is not suitable for the benefit assessment because it does not allow a comparison with the ACT. The company's study is described below.

Evidence presented by the company – GCT3013-01 study

The company included the single-arm GCT3013-01 study in its benefit assessment. This study is an ongoing trial for the treatment of adult patients with cluster of differentiation (CD)-20-positive mature B-cell neoplasia, including DLBCL *(de novo* or transformed), with epcoritamab. It included patients with relapsed, progressive and/or refractory disease following treatment with an anti-CD20 monoclonal antibody (e.g. rituximab), possibly in combination with chemotherapy and/or relapsed after autologous stem cell rescue. All standard treatment options had to have been exhausted or not be an option for the patient. The patients were

divided into 3 cohorts depending on their B-cell neoplasia (aggressive B-cell lymphomas, indolent B-cell lymphomas, mantle cell lymphomas). The study consists of a dose-finding phase and an extension phase. In the extension phase, treatment with epcoritamab is carried out in accordance with the SPC [4] and is continued until disease progression, unacceptable toxicity or the start of subsequent therapy. The primary outcome of the extension phase was the overall response rate. In Module 4 A, the company presented data from the extension phase of the study on 139 patients with relapsed or refractory DLBCL after 2 or more systemic therapies from the cohort of patients with aggressive B-cell lymphoma at the data cut-off of 21 April 2023.

The single-arm study GCT3013-01 presented by the company in Module 4 A is not suitable for the benefit assessment, as it does not allow a comparison of epcoritamab with the ACT for either of the two research questions. There are therefore no suitable data available for either question.

I 4 Results on added benefit

There are no suitable data available for the assessment of epcoritamab for the treatment of adult patients with relapsed or refractory DLBCL after at least 2 lines of systemic therapy in comparison with the ACT. This applies to both research questions. In each case, there is no hint of an added benefit of epcoritamab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of epcoritamab in comparison with the ACT is summarized in Table 5.

Table 5: Epcoritamab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[b, c]	Treatment of physician's choice, taking into account ▪ tisagenlecleucel ▪ axicabtagene ciloleucel ▪ lisocabtagene maraleucel ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with autologous stem cell transplantation if there is a response to induction therapy ▪ induction therapy with ▫ R-GDP or ▫ R-DHAP or ▫ R-ICE followed by high-dose therapy with allogeneic stem cell transplantation if there is a response to induction therapy	Added benefit not proven
2	Adults with relapsed or refractory DLBCL after at least 2 prior systemic therapies for whom CAR-T cell therapy or stem cell therapy is not an option[d]	Treatment of physician's choice, taking into account ▪ polatuzumab vedotin + bendamustine + rituximab ▪ tafasitamab + lenalidomide ▪ radiation	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, treatment with curative intent is assumed to be an option for the patients.
c. According to the G-BA, among patients who have not yet been treated with autologous stem cell transplantation, allogeneic stem cell transplantation is an option for those who are at very high risk of relapse or for whom it was not possible to obtain sufficient stem cells for autologous stem cell transplantation.
d. According to the G-BA, treatment with curative intent is not assumed to be an option for the patients.

ACT: appropriate comparator therapy; CAR: chimeric antigen receptor; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin or carboplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide

The assessment described above departs from that by the company, which derived a hint of non-quantifiable added benefit for the total population of the present therapeutic indication.

The G-BA decides on the added benefit.

I 6 References

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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