Axicabtagene ciloleucel (DLBCL and PMBCL, third line or later)

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

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

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

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Can Ünal
- Erika Baumbach
- Reza Fathollah-Nejad
- Ulrich Grouven
- Claudia Kapp
- Christopher Kunigkeit
- Katrin Nink
- Sabine Ostlender

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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
AE	adverse event
BSG	Bundessozialgericht (Federal Social Court)
CAR	chimeric antigen receptor
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EBMT	European Society for Blood and Marrow Transplantation
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICANS	immune effector cell-associated neurotoxicity syndrome
IPTW	inverse-probability-of-treatment-weighting
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
LBCL	large B-cell lymphoma
LDC	lymphocyte depletion chemotherapy
mITT	modified intention to treat
ORR	overall response rate
PFS	progression-free survival
PMBCL	primary mediastinal B-cell lymphoma
RCT	randomized controlled trial
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
tFL	transformed follicular lymphoma

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 axicabtagene ciloleucel. 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 3 July 2023.

Research question

The aim of this report is to assess the added benefit of axicabtagene ciloleucel compared with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) after 2 or more systemic therapies.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of axicabtagene ciloleucel

Research question	Therapeutic indication	ACT[a]
1	Adults with relapsed or refractory DLBCL and PMBCL after 2 or more lines of systemic therapy who are candidates for high-dose therapy[b]	Treatment of physician's choice, taking into account[c,d]: ▪ tisagenlecleucel (only for people with DLBCL), ▪ induction therapy with MINE followed by high-dose therapy with autologous stem cell transplantation, provided there was a response to induction therapy, ▪ induction therapy with MINE followed by high-dose therapy with allogeneic stem cell transplantation, provided there was a response to induction therapy
2	Adults with relapsed or refractory DLBCL and PMBCL after 2 or more systemic therapies who are not candidates for high-dose therapy	Treatment of physician's choice, taking into account[d]: ▪ CEOP, ▪ dose-adjusted EPOCH, ▪ polatuzumab vedotin + bendamustine + rituximab (only for people with DLBCL), ▪ tafasitamab + lenalidomide (only for people with DLBCL), ▪ pixantron monotherapy, ▪ radiotherapy, ▪ BSC

a. Presented is the respective ACT specified by the G-BA.
b. Patients are presumed to be eligible for high-dose therapy with curative intent.
c. When selecting therapy options, the patient's previous therapy with CAR T cell therapy, autologous stem cell transplantation, or allogeneic stem cell transplantation must be taken into account. 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. The available guidelines and scientific medical societies and/or the Drug Commission of the German Medical Association in accordance with § 35a (7) sentence 4 SGB V list unapproved drug therapies for the treatment of recurrent/refractory DLBCL/PMBCL after ≥ 2 prior therapies. According to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not deemed ACTs in the narrower sense of § 2 (1) sentence 3, § 12 SGB V.

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; CAR: chimeric antigen receptor; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; G-BA: Federal Joint Committee; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; SGB: Social Code Book

In the context of its specification of the ACT, the G-BA points out that both approved and unapproved drug therapies for relapsed or refractory DLBCL and PMBCL after 2 or more systemic therapies are mentioned in the available guidelines or by scientific medical societies and/or the Drug Commission of the German Medical Association according to § 35a (7), sentence 4 SGB V. According to the Federal Social Court (BSG) comments on the judgement dated 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized

by the G-BA in the Pharmaceuticals Directive are generally not taken into account as ACTs in the narrower sense of § 2 (1) sentence 3, § 12 SGB V.

Deviating from the ACT specified in Table 2, Module 3 A of the company's dossier lists the ACT for the entire approval population – without differentiating between the 2 research questions – as individualized therapy taking into account the biology of the disease, prior therapies, the course of the disease, and the patient's general condition, with the comparators of chimeric antigen receptor (CAR) T-cell therapy (tisagenlecleucel and lisocabtagene maraleucel) and autologous or allogeneic stem cell transplantation. The company disregarded other treatment options because, unlike CAR T-cells and stem cell transplantation, they did not represent treatment strategies with a primarily curative intent according to the S3 guideline.

The present assessment was conducted on the basis of the research questions specified by the G-BA (in terms of populations and corresponding ACTs). The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

Since no usable data are available for either of the research questions identified by the G-BA, the 2 research questions are assessed together below.

Results

Concurring with the company, the check of completeness of the study pool produced no randomized controlled trials (RCTs) directly comparing axicabtagene ciloleucel versus the ACT.

Since the company did not identify any studies for direct comparison, it conducted an information retrieval on further investigations with axicabtagene ciloleucel and found the single-arm pivotal ZUMA-1 study. The company did not conduct an information retrieval on other investigations with the ACT.

A check for completeness of the study pool for other investigations was foregone because the data submitted by the company under further investigations are unsuitable for assessing the benefit of axicabtagene ciloleucel in comparison with the ACT. However, the dossier already suggests that the company's study pool for other investigations is potentially incomplete. This is explained below.

Implausible information retrieval for the evidence presented in the dossier

For its information retrieval on further investigations with axicabtagene ciloleucel, the company reportedly excluded retrospective studies, but it included the retrospective study Bachy 2022 to derive added benefit.

The company's Module 4A does not describe any information retrieval for further investigations on the ACT. It defines neither inclusion nor exclusion criteria for a search for further investigations on the ACT, nor is a targeted search for studies with the ACT documented in Module 4A. Hence, it is unclear whether the study pool for the ACT is complete.

Overall, the information retrieval for the evidence presented in the dossier is not convincing.

Presentation and assessment of the evidence presented by the company

The company uses the results from the Bachy 2022 and ZUMA-1 studies as primary evidence. As supporting evidence, the company presents results from a metaanalysis of published registry studies to compare axicabtagene ciloleucel versus tisagenlecleucel as well as descriptive data from the EUPAS32539 study on axicabtagene ciloleucel from the current report of the European Society for Blood and Marrow Transplantation (EBMT) registry. The company did not present any studies drawing a comparison to treatment of physician's choice.

The company refrained from reexamining the SCHOLAR study-1, which it named as a relevant study in the dossier but did not use for the benefit assessment, as the study reportedly no longer adequately depicted the appropriate therapy due to the greatly changed healthcare context. The company's approach of excluding the SCHOLAR-1 study is appropriate. The healthcare context in the assessed therapeutic indication has changed due to the authorization of newer treatment options such as tafasitamab, polatuzumab vedotin, and CAR T-cells. The SCHOLAR-1 study is therefore disregarded below.

Due to several aspects, the data presented by the company are unsuitable for assessing the benefit of axicabtagene ciloleucel in comparison with the ACT. This is justified below.

Primary evidence used by the company

The Bachy 2022 study used by the company as primary evidence is a retrospective analysis of data from the French DESCAR-T registry to compare axicabtagene ciloleucel with tisagenlecleucel in propensity score-adjusted populations.

DESCAR-T registry

Patients can be included in the French DESCAR-T registry both retrospectively (from 1 July 2018 until the registry is set up) and prospectively (from the time suitability of CAR T-cell therapy is established or via participation in a clinical trial), provided they are being treated with CAR T-cell therapy or the therapeutic indication for CAR T-cell therapy has been established.

According to the registry protocol, the primary outcome is overall survival, defined as the time from determination of eligibility for CAR T-cell therapy to death. Secondary outcomes include

response, overall survival following CAR T-cell infusion, progression-free survival (PFS), health-related quality of life, and adverse events (AEs).

A statistical analysis plan (SAP) or a current study report, which are to be generated as per protocol, are not available.

Bachy 2022 study

The retrospective Bachy 2022 study included patients with DLBCL and at least 2 prior systemic therapies who were treated with axicabtagene ciloleucel or tisagenlecleucel between December 2019 and October 2021 and were entered in the DESCAR-T registry.

The primary outcome was PFS after CAR T-cell infusion. Secondary outcomes included overall survival following infusion, response, and specific AEs (haematological toxicity, cytokine release syndrome [CRS], and immune effector cell-associated neurotoxicity syndrome [ICANS]).

The Bachy 2022 study included 809 patients with DLBCL and at least 2 prior systemic therapies from the DESCAR-T registry. Of these patients, 729 received a CAR T-cell infusion (axicabtagene ciloleucel [n = 452] and tisagenlecleucel [n = 277]). After exclusion of patients with PMBCL and > 25% missing values, 672 infused patients (axicabtagene ciloleucel [n = 419] and tisagenlecleucel [n = 253]) remained, which were used for 1:1 matching using propensity score adjustment. For the adjustment, 14 possible confounders were taken into account, resulting in a 1:1 matched population of 418 patients.

The Bachy 2022 study provides results for all outcomes regarding the 1:1 propensity score-matched population. In addition, inverse-probability-of-treatment-weighting (IPTW) analyses were conducted for all efficacy outcomes, taking into account the same 14 confounders. In addition, propensity score and IPTW analyses are available for the outcomes of overall survival following infusion, PFS following infusion, and duration of response (DOR) for patients without missing values (complete case analysis) as well as propensity score and IPTW analyses for the outcome of overall survival following CAR T-cell order.

The company presents analyses from the Bachy 2022 study on the outcomes of overall survival following infusion, PFS following infusion, overall response rate (ORR), DOR, and specific AEs (haematological toxicity, CRS, and ICANS) for the 1:1 propensity score-matched population. In addition, the company analyses the outcome of overall survival following CAR T-cell order. Neither the IPTW analyses nor the complete-case analyses found in the Bachy 2022 publication were submitted.

Bachy 2022 study permits no conclusions on added benefit

Apart from the methodological description in the publication, no documents on the study design and statistical analyses in the form of a study protocol and SAP are available for the Bachy 2022 retrospective study. However, these are necessary even if nonrandomized comparisons are based on already existing data. It therefore remains unclear to what extent the presented analyses were predefined and/or whether any other analyses had been planned.

Furthermore, the only patient-relevant outcomes on which the Bachy 2022 study offers results are overall survival and individual specific AEs; consequently, a complete assessment of benefits versus harms is not possible based on the results of the Bachy 2022 study.

The Bachy 2022 study does not describe a systematic identification of potentially relevant confounders, nor does it justify the selection of confounders taken into account for the propensity score adjustment and IPTW analysis. The company's Module 4A likewise does not provide any further information on the search for and selection of the confounders taken into account. In contrast to the DESCAR-T registry protocol, according to which all patients are to be observed from the time of the treatment decision, the Bachy 2022 study observed all outcomes from the time of infusion. Consequently, the analyses in the Bachy 2022 study violate the intention-to-treat (ITT) principle.

For the described reasons, the Bachy 2022 study is generally unsuitable for assessing added benefit.

ZUMA-1 study

ZUMA-1 is a single-arm phase 1/2 study on treatment with axicabtagene ciloleucel, which enrolled adult patients with refractory DLBCL, PMBCL, or transformed follicular lymphoma (tFL) after ≥ 1 line of chemotherapy, including an anti-CD20 antibody and an anthracycline or a recurrence ≤ 12 months after autologous stem cell transplantation.

In phase 1 of the ZUMA-1 study, different regimens of lymphocyte depletion chemotherapy (LDC) with various CAR T-cell doses were tested to determine dose-limiting toxicity. Phase 2 of the study comprises the pivotal cohorts 1 and 2, which are potentially relevant for the present research question.

In study cohorts 1 and 2, patients received 1 intravenous target dose of 2×10^6 viable CAR T-cells/kg body weight or a maximum dose of 2×10^8 viable CAR T-cells from a body weight of 100 kg. Bridging therapy in the period between leukapheresis and infusion of CAR T-cells was disallowed in cohorts 1 and 2. In phase 2 of the ZUMA-1 study, a total of 111 patients were included in either cohort 1 (DLBCL; n = 81) or cohort 2 (PMBCL or tFL; n = 30) depending on

their disease subentity. Of these patients, 101 actually received treatment with axicabtagene ciloleucel (cohort 1: n = 77; cohort 2: n = 24).

Primary outcome of the study was ORR; secondary outcomes included overall survival, PFS, and AEs.

The company's Module 4 A presents both the ITT population (N = 111) and the modified ITT population (mITT), which comprises all patients who received an infusion with axicabtagene ciloleucel (N = 101).

Uncontrolled ZUMA-1 study permits no conclusions on added benefit

The results from the ZUMA-1 study alone are unsuitable for assessing the added benefit of axicabtagene ciloleucel in comparison with the ACT because they do not allow a comparison with the ACT. In addition, the prohibition of bridging therapy limits the transferability of the results from the ZUMA-1 study to the German healthcare context.

Evidence used as supplementary information by the company

In Module 4A, the company presents as supplementary information a comparison of axicabtagene ciloleucel versus tisagenlecleucel from a metaanalysis of published registry data and additional data on the efficacy and safety of axicabtagene ciloleucel from the EUPAS32539 study report.

Metaanalysis from published registry data

For the metaanalysis of published registry studies presented by the company, a bibliographic literature search was conducted in the Embase and MEDLINE databases. English-language publications from 2017 onwards on prospective and retrospective observational studies with patients with large B-cell lymphoma (LBCL) who were treated with CAR T-cells (axicabtagene ciloleucel, tisagenlecleucel or lisocabtagene maraleucel) were included. The studies were allowed to have either no comparator or CAR T-cells as comparator and had to include results on efficacy and/or safety outcome results.

The company's Module 4A states that after excluding publications which reported results on interventions other than axicabtagene ciloleucel or tisagenlecleucel or which reported no comparative quantitative results on said 2 interventions, the described literature search yielded 14 patient cohorts suitable for a comparison of axicabtagene ciloleucel versus tisagenlecleucel. For the subsequent metaanalysis from published registry studies, the company took into account only the results of individual large studies.

The company presents metaanalytically summarized results from adjusted and unadjusted analyses on the outcomes of response, overall survival, PFS, CRS, and neurotoxicity for a comparison of axicabtagene ciloleucel versus tisagenlecleucel. Thereupon, the company

descriptively compares these results separately for each of the 2 active substances versus the results from the respective approval studies ZUMA-1 (axicabtagene ciloleucel) and JULIET (tisagenlecleucel).

Reasons for the exclusion of data from the metaanalysis of published registry data

The company's dossier presents only the final analyses and aggregated data from the studies included in the metaanalysis for selected registries. The company's Module 4A does not indicate whether criteria other than study size influenced the selection, nor does it list the study publications taken into account in the respective analyses. Apart from the specific AEs of CRS and neurotoxicity, the metaanalysis does not report results for any other AE outcomes, rendering a complete assessment of benefits versus harms impossible. Notwithstanding these limitations, however, the available information clearly shows that the studies taken into account violated the ITT principle. Due to the lack of information, it is also impossible to conclusively assess whether all patients fall under the therapeutic indication (DLBCL or PMBCL from third line) and to which research question the included patients can be grouped.

The information retrieval to identify the potentially relevant studies for the metaanalysis likewise suffers from shortcomings which call into question the completeness of the study pool.

EUPAS32539 study

The EUPAS32539 study is a multicentre observational study in patients with relapsed or refractory DLBCL or PMBCL after 2 or more lines of systemic therapy and patients with relapsed or refractory follicular lymphoma after 3 or more lines of systemic therapy who are treated with axicabtagene ciloleucel in routine care. Primary outcomes are the occurrence, type, and location of secondary tumours as well as specific AEs. Secondary outcomes include overall survival, time to next therapy, and time to relapse/progression.

The data for the EUPAS32539 study originate from the EBMT registry, which records all patients who are treated with axicabtagene ciloleucel in qualified European centres and who have given informed consent, regardless of whether axicabtagene ciloleucel treatment is in line with the marketing authorization.

In Module 4A, the company presents results from the interim report of the EBMT registry. At the time of data cutoff, 979 patients with DLBCL and PMBCL had received an infusion of axicabtagene ciloleucel after at least 2 or more systemic therapies. The report contains analyses of 773 patients for whom a follow-up form was available on Day 100. The company presents descriptive results from these analyses on the outcomes of response and specific AEs (CRS and neurotoxicity).

Reasons for the exclusion of data from the EUPAS32539 study

Since they do not allow a comparison with the ACT, the results from the retrospective EUPAS32539 study alone are unsuitable for assessing the added benefit of axicabtagene ciloleucel versus the ACT. The survey of AEs is limited to a few specific AEs and therefore does not allow a complete weighing of benefits and harms. In addition, the ITT principle has been violated due to the patients being observed only after the infusion of axicabtagene ciloleucel. The study documents show that, due to lacking data on complications and/or toxicity, the follow-up form for the 206 patients who were infused but not analysed was not available. For 374 patients, information is also missing on axicabtagene ciloleucel administered in accordance with the marketing authorization. The analyses of the EUPAS32539 study are therefore subject to several uncertainties.

Conclusion

In summary, the studies presented by the company are unsuitable for assessing the added benefit of axicabtagene ciloleucel in comparison with the ACT for multiple reasons. For the Bachy 2022 study presented by the company as primary evidence regarding the comparison of axicabtagene ciloleucel versus tisagenlecleucel, basic information on the study design and statistical methodology as well as on the search for and selection of confounders taken into account is missing. The single-arm ZUMA-1 study primarily used by the company does not enable a comparison versus the ACT. In addition, the analyses presented by the company from the Bachy 2022 study, the metaanalysis from published registry data, and the EUPAS32539 study include only patients who actually received a CAR T-cell infusion, thereby violating the ITT principle. In addition, except for some specific AEs, no complete recording of AEs took place in these 3 studies, rendering an assessment of benefits versus harms impossible for these studies.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of axicabtagene ciloleucel in comparison with the ACT for either of the research questions; an added benefit is therefore not proven.

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

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

[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: Axicabtagene ciloleucel – 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 and PMBCL after 2 or more lines of systemic therapy who are candidates for high-dose therapy[b]	Treatment of physician's choice, taking into account[c,d]: ▪ tisagenlecleucel (only for people with DLBCL), ▪ induction therapy with MINE followed by high-dose therapy with autologous stem cell transplantation, provided there was a response to induction therapy, ▪ induction therapy with MINE followed by high-dose therapy with allogeneic stem cell transplantation, provided there was a response to induction therapy	Added benefit not proven
2	Adults with relapsed or refractory DLBCL and PMBCL after 2 or more systemic therapies who are not candidates for high-dose therapy	Treatment of physician's choice, taking into account[d]: ▪ CEOP, ▪ dose-adjusted EPOCH, ▪ polatuzumab vedotin + bendamustine + rituximab (only for people with DLBCL), ▪ tafasitamab + lenalidomide (only for people with DLBCL), ▪ pixantron monotherapy, ▪ radiotherapy, ▪ BSC	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Patients are presumed to be eligible for high-dose therapy with curative intent.
c. When selecting therapy options, the patient's previous therapy with CAR T-cell therapy, autologous stem cell transplantation, or allogeneic stem cell transplantation must be taken into account. 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. The available guidelines and scientific medical societies and/or the Drug Commission of the German Medical Association in accordance with § 35a (7) sentence 4 SGB V list unapproved drug therapies for the treatment of recurrent/refractory DLBCL/PMBCL after ≥ 2 prior therapies. According to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not deemed ACTs in the narrower sense of § 2 (1) sentence 3, § 12 SGB V.

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; CAR: chimeric antigen receptor; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; G-BA: Federal Joint Committee; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; SGB: Social Code Book

The G-BA decides on the added benefit.

Supplementary note

The results of the assessment deviate from the results of the G-BA assessment conducted in the context of market launch in 2018 and the assessment after expiry of the term in 2022. In said assessments, the G-BA had determined a non-quantifiable added benefit of axicabtagene ciloleucel. However, due to the orphan drug status, the added benefit in these assessments had been deemed as proven by way of approval irrespective of the underlying data.

I 2 Research question

The aim of this report is to assess the added benefit of axicabtagene ciloleucel compared with the ACT in adult patients with relapsed or refractory DLBCL and PMBCL after 2 or more systemic therapies.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of axicabtagene ciloleucel

Research question	Therapeutic indication	ACT[a]
1	Adults with relapsed or refractory DLBCL and PMBCL after 2 or more lines of systemic therapy who are candidates for high-dose therapy[b]	Treatment of physician's choice, taking into account[c,d]: ▪ tisagenlecleucel (only for people with DLBCL), ▪ induction therapy with MINE followed by high-dose therapy with autologous stem cell transplantation, provided there was a response to induction therapy, ▪ induction therapy with MINE followed by high-dose therapy with allogeneic stem cell transplantation, provided there was a response to induction therapy
2	Adults with relapsed or refractory DLBCL and PMBCL after 2 or more systemic therapies who are not candidates for high-dose therapy	Treatment of physician's choice, taking into account[d]: ▪ CEOP, ▪ dose-adjusted EPOCH, ▪ polatuzumab vedotin + bendamustine + rituximab (only for people with DLBCL), ▪ tafasitamab + lenalidomide (only for people with DLBCL), ▪ pixantron monotherapy, ▪ radiotherapy, ▪ BSC

a. Presented is the respective ACT specified by the G-BA.
b. Patients are presumed to be eligible for high-dose therapy with curative intent.
c. When selecting therapy options, the patient's previous therapy with CAR T-cell therapy, autologous stem cell transplantation, or allogeneic stem cell transplantation must be taken into account. 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. The available guidelines and scientific medical societies and/or the Drug Commission of the German Medical Association in accordance with § 35a (7) sentence 4 SGB V list unapproved drug therapies for the treatment of recurrent/refractory DLBCL/PMBCL after ≥ 2 prior therapies. According to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not deemed ACTs in the narrower sense of § 2 (1) sentence 3, § 12 SGB V.

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; CAR: chimeric antigen receptor; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; G-BA: Federal Joint Committee; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; SGB: Social Code Book

In the context of its specification of the ACT, the G-BA points out that both approved and unapproved drug therapies for relapsed or refractory DLBCL and PMBCL after 2 or more systemic therapies are mentioned in the available guidelines or by scientific medical societies and/or the Drug Commission of the German Medical Association according to § 35a (7) sentence 4 SGB V. According to the BSG comments on the judgement dated 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not taken into account as ACTs in the narrower sense of § 2 (1) sentence 3, § 12 SGB V.

Deviating from the ACT specified in Table 4, Module 3A of the company's dossier lists the ACT for the entire approval population – without differentiating between the 2 research questions – as individualized therapy taking into account the biology of the disease, prior therapies, the course of the disease, and the patient's general condition, with the comparators of CAR T-cell therapy (tisagenlecleucel and lisocabtagene maraleucel) and autologous or allogeneic stem cell transplantation. The company did not take into account any other treatment options because, in contrast to CAR T-cells and stem cell transplantation, they did not represent treatment strategies with a primarily curative intent as per S3 guideline [3].

The present assessment was conducted on the basis of the research questions specified by the G-BA (in terms of populations and corresponding ACTs). The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

Since no usable data are available for any of the research questions named by the G-BA, the 2 research questions are assessed together below in a joint part of the report (see Chapters I 3 to I 5).

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 axicabtagene ciloleucel (status: 3 April 2023)
- bibliographical literature search on axicabtagene ciloleucel (last search on 3 April 2023)
- search in trial registries / trial results databases for studies on axicabtagene ciloleucel (last search on 3 April 2023)
- search on the G-BA website for axicabtagene ciloleucel (last search on 3 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on axicabtagene ciloleucel (last search on 12 July 2023); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

Concurring with the company, the check of completeness of the study pool produced no RCTs directly comparing axicabtagene ciloleucel versus the ACT.

Further investigations

Since the company did not identify any studies for a direct comparison, it conducted an information retrieval on further investigations with axicabtagene ciloleucel, which identified the single-arm pivotal ZUMA-1 study [4].

The company did not obtain any information on further investigations with the ACT but cited the study SCHOLAR-1 [5], which it sponsored but ended up not using for the benefit assessment. In addition, the company used the Bachy 2022 study [6] to derive added benefit.

A check for completeness of the study pool for other investigations was foregone because the data submitted by the company under further investigations are unsuitable for assessing the benefit of axicabtagene ciloleucel in comparison with the ACT. However, the dossier already suggests that the company's study pool for other investigations is potentially incomplete. This is explained below.

Implausible information retrieval of the evidence presented in the dossier

For its information retrieval on further investigations with axicabtagene ciloleucel, the company reportedly excluded retrospective studies. However, the Bachy 2022 study, which the company included and subsequently used as primary evidence for its benefit assessment (see Section I 3.1.1.1), is a retrospective study on the efficacy and safety of axicabtagene

ciloleucel and tisagenlecleucel based on data from the French registry for CAR T-cell therapies (Dispositif d'Enregistrement et Suivi des patients traités par CAR T-cells [DESCAR-T]). The information retrieval described in the dossier fails to clarify how the company found this study.

In Module 4A, the company describes its information retrieval for further investigations on axicabtagene ciloleucel but does not provide any information on the information retrieval for further investigations on the ACT. Hence, it remains unclear on what basis studies on the ACT were identified and included. Hence, it is unclear whether the study pool for the ACT is complete.

Overall, the information retrieval for the evidence presented in the dossier is not plausible.

Implausible exclusion of the JapicCTI-183914 study

During the check for completeness of the company's study pool for axicabtagene ciloleucel, the JapicCTI-183914 study [7] was identified.

The JapicCTI-183914 study is a single-arm, multicentre, open-label phase II study evaluating the efficacy and safety of axicabtagene ciloleucel in patients from Japan. Module 4A shows that the company identified the JapicCTI-183914 study in study registries during its search for further investigations with the drug to be assessed but excluded it, citing the wrong patient population, lack of transferability of the study results, and incorrect publication type. The information available in the primary publication Kato 2022 [8] reveals that the JapicCTI-183914 study and the ZUMA-1 pivotal study used by the company (see Section I 3.1.1.2) share comparable characteristics. The JapicCTI-183914 study included patients in the present therapeutic indication. Although the information on the intervention is limited, there is no evidence of any use suggesting a departure from the Summary of Product Characteristics (SPC) [9]. Thus, the company's reasoning for excluding the study is not plausible, irrespective of whether the JapicCTI-183914 study would end up being suitable for assessing added benefit. Since overall, the company failed to present any suitable data for deriving added benefit versus the ACT, however, this remained without consequence.

Conclusion on the company's information retrieval

In summary, the company's study pool is potentially incomplete due to (a) the failure to search for further investigations with the ACT, (b) incomplete documentation of the search conducted as well as (c) implausible selection of the included studies. Irrespective of these shortcomings, the data presented by the company were unsuitable for drawing conclusions on the added benefit of axicabtagene ciloleucel in comparison with the ACT. This is justified below.

I 3.1 Presentation and assessment of the evidence presented by the company

In Section 4.2.5.1 of the dossier's Module 4A, the company reports including the studies ZUMA-1, Bachy 2022, and SCHOLAR-1 in its assessment. Among these, the company uses the results from the Bachy 2022 and ZUMA-1 studies as primary evidence. As supporting evidence, the company presents results from a metaanalysis of published registry studies [10] for a comparison of axicabtagene ciloleucel versus tisagenlecleucel and descriptive data from the EUPAS32539 study [11] on response and selected AEs after treatment with axicabtagene ciloleucel from the current report of the EBMT registry. The company did not present any studies comparing to treatment of physician's choice.

The SCHOLAR-1 study has already been submitted by the company as part of the European authorization [12] and the orphan drug assessments (procedure numbers of the G-BA 2018-11-01-D-406, 2018-11-01-D-416 and 2022-05-15-D-820) [13-15] and used for a comparison of individual arms from different studies. The company refrained from reexamining the SCHOLAR-1 study in the present dossier because the study reportedly no longer adequately depicts the appropriate therapy due to major changes in the healthcare context. The company's approach of excluding the SCHOLAR-1 study is appropriate. The healthcare context in the therapeutic indication to be assessed has changed due to the approval of newer treatment options such as tafasitamab, polatuzumab vedotin, and CAR T-cells, which were not available to the patients included in the SCHOLAR-1 study (see also underlying reasons [16] on the benefit assessment procedure [G-BA procedure number 2022-05-15-D-820]). The SCHOLAR-1 study is therefore disregarded below.

Because of several aspects, the data presented by the company are unsuitable for the benefit assessment of axicabtagene ciloleucel in comparison with the ACT. This is justified below.

Table 6 of the full dossier assessment provides an overview of the evidence presented by the company and the main points of criticism that led to its disregard.

I 3.1.1 Primary evidence used by the company

I 3.1.1.1 Bachy 2022 study

The Bachy 2022 study used by the company as primary evidence is a retrospective analysis of data from the French DESCAR-T registry to compare axicabtagene ciloleucel with tisagenlecleucel in propensity score-adjusted populations. The company is not the sponsor of the study and bases the results presented in the dossier on the publication of the study [6] as well as the protocol [17] of the DESCAR-T registry (version 6.0 dated 30 November 2021), whose sponsor is the Lymphoma Academic Research Organisation (LYSARC).

DESCAR-T registry

The French DESCAR-T registry was set up to answer healthcare questions raised by CAR T-cell therapies and their use in routine medical care. It is also intended to provide additional data for health authorities if required.

Patients can be included in the DESCAR-T registry both retrospectively and prospectively. Patients who had been treated with CAR T-cells before the registry was set up on 1 July 2018 are included retrospectively. Patients for whom the suitability or therapeutic indication of CAR T-cell therapy is determined or who are being treated as part of a clinical trial in a therapeutic indication covered by the registry are prospectively included.

According to the registry protocol, the primary outcome is overall survival, defined as the time from determination of eligibility for CAR T-cell therapy to death. Secondary outcomes include response, overall survival following CAR T-cell infusion, progression-free survival (PFS), health-related quality of life, and AEs. All included patients are to be followed for 15 years, regardless of whether they receive CAR T-cell therapy.

According to the DESCAR-T registry protocol, an SAP and annual reports are to be drawn up. However, the dossier does not include an SAP or a current study report.

Study characteristics and design of the Bachy 2022 study

The retrospective Bachy 2022 study included patients with DLBCL and at least 2 prior systemic therapies who were treated with axicabtagene ciloleucel or tisagenlecleucel between December 2019 and October 2021 and were entered in the DESCAR-T registry.

The primary outcome was PFS following CAR T-cell infusion. Secondary outcomes included overall survival following infusion, response, and specific AEs (haematological toxicity, CRS, and ICANS).

The Bachy 2022 study included 809 patients with DLBCL and at least 2 prior systemic therapies from the DESCAR-T registry who were determined to be eligible for CAR T-cell therapy and for whom axicabtagene ciloleucel (n = 494) or tisagenlecleucel (n = 315) was ordered. Of these patients, 80 received no infusion, whereas 729 patients received an infusion with a CAR T-cell (axicabtagene ciloleucel [n = 452] or tisagenlecleucel [n = 277]). The most common reasons for not administering an infusion were progression of the disease or death (n = 60). After exclusion of patients with PMBCL (n = 34) and > 25% missing values (n = 23), 672 infused patients (axicabtagene ciloleucel [n = 419] and tisagenlecleucel [n = 253]) remained, which were used for 1:1 matching using propensity score adjustment. For the adjustment, 14 possible confounders were taken into account, resulting in a 1:1 matched population of 418 patients.

The Bachy 2022 study provides results for all outcomes for the 1:1 propensity score-matched population. In addition, IPTW analyses were conducted for all efficacy outcomes, taking into account the same 14 confounders. Further, propensity score and IPTW analyses are available for the outcomes of overall survival following infusion, PFS following infusion, and DOR for patients without missing values (complete case analysis [N = 348]) as well as propensity score and IPTW analyses for the outcome overall survival following CAR T-cell order.

The data cutoff date for the analyses was 18 October 2021. The median observation period was 11.7 months.

Data submitted by the company from the Bachy 2022 study

In Module 4A, the company presents analyses from the Bachy 2022 study on the outcomes of overall survival following infusion, PFS following infusion, ORR, DOR, and specific AEs (haematological toxicity, CRS, and ICANS) for the 1:1 propensity score-matched population. Additionally, the company analyses the outcome of overall survival following CAR T-cell order from the Bachy 2022 study. As in Bachy 2022, no effect estimator (e.g. in the form of a hazard ratio) is reported for this analysis. Neither the IPTW analyses nor the complete-case analyses found in the Bachy 2022 publication were submitted.

Irrespective of the suitability of the DESCAR-T registry for conducting a meaningful registry study, the data presented by the company from the Bachy 2022 study are unsuitable for assessing the added benefit of axicabtagene ciloleucel versus the ACT in patients with DLBCL and PMBCL after 2 or more systemic therapies. This is justified below.

Bachy 2022 study permits no conclusions on added benefit

The Bachy 2022 study used by the company is a retrospective study for which no documents on study design or statistical analyses in the form of a study protocol or an SAP are available, except for a methodological description in the publication. However, these are necessary even if nonrandomized comparisons are based on already existing data. It therefore remains unclear to what extent the presented analyses were predefined and/or whether any other analyses had been planned.

Irrespective of the uncertainties regarding the study design, the Bachy 2022 study provides results only on overall survival and on individual specific AEs as patient-relevant outcomes, rendering an exhaustive weighing of benefits versus harms impossible based on the results of the Bachy 2022 study. Additionally, the Bachy 2022 study is unsuitable for deriving added benefit for the reasons discussed below.

No information on the identification of potential confounders

Since structural equivalence between treatment groups is not necessarily ensured in in non-randomized studies, the estimation of the treatment effect must take into account any

between-group differences in potential confounders, i.e. factors which are related to both the treatment and outcomes and might thus alter the estimation. This requires, first, that relevant confounders are systematically identified (e.g. on the basis of scientific literature in consultation with experts) and prespecified in the study protocol [18] (for an exemplary procedure, see Pufulete 2022 [19]). The Bachy 2022 study does not describe a systematic identification of potentially relevant confounders, nor does it justify the selection of confounders taken into account for the propensity score adjustment and IPTW analysis. The company's Module 4A likewise does not provide any further information on the search for and selection of the confounders. Based on the information available on the Bachy 2022 study, it is also impossible to assess the extent to which the selection of confounders was prespecified or, since the DESCAR-T registry dataset did not record them sufficiently or at al, potentially relevant confounders were disregarded.

Unsuitable analysis strategy

For CAR T-cell therapy, the patient's own T-cells are removed by means of leukapheresis and then genetically modified before they can be infused into the patient. In the interval between the treatment decision and the infusion, the disease may worsen, bridging therapies may be necessary, and patients may die while "waiting". In the Bachy 2022 study, for example, 80 of the 809 patients who were intended to receive CAR T-cell therapy did not receive an infusion of axicabtagene ciloleucel or tisagenlecleucel. The main reason was progression of disease or the death of patients. In contrast to the DESCAR-T registry protocol, according to which all patients are to be observed from the time of the treatment decision, the Bachy 2022 study observed all outcomes from the time of infusion. This means that the ITT principle is violated in the analyses of the Bachy 2022 study. One exception is the overall survival outcome, for which additional analyses are available from the time the CAR T-cells were ordered. However, no effect estimator is reported for this. In addition, no further information on patient characteristics or after adjustment is available for this population.

Unclear assignment of the included patients to the research questions

Less than 25% of the Bachy 2022 participants had prior stem cell transplantation. No information is available on whether they received an autologous or allogeneic stem cell transplant. Prior to the approval of CAR T-cells, autologous stem cell transplantation was the standard second-line therapy for patients with DLBCL who were eligible for high-dose therapy [3]. Consequently, > 75% of the patients in the Bachy 2022 study were either (a) patients whose disease did not respond to induction therapy and therefore did not receive autologous stem cell therapy despite being eligible for high-dose therapy (research question 1), or (b) patients for whom high-dose therapy is not an option (research question 2). Based on the available information and in the absence of specific inclusion and exclusion criteria, it is therefore impossible to adequately allocate the patients included in the Bachy 2022 study to the appropriate research questions.

I 3.1.1.2 ZUMA-1 study

ZUMA-1 is a single-arm phase 1/2 study on treatment with axicabtagene ciloleucel which enrolled adult patients with refractory DLBCL, PMBCL, or tFL after ≥ 1 line of chemotherapy, including an anti-CD20 antibody and an anthracycline or a recurrence ≤ 12 months after autologous stem cell transplantation.

In phase 1 of the ZUMA-1 study, different regimens of LDC with various CAR T-cell doses were tested to determine dose-limiting toxicity. Phase 2 of the study comprises a total of 6 cohorts, with cohorts 1 and 2 representing the pivotal cohorts of the study. In cohorts 3 to 6, treatment was not in line with the specifications of the SPC [9]. Thus, only the pivotal cohorts 1 and 2 of the ZUMA-1 study are potentially relevant for the present research question.

In cohorts 1 and 2 of the study, patients received 1 intravenous target dose of 2×10^6 viable CAR T-cells/kg body weight or a maximum dose of 2×10^8 viable CAR T-cells from a body weight of 100 kg. Bridging therapy in the period between leukapheresis and infusion of CAR T-cells was disallowed in cohorts 1 and 2. In phase 2 of the ZUMA-1 study, a total of 111 patients were included in either cohort 1 (DLBCL; n = 81) or cohort 2 (PMBCL or tFL; n = 30) depending on their disease subentity. Of these patients, 101 actually received treatment with axicabtagene ciloleucel (cohort 1: n = 77; cohort 2: n = 24).

After the axicabtagene ciloleucel infusion, patients were followed up for periods of up to 15 years.

The primary outcome of the study was ORR; secondary outcomes included overall survival, PFS and AEs.

Further details on the ZUMA-1 study can also be found in benefit assessment A22-90 [20] and the information in the benefit assessment procedure for axicabtagene ciloleucel (procedure number of the G-BA 2022-05-15-D-820) [15].

Data cutoffs

According to the company, 6 data cutoffs are available for the ZUMA-1 study:

- data cutoff 1: 27 January 2017 (primary data cutoff)
- data cutoff 2: 11 August 2017 (data cutoff subsequently presented in the course of the approval procedure)
- data cutoff 3: 11 August 2018 (unplanned interim data cutoff)
- data cutoff 4: 11 August 2019 (unplanned interim data cutoff)
- data cutoff 5: 11 August 2020 (unplanned interim data cutoff)

- data cutoff 6: 11 August 2021 (unplanned interim data cutoff)

Data cutoffs 3 to 6 were not prespecified and were carried out as part of annual safety update reports and interim reports every 5 years as required by the European Medicines Agency (EMA).

Presented results

In Module 4A of the dossier, the company presents analyses on overall survival, PFS, and response for the 11 August 2018 data cutoff and additionally for the 11 August 2021 data cutoff for both the ITT population (N = 111) and the modified ITT population (mITT), which comprises all patients who received an infusion with axicabtagene ciloleucel (N = 101). For AE outcomes, the company presents analyses only from the 11 August 2018 data cutoff.

Uncontrolled ZUMA-1 study permits no conclusions on added benefit

The company presents the results of the uncontrolled ZUMA-1 study and conducts descriptive analyses of the results. The results from the ZUMA-1 study alone are unsuitable for assessing the added benefit of axicabtagene ciloleucel in comparison with the ACT because they do not allow a comparison with the ACT. In addition, in pivotal cohorts 1 and 2 of the ZUMA-1 study, bridging therapy was not permitted in the period between leukapheresis and infusion of CAR T-cells. As per S3 guideline, in the treatment of a second or later relapse, the time until CAR T-cells can be administered must be bridged ideally without further progression of the underlying disease, and bridging therapy should be offered to induce remission [3]. The prohibition of bridging therapy limits the transferability of the results from the ZUMA-1 study to the German healthcare context.

I 3.1.2 Evidence used as supplementary information by the company

In Module 4A, the company presented as supplementary evidence a comparison of axicabtagene ciloleucel versus tisagenlecleucel from a metaanalysis [10] of published registry data and additional data on the efficacy and safety of axicabtagene ciloleucel from the report [11] on the EUPAS32539 study.

I 3.1.2.1 Metaanalysis from published registry data

For the metaanalysis of published registry studies presented by the company, a bibliographic literature search was conducted in the Embase and MEDLINE databases (search conducted on 21 July 2022). English-language publications from 2017 onwards on prospective and retrospective observational studies with patients with large B-cell lymphoma (LBCL) who had been treated with CAR T-cells (axicabtagene ciloleucel, tisagenlecleucel, or lisocabtagene maraleucel) were included. The studies were allowed to have either no comparator or CAR T-cells as comparator and had to include results on efficacy and/or safety outcome results. Publications on patients in clinical studies, RCTs, case studies, case reports, and publications

with a population size < 10 patients were excluded. A manual search was also carried out for 15 conferences.

After excluding publications reporting either results on interventions other than axicabtagene ciloleucel or tisagenlecleucel or no comparative quantitative results on these 2 interventions, 14 patient cohorts were found for a comparison of axicabtagene ciloleucel versus tisagenlecleucel.

Regarding the subsequent metaanalysis of published registry studies, the company stated that it took into account only the results from individual large studies. These include studies on the following registries: Centre for International Blood and Marrow Transplant Research (CIBMTR) from the United States, DESCAR-T from France, Grupo Español de Linfomas y Trasplantes de Médula Ósea / Grupo Español de Trasplante Hematopoyético y Terapia Celular (GELTAMO / GETH) from Spain, German Lymphoma Alliance / Deutsches Register für Stammzelltransplantation (GLA / DRST) from Germany, Societa Italiana di Ematologia (SIE) from Italy, and UK10 from the United Kingdom.

Presented results

The company presents metaanalytically summarized results from adjusted and unadjusted analyses on the outcomes of response, overall survival, PFS, CRS, and neurotoxicity for a comparison of axicabtagene ciloleucel versus tisagenlecleucel. The company then compares these results separately for each of the 2 drugs versus the results from the respective approval studies ZUMA-1 (axicabtagene ciloleucel) and JULIET (tisagenlecleucel) in descriptive form.

Reasons for the exclusion of data from the metaanalysis of published registry studies

The company's dossier presents only the final analyses and aggregated data from the studies included in the metaanalysis for selected registries. The company's Module 4 A does not state its reasons for taking into account these studies, other than their size. In addition, the analyses presented by the company do not include the SIE registry from Italy. The company fails to provide a reason for this as well. The company did not provide a list of the study publications taken into account for the individual analyses. With the exception of the publications on the DESCAR-T (Bachy 2022) and GLA/DRST (Bethge 2022 [21]) registers, the underlying full texts for the included studies were not included in the dossier. The metaanalyses presented by the company contained data from adjusted and unadjusted comparisons. Irrespective of a further methodological review including the adjustment methods (for Bachy 2022, see Section I 3.1.1.1), the analyses presented by the company are already unsuitable for the reasons discussed below.

Apart from the specific AEs of CRS and neurotoxicity, the metaanalysis does not report results for any other AE outcomes, rendering a complete assessment of benefits versus harms impossible.

In addition, the available information clearly shows that the included studies provide data only on patients who were infused with CAR T-cells. This means that the ITT principle has been violated. Due to the lack of information, it is also impossible to conclusively assess whether all patients fall under the therapeutic indication (DLBCL or PMBCL from third line) and to which research question the included patients can be allocated.

The information retrieval to identify the potentially relevant studies for the metaanalysis likewise suffers from shortcomings which call into question the completeness of the study pool. For example, no study registries were taken into account for the search, and the last search was conducted on 21 July 2022, which is longer ago than the 3 months specified in the dossier template [22]. The search was limited to publications published from 2017 onwards and was only conducted for CAR T-cells and not for the ACT. Furthermore, the information provided in the dossier fails to clarify how the company identified the JULIET study, which it ultimately used for the descriptive comparison of the data from the metaanalysis.

I 3.1.2.2 EUPAS32539 study

The EUPAS32539 study was set up as a condition of the European marketing authorization with the aim of collecting long-term data on the safety of axicabtagene ciloleucel. The EUPAS32539 study is a multicentre observational study in patients with relapsed or refractory DLBCL or PMBCL after 2 or more lines of systemic therapy and patients with relapsed or refractory follicular lymphoma after 3 or more lines of systemic therapy who are treated with axicabtagene ciloleucel in routine care. Primary outcomes are the occurrence, type, and location of secondary tumours as well as specific AEs. Secondary outcomes include overall survival, time to next therapy, and time to relapse/progression.

The data for the EUPAS32539 study originate from the EBMT registry, which records all patients who are treated with axicabtagene ciloleucel in qualified European centres and who have given informed consent, regardless of whether axicabtagene ciloleucel treatment is in line with the marketing authorization. Patient enrolment can begin up to 1 week before or at any time after an infusion of axicabtagene ciloleucel. Patients are then to be followed up for 15 years. The plan is to prepare a report on the primary and secondary outcomes annually in the first 5 years of the study and every 2 years thereafter.

Presented results

In Module 4 A, the company presents results from the interim report of the EBMT registry for the 1 March 2023 data cutoff. At the time of data cutoff, 979 patients with DLBCL and PMBCL had received an infusion of axicabtagene ciloleucel after at least 2 or more systemic therapies. The report contains analyses of 773 patients for whom a follow-up form was available on Day 100. The company presents descriptive results from these analyses on the outcomes of response and specific AEs (CRS and neurotoxicity).

Reasons for the exclusion of data from the EUPAS32539 study

Since they do not allow a comparison with the ACT, the results from the retrospective EUPAS32539 study alone are unsuitable for assessing the added benefit of axicabtagene ciloleucel versus the ACT. The survey of AEs is limited to a few specific AEs and therefore does not allow a complete weighing of benefits and harms. Patients are observed starting only from the infusion of axicabtagene ciloleucel rather than from the decision to treat, thereby violating the ITT principle. In addition, the EBMT registry report does not include an analysis of all patients treated with axicabtagene ciloleucel. Of the 979 patients who received an infusion of axicabtagene ciloleucel, 773 patients (79%) for whom a Day 100 follow-up form was available were analysed. The study documents show that this form was not available for the remaining 206 patients due to missing information on complications and/or toxicity. For 374 patients (38%), information on the administration of axicabtagene ciloleucel in accordance with the marketing authorization is also missing. The analyses of the EUPAS32539 study are therefore subject to several uncertainties. In addition, the company presents the results of the EUPAS32539 study only descriptively and uses them only as supplementary information.

Conclusion

In summary, the studies presented by the company are unsuitable for assessing the added benefit of axicabtagene ciloleucel in comparison with the ACT for multiple reasons. The company presented the Bachy 2022 study as primary evidence for the comparison of axicabtagene ciloleucel versus tisagenlecleucel. Yet basic information on the study design and statistical methodology as well as on the search for and selection of confounders taken into account is missing. The single-arm ZUMA-1 study primarily used by the company does not permit a comparison versus the ACT. In addition, the analyses presented by the company from the Bachy 2022 study, the metaanalysis from published registry data, and the EUPAS32539 study only include patients who received an infusion with CAR T-cells, thereby violating the ITT principle. In addition, except for some specific AEs, no complete recording of AEs took place in these 3 studies, rendering an assessment of benefits versus harms impossible for these studies.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of axicabtagene ciloleucel compared with the ACT for the treatment of relapsed or refractory DLBCL and PMBCL in adults after 2 or more systemic therapies. There is no hint of added benefit of axicabtagene ciloleucel in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for axicabtagene ciloleucel in comparison with the ACT.

Table 5: Axicabtagene ciloleucel – 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 and PMBCL after 2 or more lines of systemic therapy who are candidates for high-dose therapy[b]	Treatment of physician's choice, taking into account[c,d]: ▪ tisagenlecleucel (only for people with DLBCL), ▪ induction therapy with MINE followed by high-dose therapy with autologous stem cell transplantation, provided there was a response to induction therapy, ▪ induction therapy with MINE followed by high-dose therapy with allogeneic stem cell transplantation, provided there was a response to induction therapy	Added benefit not proven
2	Adults with relapsed or refractory DLBCL and PMBCL after 2 or more systemic therapies who are not candidates for high-dose therapy	Treatment of physician's choice, taking into account[d]: ▪ CEOP, ▪ dose-adjusted EPOCH, ▪ polatuzumab vedotin + bendamustine + rituximab (only for people with DLBCL), ▪ tafasitamab + lenalidomide (only for people with DLBCL), ▪ pixantron monotherapy, ▪ radiotherapy, ▪ BSC	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Patients are presumed to be eligible for high-dose therapy with curative intent.
c. When selecting therapy options, the patient's previous therapy with CAR T-cell therapy, autologous stem cell transplantation, or allogeneic stem cell transplantation must be taken into account. 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. The available guidelines and scientific medical societies and/or the Drug Commission of the German Medical Association in accordance with § 35a (7) sentence 4 SGB V list unapproved drug therapies for the treatment of recurrent/refractory DLBCL/PMBCL after ≥ 2 prior therapies. According to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not deemed ACTs in the narrower sense of § 2 (1) sentence 3, § 12 SGB V.

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; CAR: chimeric antigen receptor; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; G-BA: Federal Joint Committee; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; SGB: Social Code Book

The assessment described above departs from that by the company, which derived a hint of considerable added benefit for the entire therapeutic indication of axicabtagene ciloleucel, irrespective of the research questions.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in connection with the market launch in 2018 and the assessment after expiry of the term in 2022. In said assessment, the G-BA had determined a non-quantifiable added benefit of axicabtagene ciloleucel. However, due to the special situation for orphan drugs, the added benefit in that assessment had been regarded as proven by way of approval irrespective of the underlying data.

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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