Axicabtagene ciloleucel (DLBCL and HGBL, second line)

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 patient organization Leukämie und Lymphom SHG Ruhr-Lippe e. V. (Leukaemia and Lymphoma Self-Help Group Ruhr-Lippe) for participating in the written exchange about disease experience, treatment experience and treatment goals. The respondent and the patient organization 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
AE	adverse event
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)
CD	cluster of differentiation
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HDCT	high-dose chemotherapy
HGBL	high-grade B-cell lymphoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MINE	mesna, ifosfamide, mitoxantrone and etoposide
MMRM	mixed-effects model with repeated measures
PR	partial response
PT	Preferred Term
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
R-ESHAP	rituximab, etoposide, methylprednisolone, cytarabine, cisplatin
R-GDP	rituximab, dexamethasone, gemcitabine, cisplatin
R-ICE	rituximab, ifosfamide, etoposide, carboplatin
RCT	randomized controlled trial
sAAIPI	second-line age-adjusted International Prognostic Index
SAE	serious adverse event
SCT	stem cell transplantation
SD	stable disease
SGB	Sozialgesetzbuch (Social Code Book)

Abbreviation	Meaning
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SPC	Summary of Product Characteristics
VAS	visual analogue scale
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug 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 30 June 2023. Irrespective of the research question of the aforementioned commission, the G-BA commissioned IQWiG with the analysis and presentation (methodological review and presentation of the results) of the ZUMA-7 study.

Research question

The aim of the present report is the assessment of the added benefit of axicabtagene ciloleucel in comparison with the appropriate comparator therapy (ACT) in adult patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

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

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

Research question	Therapeutic indication	ACT[a]
Adults with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom		
1	high-dose therapy is an option[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy
2	high-dose therapy is not an option[d]	Treatment of physician's choice[e], taking into account ▪ pola-BR[f] ▪ tafasitamab + lenalidomide[f]

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research question 2). Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
c. In the line of treatment, allogeneic stem cell transplantation is an option in patients who have a very high risk of relapse or in whom sufficient stem cell collection for autologous stem cell transplantation was not possible.
d. Patients are assumed to be not eligible for high-dose therapy and to generally continue antineoplastic treatment after first-line immunotherapy.
e. A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
f. The approval of pola-BR and tafasitamab + lenalidomide relates exclusively to DLBCL (approval of 2020/2021). With the updated WHO classification of 2022, HGBL was newly listed as a definite entity. Prior to this update, aggressive lymphomas with MYC and BCL2/6 rearrangements were classified as DLBCL, so that HGBL was not specified separately in the therapeutic indication at the time of approval of pola-BR and tafasitamab + lenalidomide. Therefore, specifying these treatment options for both DLBCL and HGBL is considered appropriate.

ACT: appropriate comparator therapy; BSG: Federal Social Court; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; MINE: combination therapy of mesna, ifosfamide, mitoxantrone and etoposide; pola-BR: polatuzumab in combination with bendamustine and rituximab; SGB: Social Code Book; WHO: World Health Organization

Regarding the determination of the ACT for both research questions, the G-BA pointed out that the present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) or treatment (research question 2) in adults with DLBCL or HGBL, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy, and for whom high-dose chemotherapy (HDCT) is an option or not an option. In addition, the G-BA pointed out

for all research questions that drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

For research question 1, the company followed the G-BA's specification of HDCT with autologous or allogeneic stem cell transplantation (SCT) as ACT in the case of response to induction therapy, but deviated from the specified induction therapies and instead specified an induction therapy of physician's choice. For research question 2, the company followed the G-BA's specification of treatment of physician's choice as ACT, but did not limit the selection of therapies to the 2 drug combinations specified by the G-BA, and cited additional options instead.

The approach of the company is not followed. The present assessment is conducted for the research questions listed in Table 2.

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

Research question 1: patients for whom high-dose therapy is an option

Study pool and study design

The ZUMA-7 study is used for the comparison of axicabtagene ciloleucel versus induction therapy followed by HDCT with autologous SCT if there is a response to induction therapy (hereinafter referred to as "induction + HDCT + autologous SCT").

The ZUMA-7 study is an ongoing, open-label, multicentre RCT comparing axicabtagene ciloleucel versus induction + HDCT + autologous SCT in adult patients with DLBCL or HGBL according to the 2016 World Health Organization (WHO) classification.

Patients had to have refractory or relapsed disease within 12 months after first-line chemoimmunotherapy including an anti-cluster of differentiation 20 (CD20) monoclonal antibody (except in CD20-negative tumours) and an anthracycline. It also had to be intended to proceed to HDCT and autologous SCT if patients responded to induction therapy. Patients had to be in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and have adequate organ function and radiographically documented disease. Patients with previous SCT, brain metastases or tumour cells in the cerebrospinal fluid, as well as all patients who had received > 1 line of therapy for DLBCL were excluded from the study.

A total of 359 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with axicabtagene ciloleucel (N = 180) or to induction + HDCT + autologous SCT (N = 179).

Axicabtagene ciloleucel treatment was administered in compliance with the Summary of Product Characteristics (SPC) [1]. If needed, patients could receive bridging therapy with corticosteroids at the discretion of the investigator in the period between leukapheresis and lymphodepletion.

In the comparator arm, patients initially received induction therapy with 2 to 3 cycles of R-ICE (rituximab, ifosfamide, etoposide, carboplatin), R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, cisplatin [or oxaliplatin]) or R-GDP (rituximab, dexamethasone, gemcitabine, cisplatin [or carboplatin]) at the discretion of the investigator. Patients who achieved a partial or complete response (PR or CR) by the Lugano Classification after 2 to 3 cycles of induction therapy (approximately on Day 50) received subsequent HDCT and autologous SCT.

The primary outcome of the ZUMA-7 study was event-free survival (EFS) per blinded central review, operationalized as the time from randomization to death, disease progression, failure to achieve CR or PR by Day 150 after randomization, or commencement of new lymphoma therapy. Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects.

Limitations of the study – bridging therapies

CAR T-cell therapy is a multi-stage process starting with leukapheresis and genetic modification of the T-cells. The production of CAR T-cells takes several weeks. According to the S3 guideline of the German Association of the Scientific Medical Societies (AWMF), various bridging therapy options should be offered during the waiting period for CAR T-cells to induce remission. In general, these are chemoimmunotherapies, but targeted substances or radiotherapy are also possible. In the ZUMA-7 study, however, corticosteroids were the only permitted bridging therapy, which was used in 36% of patients in the intervention arm. The restriction of bridging therapy to corticosteroids in the ZUMA-7 study is not appropriate and does not adequately reflect the health care context. This therefore represents a relevant limitation of the ZUMA-7 study.

Implementation of the appropriate comparator therapy

The G-BA defined induction therapy with mesna, ifosfamide, mitoxantrone and etoposide (MINE), followed by HDCT with autologous or allogeneic SCT in case of response to induction therapy, as ACT for axicabtagene ciloleucel for the treatment of adults with DLBCL or HGBL, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy, and who are eligible for HDCT. The ACT therefore consists of several

components: induction therapy, HDCT, and SCT. The regimen used in the comparator arm of the ZUMA-7 study differs from the G-BA's ACT with regard to the induction therapy (R-DHAP, R-ICE, R-ESHAP or R-GDP instead of MINE), but not with regard to the HDCT and the SCT.

Rituximab and platinum-based induction regimens, such as the R-DHAP, R-ICE and R-GDP regimens mainly used in the ZUMA-7 study, have long been established in clinical care practice in the present therapeutic indication. There is nothing to suggest that an induction therapy with these regimens is less effective than an induction therapy with MINE. In this specific data constellation, the ZUMA-7 study can therefore be interpreted for research question 1 of the present assessment, although the induction regimens used in the study do not correspond to the MINE scheme. The uncertainty resulting from the fact that the ACT was not fully implemented in the comparator arm of the study is taken into account when assessing the certainty of the results. In addition, no conclusions on the extent of the added benefit can be derived from the results of the study for this reason. However, as no suitable data for the benefit assessment are available anyway, the incomplete implementation of the ACT in the comparator arm has no consequences for the present benefit assessment (for justification, see below).

Data cut-offs

For the ongoing ZUMA-7 study, 2 data cut-offs are available:

- First data cut-off from 18 March 2021: primary EFS analysis, planned after 250 EFS events; also represents the first interim analysis for overall survival
- Second data cut-off from 25 January 2023: primary analysis on overall survival, planned after approximately 210 events in the outcome of overall survival or at the latest 5 years after randomization of the first patient

The second data cut-off from 25 January 2023 is the relevant data cut-off for the benefit assessment because the follow-up period was almost 2 years longer. However, there are problems with the conduct of the study and with the completeness of the data, which are explained below.

The company made relevant changes to the study protocol (especially with version 5.0 of 25 June 2020), and it is not sufficiently certain that these changes were made without knowledge of the data. For example, the primary EFS analysis event trigger was modified from 270 to 250 EFS events, and the required duration of follow-up was increased from 150 days to at least 9 months. In this protocol amendment, the company also added a second interim analysis of overall survival, which was to occur when approximately 160 deaths have been observed or no later than 4 years after the first patient was randomized. The trigger for the final analysis of overall survival was also adjusted so that it was to occur no later than 5 years

after the first patient was randomized. The time component of 5 years ultimately also prompted the second data cut-off. In the European Public Assessment Report (EPAR), the European Medicines Agency (EMA) points out that, for example, biostatisticians had continuous access to the study data during the conduct of the study and that no clearly defined firewall was in place to separate individuals involved in the monitoring of the study from individuals involved in the conduct of the study. It can therefore not be excluded that changes to the triggers for the analyses of the study were data-driven.

The potentially data-driven changes to the study protocol are taken into account in the risk of bias across outcomes.

The company presented the results of the second data cut-off from 25 January 2023 in Module 4 A and used them for its assessment. This approach is appropriate, but the company's dossier lacks results on relevant outcomes at the second data cut-off without justification. The absence of this data would constitute an incompleteness of content. However, as a relevant proportion of the data from the ZUMA-7 study is not suitable for the benefit assessment, no incompleteness with regard to content was identified (see below for justification).

Risk of bias

The ZUMA-7 study has a high risk of bias across outcomes. This is due to uncertainties in the conduct of the study. As described above, the EMA found that there was no sufficiently secure separation between study conduct and study monitoring, so that the described changes to the triggers for the analyses were potentially data-driven. This risk of bias affects all data cut-offs and outcomes. The risk of bias across outcomes is therefore rated as high.

Results

The data presented by the company for the relevant outcomes of overall survival, failure of the curative treatment approach, symptoms (recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]), health status (recorded with the with EQ-5D visual analogue scale [VAS]), health-related quality of life (recorded with the EORTC QLQ-C30), and side effects are unsuitable for the benefit assessment. This is justified below.

Overall survival

Three aspects are decisive for the lack of interpretability of the results for the outcome of overall survival. Firstly, due to the potentially data-driven changes to the study protocol, there is already a high risk of bias across outcomes and thus also a high outcome-specific risk of bias for the outcome of overall survival. Secondly, information on the subsequent therapies administered is missing for the relevant second data cut-off. In the present therapeutic indication, failure of the curative treatment approach means transition to the third (still

potentially curative) line of therapy, for which, according to the S3 guideline, CAR T-cell therapies are the principal option in the comparator arm. Due to the lack of information on subsequent therapies, it is not possible to adequately clarify whether the subsequent therapies administered at the second data cut-off are in line with S3 guideline recommendations. Furthermore, although the effect observed at the second data cut-off for the outcome of overall survival is statistically significant, the effect shown based on the upper limit of the confidence interval is of only minor extent. Taking into account the high risk of bias, the lack of information on subsequent therapies at the second data cut-off, and the minor extent of the effect, it remains unclear whether there is an actual advantage of axicabtagene ciloleucel in the outcome of overall survival. The results can therefore not be interpreted in the present data situation without further information.

Failure of the curative treatment approach

For the composite outcome of failure of the curative treatment approach, relevant data are missing for the second data cut-off, there are unexplained discrepancies between blinded central review and investigator assessment for the first data cut-off, and the component of new lymphoma therapy does not reflect failure of the curative approach with sufficient certainty. The analyses presented by the company are therefore unsuitable for the benefit assessment.

Symptoms, health status, and health-related quality of life

For the outcomes of symptoms, health status and health-related quality of life, analyses of the patient-reported outcomes are missing for the second data cut-off, the data quality (patients not included and high proportion of missing values in the analyses) is inadequate, and, in addition, the company did not present any suitable analyses. The outcomes of symptoms, health status and health-related quality of life recorded in the ZUMA-7 study are therefore not suitable for the benefit assessment.

Outcomes on side effects

The analyses presented by the company on outcomes in the outcome category of side effects are unsuitable because they are based on an incomplete analysis population and because no time-to-event analyses were presented in the presence of potentially marked differences in observation periods.

Final assessment and summary

There are serious deficiencies in the data presented by the company. Some of the deficiencies on outcomes described above can potentially be addressed by the company (e.g. analysis population and time-to-event analyses for adverse event [AE] outcomes and incompleteness of the data presented). Other deficiencies (e.g. the insufficient data quality for the patient-reported outcomes, the inconsistent results in the EFS outcome, the potentially data-driven analyses due to insufficient separation between study conduct and study monitoring, and

insufficient bridging therapies), however, are due to the study conduct and can therefore no longer be remedied.

In summary, there are no suitable data for the assessment of axicabtagene ciloleucel versus the ACT induction + HDCT + autologous SCT for the relevant research question, neither on the benefit nor on the harm side. Therefore, it is impossible to weigh benefits versus harm.

Results on added benefit

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

Research question 2: patients for whom high-dose therapy is not an option

Results

Evidence presented by the company – ALYCANTE study

The company conducted an information retrieval for other investigations with axicabtagene ciloleucel and presented data from the single-arm ALYCANTE study in its dossier. In this study, 62 patients with relapsed or refractory DLBCL after first-line therapy, for whom autologous stem cell transplantation was not an option, were treated with axicabtagene ciloleucel. The company conducted no information retrieval on other investigations with the ACT. The evidence of the single-arm ALYCANTE study presented by the company did not investigate a comparison with the G-BA's ACT and is therefore not suitable for the benefit assessment.

Results on added benefit

Since no relevant study is available for the present research question, there is no hint of added benefit of axicabtagene ciloleucel in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 summarizes the result of the assessment of the added benefit of axicabtagene ciloleucel in comparison with the ACT.

[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 [2,3].

Table 3: Axicabtagene ciloleucel – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom			
1	high-dose therapy is an option[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy	Added benefit not proven
2	high-dose therapy is not an option[d]	Treatment of physician's choice[e], taking into account ▪ pola-BR[f] ▪ tafasitamab + lenalidomide[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research question 2). Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
c. In the line of treatment, allogeneic stem cell transplantation is an option in patients who have a very high risk of relapse or in whom sufficient stem cell collection for autologous stem cell transplantation was not possible.
d. Patients are assumed to be not eligible for high-dose therapy and to generally continue antineoplastic treatment after first-line immunotherapy.
e. A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
f. The approval of pola-BR and tafasitamab + lenalidomide relates exclusively to DLBCL (approval of 2020/2021). With the updated WHO classification of 2022, HGBL was newly listed as a definite entity. Prior to this update, aggressive lymphomas with MYC and BCL2/6 rearrangements were classified as DLBCL, so that HGBL was not specified separately in the therapeutic indication at the time of approval of pola-BR and tafasitamab + lenalidomide. Therefore, specifying these treatment options for both DLBCL and HGBL is considered appropriate.

ACT: appropriate comparator therapy; BSG: Federal Social Court; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; MINE: combination therapy of mesna, ifosfamide, mitoxantrone and etoposide; pola-BR: polatuzumab in combination with bendamustine and rituximab; SGB: Social Code Book; WHO: World Health Organization

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of axicabtagene ciloleucel in comparison with the ACT in adult patients with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

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

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

Research question	Therapeutic indication	ACT[a]
Adults with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom		
1	high-dose therapy is an option[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy
2	high-dose therapy is not an option[d]	Treatment of physician's choice[e], taking into account ▪ pola-BR[f] ▪ tafasitamab + lenalidomide[f]

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research question 2). Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
c. In the line of treatment, allogeneic stem cell transplantation is an option in patients who have a very high risk of relapse or in whom sufficient stem cell collection for autologous stem cell transplantation was not possible.
d. Patients are assumed to be not eligible for high-dose therapy and to generally continue antineoplastic treatment after first-line immunotherapy.
e. A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
f. The approval of pola-BR and tafasitamab + lenalidomide relates exclusively to DLBCL (approval of 2020/2021). With the updated WHO classification of 2022, HGBL was newly listed as a definite entity. Prior to this update, aggressive lymphomas with MYC and BCL2/6 rearrangements were classified as DLBCL, so that HGBL was not specified separately in the therapeutic indication at the time of approval of pola-BR and tafasitamab + lenalidomide. Therefore, specifying these treatment options for both DLBCL and HGBL is considered appropriate.

ACT: appropriate comparator therapy; BSG: Federal Social Court; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; MINE: combination therapy of mesna, ifosfamide, mitoxantrone and etoposide; pola-BR: polatuzumab in combination with bendamustine and rituximab; SGB: Social Code Book; WHO: World Health Organization

Regarding the determination of the ACT for both research questions, the G-BA pointed out that the present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) or treatment (research question 2) in adults with DLBCL or HGBL, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy, and for whom HDCT is an option or not an option. In addition, the G-BA pointed out for all research questions that drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

For research question 1, the company followed the G-BA's specification of HDCT with autologous or allogeneic SCT as ACT in the case of response to induction therapy, but deviated from the specified induction therapies and instead specified an induction therapy of physician's choice. For research question 2, the company followed the G-BA's specification of treatment of physician's choice as ACT, but did not limit the selection of therapies to the 2 drug combinations specified by the G-BA, and cited additional options instead.

The approach of the company is not followed. The present assessment is conducted for the research questions listed in Table 4.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of added benefit.

I 3 Research question 1: patients for whom high-dose therapy is an option

I 3.1 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 5 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

No additional relevant study was identified from the check of the completeness.

Evidence provided by the company

Comparison with induction therapy + HDCT + autologous SCT – ZUMA-7 study

Although the comparator therapy in the ZUMA-7 study does not represent a complete implementation of the G-BA's ACT, it can be interpreted for research question 1 of the present benefit assessment (for explanation, see Section I 3.1.2). The check of completeness of the study pool did not identify any further RCT for the comparison of axicabtagene ciloleucel versus induction therapy followed by HDCT with autologous SCT if there is a response to induction therapy (hereinafter referred to as "induction + HDCT + autologous SCT").

I 3.1.1 Studies included

For research question 1 of the benefit assessment, the study comparing axicabtagene ciloleucel with induction + HDCT + autologous SCT presented in the following table is included (for explanation, see Section I 3.1.2).

Table 5: Study pool – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
KTE-C19-107 (ZUMA-7[d])	Yes	Yes	No	Yes [4-6]	Yes [7,8]	Yes [9-12]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: EPAR.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; EPAR: European Public Assessment Report; G-BA: Federal Joint Committee; HDCT: high-dose chemotherapy; RCT: randomized controlled trial; SCT: stem cell transplantation

I 3.1.2 Study and patient characteristics

Table 6 and Table 7 describe the ZUMA-7 study.

Table 6: Characteristics of the included study – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ZUMA-7	RCT, parallel, open-label	Adult patients with ▪ DLBCL or HGBL[b] with refractory or relapsed disease[c] < 12 months after first-line therapy[d] ▪ ECOG PS ≤ 1	Axicabtagene ciloleucel (N = 180) Induction + HDCT + autologous SCT (N = 179)	Screening: up to 2 weeks Treatment: ▪ Axicabtagene ciloleucel: single infusion, approx. 4 weeks after leukapheresis; optional bridging therapy and lymphodepletion beforehand ▪ Comparator therapy: 2–3 cycles of 2–3 weeks of induction therapy followed by HDCT and autologous SCT Observation[e]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	77 centres in Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Spain, Sweden Switzerland, United Kingdom, United States 1/2018–ongoing Data cut-offs: ▪ 18 March 2021[f] ▪ 25 January 2023[g]	Primary: EFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. DLBCL not otherwise specified including activated B-cell like or germinal centre like DLBCL, high-grade B-cell lymphoma with or without MYC and BCL2 and/or BCL6 rearrangement, large-cell transformation from follicular lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, DLBCL associated with chronic inflammation, primary cutaneous DLBCL, leg type, and EBV-positive DLBCL.
c. Refractory disease was defined as PD or SD after at least 4 cycles as best response to first-line therapy, or PR as best response after at least 6 cycles of first-line therapy, and biopsy-proven residual disease or disease progression within 12 months. Disease progression ≤ 12 months after CR was defined as relapsed disease.
d. Rituximab and anthracycline-based chemoimmunotherapy
e. Outcome-specific information is described in Table 11.
f. Interim analysis after 250 EFS events (was adapted with version 5 of the study protocol; for the consequences, see the following text section).
g. Final analysis of overall survival (was planned after the occurrence of approximately 210 deaths or no later than 5 years after randomization; was adapted with version 5 of the study protocol; for the consequences, see the following text section).

AE: adverse event; CR: complete response; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: event-free survival; HDCT: high-dose chemotherapy; HGBL: high-grade B-cell lymphoma; N: number of randomized patients; PD: progressive disease; PR: partial response; RCT: randomized controlled trial; SCT: stem cell transplantation; SD: stable disease

Table 7: Characteristics of the intervention – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study	Intervention	Comparison
ZUMA-7	**Axicabtagene ciloleucel** single dose of axicabtagene ciloleucel IV[a] target dose 2 × 10^6 anti-CD19 CAR T-cells/kg body weight ▪ minimum 1 × 10^6 anti-CD19 CAR T-cells/kg body weight ▪ maximum 2 x 10^8 anti-CD19 CAR T-cells (in patients with > 100 kg body weight). <u>Preparation:</u> ▪ leukapheresis approx. 5 days after randomization <u>Optional bridging therapy:</u> ▪ corticosteroids (dexamethasone 20–40 mg or equivalent for 1–4 days) at the investigator's discretion for patients with high disease burden at screening; after leukapheresis through 5 days prior to axicabtagene ciloleucel infusion <u>Chemotherapy for lymphodepletion:</u> ▪ 3-day conditioning regimen of fludarabine (30 mg/m²/day) and cyclophosphamide (500 mg/m²/day) <u>Approximately 60 minutes before administration of axicabtagene ciloleucel</u> ▪ paracetamol 650 mg orally or equivalent ▪ diphenhydramine 12.5 mg orally or IV or equivalent	**Induction + HDCT + autologous SCT** induction chemotherapy of investigator's choice for 2–3 cycles of 2–3 weeks each ▪ R-ICE: ▫ rituximab 375 mg/m² before chemotherapy ▫ ifosfamide 5 g/m² 24h-CI on Day 2 with mesna ▫ carboplatin area under the curve (AUC) 5 on Day 2, maximum dose 800 mg ▫ etoposide 100 mg/m² daily on Days 1–3 ▪ R-DHAP: ▫ rituximab 375 mg/m² before chemotherapy ▫ dexamethasone 40 mg daily on Days 1–4 ▫ high-dose cytarabine 2 g/m² every 12 hours for 2 doses on Day 2 following platinum ▫ cisplatin 100 mg/m² daily CI on Days 1–4 (or oxaliplatin 100 mg/m²) ▪ R-ESHAP: ▫ rituximab 375 mg/m² on Day 1 ▫ etoposide 40 mg/m² daily IV on Days 1–4 ▫ methylprednisolone 500 mg daily IV on Days 1–4 or 5 ▫ cisplatin 25 mg/m² daily on Days 1–4 ▫ cytarabine 2 g/m² on Day 5 ▪ R-GDP ▫ rituximab 375 mg/m² on Day 1 (or Day 8) ▫ gemcitabine 1 g/m²on Days 1 and 8 ▫ dexamethasone 40 mg on Days 1–4 ▫ cisplatin 75 mg/m² on Day 1 (or carboplatin AUC = 5) followed by HDCT and autologous SCT for responders[b]
	Pretreatment ▪ anthracycline containing chemotherapy and an anti-CD20 monoclonal antibody unless tumour was CD20 negative **Disallowed pretreatment** ▪ history of autologous or allogeneic stem cell transplant ▪ ≥ 1 line of therapy for DLBCL ▪ systemic immunostimulatory drugs (including, but not limited to, interferon and interleukin 2) ≤ 6 weeks or 5 half-lives of the drug, whichever is shorter ▪ prior CAR T-cell therapy or other genetically modified T-cell therapy ▪ live vaccines ≤ 6 weeks prior to study start **Disallowed concomitant treatment** ▪ other lymphoma therapies such as immunotherapy, targeted drugs (e.g. CD19-targeted therapy), radiation (outside HDCT) or high-dose corticosteroids	

Table 7: Characteristics of the intervention – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study	Intervention	Comparison
a. After consultation with the sponsor, there was the possibility of a second lymphodepletion and subsequent treatment with axicabtagene ciloleucel for patients who achieved PR or CR on Day 50 and subsequently experienced disease progression. This does not concur with the requirements of the SPC. b. If there was partial or complete response to induction therapy, HDCT (e.g. BEAM or CBV with or without total body irradiation) and autologous SCT were initiated per regional and institutional standards. BEAM: carmustine (BCNU), etoposide, cytarabine and melphalan; CAR: chimeric antigen receptor; CBV: cyclophosphamide, carmustine (BCNU), VP-16; CD: cluster of differentiation; CI: continuous infusion; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HDCT: high-dose chemotherapy; IV: intravenous; PR: partial response; RCT: randomized controlled trial; SCT: stem cell transplantation; SPC: Summary of Product Characteristics		

Study design

The ZUMA-7 study is an ongoing, open-label, multicentre RCT comparing axicabtagene ciloleucel versus induction + HDCT + autologous SCT in adult patients with DLBCL or HGBL according to the 2016 WHO classification [13].

Patients had to have refractory or relapsed disease within 12 months after first-line chemoimmunotherapy including an anti-CD20 monoclonal antibody (except in CD20-negative tumours) and an anthracycline. It also had to be intended to proceed to HDCT and autologous SCT if patients responded to induction therapy. Patients had to be in good general health corresponding to an ECOG PS of 0 or 1, and have adequate organ function and radiographically documented disease. Patients with previous SCT, brain metastases or tumour cells in the cerebrospinal fluid, as well as all patients who had received > 1 line of therapy for DLBCL were excluded from the study.

A total of 359 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with axicabtagene ciloleucel (N = 180) or to induction + HDCT + autologous SCT (N = 179). Randomization was stratified by response to first-line therapy (primary refractory versus relapse ≤ 6 months versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (sAAIPI) (0 or 1 versus 2 or 3).

Axicabtagene ciloleucel treatment was administered in compliance with the SPC [1]. Leukapheresis was performed within 5 days of randomization. Chemotherapy for lymphodepletion was given over 3 days on Days 5 to 3 before the infusion of axicabtagene ciloleucel. If needed, patients could receive bridging therapy with corticosteroids at the discretion of the investigator in the period between leukapheresis and lymphodepletion. Bridging therapy in the form of chemoimmunotherapy was not permitted in the ZUMA-7 study (see also below). Patients with disease progression following response by Day 50 could receive another lymphodepletion and treatment with axicabtagene ciloleucel.

In the comparator arm, patients initially received induction therapy with 2 to 3 cycles of R-ICE, R-DHAP, R-ESHAP or R-GDP at the discretion of the investigator. Patients who achieved PR or CR by the Lugano Classification [14] after 2 to 3 cycles of induction therapy (approximately on Day 50) received subsequent HDCT and autologous SCT. The response was assessed by the investigator. Treatment in the comparator arm of the study largely corresponds to the specifications for the treatment regimen according to the S3 guideline [15]. The R-ESHAP regimen administered in the ZUMA-7 study is not explicitly listed in the S3 guideline, but was only used in 3% of patients in the study. The use of R-ESHAP therefore has no consequences for the benefit assessment.

Subsequent antineoplastic therapies were at the discretion of the investigator in both study arms and were possible without restriction.

According to the planning of the study, follow-up observation was up to 15 years for patients in the intervention arm and up to 5 years for patients in the comparator arm.

The primary outcome of the ZUMA-7 study was EFS per blinded central review, operationalized as the time from randomization to death, disease progression, failure to achieve CR or PR by Day 150 after randomization, or commencement of new lymphoma therapy. Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects.

Limitations of the study – bridging therapies

CAR T-cell therapy is a multi-stage process starting with leukapheresis and genetic modification of the T-cells. The production of CAR T-cells takes several weeks. In the ZUMA-7 study, the average period from leukapheresis to axicabtagene ciloleucel infusion was about 27 days. According to the S3 guideline of the AWMF, various bridging therapy options should be offered during the waiting period for CAR T-cells to induce remission (referring to the third line of treatment) [15]. In general, these are chemoimmunotherapies, but targeted substances or radiotherapy are also possible. In the ZUMA-7 study, however, corticosteroids were the only permitted bridging therapy, which was used in 36% of patients in the intervention arm. The restriction of bridging therapy to corticosteroids in the ZUMA-7 study is not appropriate and does not adequately reflect the health care context. This therefore represents a relevant limitation of the ZUMA-7 study.

Implementation of the appropriate comparator therapy

The G-BA defined induction therapy with MINE, followed by HDCT with autologous or allogeneic SCT in case of response to induction therapy, as ACT for axicabtagene ciloleucel for the treatment of adults with DLBCL or HGBL, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy, and who are eligible for HDCT. The ACT therefore consists of several components: induction therapy, HDCT, and SCT. The regimen

used in the comparator arm of the ZUMA-7 study differs from the G-BA's ACT with regard to the induction therapy (R-DHAP, R-ICE, R-ESHAP or R-GDP instead of MINE), but not with regard to the HDCT and the SCT.

Rituximab and platinum-based induction regimens, such as the R-DHAP, R-ICE and R-GDP regimens mainly used in the ZUMA-7 study, have long been established in clinical care practice in the present therapeutic indication [15,16]. There is nothing to suggest that an induction therapy with these regimens is less effective than an induction therapy with MINE. In this specific data constellation, the ZUMA-7 study can therefore be interpreted for research question 1 of the present assessment, although the induction regimens used in the study do not correspond to the MINE scheme. The uncertainty resulting from the fact that the ACT was not fully implemented in the comparator arm of the study is taken into account when assessing the certainty of the results. In addition, no conclusions on the extent of the added benefit can be derived from the results of the study for this reason. However, as no suitable data for the benefit assessment are available anyway (see Section I 3.2.1), the incomplete implementation of the ACT in the comparator arm has no consequences for the present benefit assessment.

Data cut-offs

For the ongoing ZUMA-7 study, 2 data cut-offs are available:

- First data cut-off from 18 March 2021: primary EFS analysis, planned after 250 EFS events; also represents the first interim analysis for overall survival
- Second data cut-off from 25 January 2023: primary analysis on overall survival, planned after approximately 210 events in the outcome of overall survival or at the latest 5 years after randomization of the first patient

The second data cut-off from 25 January 2023 is the relevant data cut-off for the benefit assessment because the follow-up period was almost 2 years longer. However, there are problems with the conduct of the study and with the completeness of the data, which are explained below.

The company made relevant changes to the study protocol (especially with version 5.0 of 25 June 2020), and it is not sufficiently certain that these changes were made without knowledge of the data. For example, the primary EFS analysis event trigger was modified from 270 to 250 EFS events, and the required duration of follow-up was increased from 150 days to at least 9 months. In this protocol amendment, the company also added a second interim analysis of overall survival, which was to occur when approximately 160 deaths have been observed or no later than 4 years after the first patient was randomized. However, this analysis was not performed because the primary EFS analysis already was an adequate representation

of the criteria of the planned second interim analysis on overall survival. The trigger for the final analysis of overall survival was also adjusted so that it was to occur no later than 5 years after the first patient was randomized. The time component of 5 years ultimately also prompted the second data cut-off. In the EPAR, the EMA points out that, for example, biostatisticians had continuous access to the study data during the conduct of the study and that no clearly defined firewall was in place to separate individuals involved in the monitoring of the study from individuals involved in the conduct of the study [12]. It can therefore not be excluded that changes to the triggers for the analyses of the study were data-driven. In addition, a futility analysis was carried out approximately 8 months before the above-mentioned adjustments to the study protocol. This issue was not addressed by the company in the dossier. The potentially data-driven changes to the study protocol are taken into account in the risk of bias across outcomes.

The company presented the results of the second data cut-off from 25 January 2023 in Module 4 A and used them for its assessment. This approach is appropriate, but the company's dossier lacks results on relevant outcomes at the second data cut-off without justification. The absence of this data would constitute an incompleteness of content. However, as a relevant proportion of the data from the ZUMA-7 study is not suitable for the benefit assessment, no incompleteness with regard to content was identified. The missing data and the reasons for the unsuitability of the data are explained in Section I 3.2.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ZUMA-7	
Mortality	
Overall survival	Up to 15 years[a] or until death, lost to follow-up, or withdrawal of consent
Morbidity	
EFS	Up to 15 years[a] or until death, lost to follow-up, or withdrawal of consent
Symptoms (EORTC QLQ-C30) Health status (EQ-5D VAS)	Up to 24 months after randomization
Health-related quality of life (EORTC QLQ-C30)	Up to 24 months after randomization
Side effects	
All outcomes in the side effects category	Up to 5 months after randomization or commencement of new lymphoma therapy, whichever occurs first[b]

a. The patients in the comparator arm were observed for up to 5 years.
b. Targeted SAEs, defined as neurological or haematological events, infections, autoimmune disorders and secondary malignancies, are observed and reported for up to 15 years in the intervention arm and for up to 5 years in the comparator arm, or until disease progression, whichever occurs first.

AE: adverse event; EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; HDCT: high-dose chemotherapy; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SCT: stem cell transplantation; VAS: visual analogue scale

In the ZUMA-7 study, a follow-up observation of up to 5 years (comparator arm) and 15 years (intervention arm) was planned for the outcomes of overall survival and EFS.

The observation periods for the outcomes on symptoms, health status and health-related quality of life are systematically shortened, as they were only recorded for the period up to 24 months after randomization. The observation periods for outcomes in the side effects category are also systematically shortened, as they were only recorded for the period up to 5 months after randomization or commencement of new lymphoma therapy, whichever occurred first. Only targeted serious adverse events (SAEs), defined as neurological or haematological events, infections, autoimmune disorders and secondary malignancies, were observed and reported for up to 15 years in the intervention arm and for up to 5 years in the comparator arm, or until disease progression, whichever occurs first. However, drawing a reliable conclusion on the total study period or the time to patient death would require recording all these outcomes for the total period.

Table 9 shows the characteristics of the patients in the included study.

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Characteristic Category	Axicabtagene ciloleucel N[a] = 180	Induction + HDCT + autologous SCT N[a] = 179
ZUMA-7		
Age [years], mean (SD)	57 (12)	57 (12)
Age group, n (%)		
< 65 years	129 (72)	121 (68)
≥ 65 years	51 (28)	58 (32)
Sex [F/M], %	39/61	29/71
Family origin, n (%)		
Native American or Native Alaskan	0 (0)	1 (1)
Asian	12 (7)	10 (6)
Black or African American	11 (6)	7 (4)
Native Hawaiian and other Pacific Islander	2 (1)	1 (1)
White	145 (81)	152 (85)
Other	10 (6)	8 (4)
Region, n (%)		
North America	140 (78)	130 (73)
Europe	34 (19)	45 (25)
Israel	4 (2)	2 (1)
Australia	2 (1)	2 (1)
ECOG PS at baseline, n (%)		
0	95 (53)	100 (56)
1	85 (47)	79 (44)
Disease type according to investigator, n (%)		
DLBCL NOS	110 (61)	116 (65)
THRBCL	5 (3)	6 (3)
EBV-positive DLBCL	2 (1)	0 (0)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)
HGBL with or without MYC and BCL2 and/or BCL6 rearrangement	43 (24)	27 (15)
Primary cutaneous DLBCL, leg type	1 (1)	0 (0)
Other	0 (0)	3 (2)
Prognostic marker according to central laboratory, n (%)		
HGBL double-hit	25 (14)	15 (8)
HGBL triple-hit	7 (4)	10 (6)
Double-expressor lymphoma	57 (32)	62 (35)
MYC rearrangement	15 (8)	7 (4)
Not applicable[b]	74 (41)	70 (39)
Missing	2 (1)	15 (8)

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Characteristic **Category**	**Axicabtagene ciloleucel** **N[a] = 180**	**Induction + HDCT + autologous SCT** **N[a] = 179**
Molecular subtype according to central laboratory[c], n (%)		
Germinal centre like (GCB like)	109 (61)	99 (55)
Activated B-cell like (ABC like)	16 (9)	9 (5)
Not classified	17 (9)	14 (8)
Not applicable	10 (6)	17 (9)
Missing	28 (16)	40 (22)
CD19 IHC-positive[d] at baseline according to central laboratory, n (%)		
Yes	145 (81)	134 (75)
No	13 (7)	12 (7)
Missing[e]	22 (12)	33 (18)
Disease duration	ND	ND
Prior response status[f], n (%)		
Refractory	133 (74)	131 (73)
Relapsed[g]	47 (26)	48 (27)
sAAIPI at baseline, n (%)[h]		
0 or 1	98 (54)	100 (56)
2 or 3	82 (46)	79 (44)
Ann Arbor stage, n (%)		
I	10 (6)	6 (3)
II	31 (17)	27 (15)
III	35 (19)	33 (18)
IV	104 (58)	113 (63)
Treatment discontinuation[g], n (%)[i]	8 (4)	79 (44)
Study discontinuation[g], n (%)[j]	87 (48)	105 (59)

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Characteristic Category	Axicabtagene ciloleucel N[a] = 180	Induction + HDCT + autologous SCT N[a] = 179

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. If the disease type is DLBCL NOS, HGBL NOS, other or not confirmed, "not applicable" with regard to prognostic markers is indicated according to the central laboratory.
c. According to the company, missing data sets on molecular subtypes according to the central laboratory are due to insufficient or unavailable tissue samples. Not applicable here means that the sample did not fulfil the quality requirements.
d. CD19 IHC-positive status is defined as having an H-score of staining ≥ 5.
e. According to the company, missing H-scores are mainly due to insufficient quality, missing biopsies in the central laboratory, CD19-negative status or missing tumour tissue in the sample.
f. For the data recorded via IXRS, relapse after first-line therapy was assessed as follows: For patients included up to Amendment 4, the period ≤ 6 months after the start of first-line therapy was taken into account, whereas for patients included after Amendment 4, the period ≤ 6 months since first-line therapy was taken into account. This also applies to relapses > 6 months and ≤ 12 months.
g. Institute's calculation based on data from Module 4 A.
h. sAAIPI at baseline according to IXRS. The following data on sAAIPI at baseline according to the clinical database are available for the intervention vs. comparator arm: sAAIPI 0: 26 (14%) vs. 18 (10%); sAAIPI 1: 68 (38%) vs. 82 (46%); sAAIPI 2: 86 (48%) vs. 79 (44%); sAAIPI 3[g]: 0 (0%) vs. 0 (0%).
i: The most common reason for treatment discontinuation in the intervention arm was AE (50%) and in the comparator arm, disease progression (90%).
j. The data on patients who discontinued the study include deaths. This was the most common reason for study discontinuation in both study arms (intervention arm: 94% vs. comparator arm: 81%).

AE: adverse event; BCL: B-cell lymphoma; CD: cluster of differentiation; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HDCT: high-dose chemotherapy; HGBL: high-grade B-cell lymphoma; IHC: immunohistochemistry; IXRS: interactive voice/web response system; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; NOS: not otherwise specified; RCT: randomized controlled trial; sAAIPI: second-line age-adjusted International Prognostic Index; SCT: stem cell transplantation; SD: standard deviation; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma

The demographic and clinical characteristics of the patients in both treatment arms of the ZUMA-7 study are largely comparable. The mean age was 57 years. About 70% of patients were < 65 years old. The sex ratio differed slightly, with a slightly lower proportion of men in the intervention arm (61%) versus 71% of men in the comparator arm. The majority of patients were of white family origin and were recruited exclusively in Europe, North America, Israel or Australia. The disease was DLBCL in the majority of patients, and most patients had refractory disease (about 74%). The company did not provide any information on the patients' median disease duration. The EMA also pointed out in the EPAR that patients with an activated B-cell-like molecular subtype were underrepresented in the ZUMA-7 study [12]. The proportion of patients with this subtype was only about 7%.

Course of therapy and administered therapies

Table 10 shows the course of treatment and the administered therapies in the study presented by the company.

Table 10: Information on the course of therapy and administered therapies – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study Therapy administered Category	Axicabtagene ciloleucel N = 180	Induction + HDCT + autologous SCT N = 179
ZUMA-7 study		
Leukapheresis, n (%)	178 (99)	–
Bridging therapy[a], n (%)	65 (36)	–
Lymphodepletion, n (%)	172 (96)	–
Infusion of axicabtagene ciloleucel, n (%)	170 (94)[b]	–
Retreatment with axicabtagene ciloleucel, n (%)	10 (6)	–
Induction therapy, n (%)	–	168 (94)[c]
Therapy regimen for induction therapy		
R-DHAP	–	37 (22)[d]
R-ICE	–	84 (50)[d]
R-ESHAP	–	5 (3)[d]
R-GDP	–	42 (25)[d]
HDCT, n (%)	–	64 (36)
Autologous SCT, n (%)	–	62 (35)

a. Only corticosteroids were permitted as bridging therapy.
b. 2 patients did not undergo leukapheresis (1 due to progression, 1 proved unsuitable); 6 patients did not receive lymphodepletion (2 had died, 2 due to AEs, 1 due to progression, 1 had no progression after first-line at the start of the study), 2 patients did not receive axicabtagene ciloleucel infusion (due to AEs). 8 of the patients listed above discontinued the study in the intervention arm without axicabtagene ciloleucel treatment (all 8 had died).
c. 8 patients decided against treatment, 1 patient was lost to follow-up, 1 had a negative biopsy and 1 had a false positive FDG-PET/CT. 8 of these patients discontinued the study without treatment with induction therapy (6 withdrawal of informed consent, 1 death, 1 lost to follow-up).
d. Percentages refer to patients who received at least one dose of induction therapy (n = 168).

AE: adverse event; HDCT: high-dose chemotherapy; n: number of patients in the category; N: number of randomized patients; FDG-PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; RCT: randomized controlled trial; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin (or oxaliplatin); R-ESHAP: rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; SCT: stem cell transplantation

94% of patients in the intervention arm received an infusion of axicabtagene ciloleucel. Patients with PR or CR by Day 50 with subsequent progression had the opportunity to receive another infusion of axicabtagene ciloleucel. This does not concur with the requirements of the SPC. Since only 6% of patients received such a repeat treatment, this has no consequences for

the present assessment. 36% of patients in the intervention arm received bridging therapy, which was given at the investigator's discretion and consisted solely of corticosteroids. 10 patients did not receive treatment with axicabtagene ciloleucel (see Table 10 for the reasons). In 8 patients, the study was discontinued due to death before treatment with axicabtagene ciloleucel. The reasons for the deaths are unclear, as no further information is available on these 8 patients.

In the comparator arm, about 94% of patients received induction therapy, 36% received HDCT and 35% received autologous SCT. At about 50%, the most frequently used treatment regimen for induction was R-ICE with. 11 patients did not receive induction therapy (see Table 10 for the reasons), 8 patients discontinued the study without treatment with induction therapy, most frequently due to withdrawal of informed consent.

Information on the course of the study

Table 11 shows the mean and median treatment durations of the patients and the mean and median observation periods for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study **Duration of the study phase** **Outcome category**	**Axicabtagene ciloleucel** **N = 180**	**Induction + HDCT + autologous SCT** **N = 179**
ZUMA-7		
Treatment duration[a] [days]		
Median [Q1; Q3]	26.0 [16; 52]	ND
Mean (SD)	26.9 (6.1)	ND
Observation period [months]		
Overall survival [b]		
Median [Q1; Q3]	41.1 [12.6; 47.5]	21.2 [7.8; 45.4]
Mean (SD)	31.8 (18.5)	26.8 (19.0)
Failure of the curative approach or EFS	ND	ND
Symptoms, health-related quality of life (EORTC QLQ-C30)	ND	ND
Health status (EQ-5D VAS)	ND	ND
Side effects	ND	ND

a. The time from leukapheresis to infusion of axicabtagene ciloleucel is indicated (in the intervention arm). The duration of treatment in the comparator arm is not provided in the company's dossier.
b. The company calculated the actual observation period as (day of death or last known day alive – day of randomization + 1)/30.4375.

EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; HDCT: high-dose chemotherapy; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SCT: stem cell transplantation; SD: standard deviation; VAS: visual analogue scale

Information on the treatment durations and observation periods is incomplete in the dossier. The median treatment duration in the intervention arm, defined as the time from leukapheresis to infusion of axicabtagene ciloleucel, was 26 days. The treatment duration in the comparator arm was not specified. At the time of the second data cut-off on 25 January 2023, the observation period for overall survival differed notably between the arms. The observation periods for the other outcomes are missing.

Although the company presented neither outcome-specific observation periods nor information on the duration of treatment in the comparator arm, it can be assumed on the basis of the available data that, compared with overall survival, the observation periods are notably shortened for the outcomes on symptoms, health-related quality of life and side effects (see Table 8) and differ between the study arms. The different observation periods between the study arms for the patient-reported outcomes result from the strong and differential increase in missing values between the treatment arms (see Section I 3.2). Besides, the side effects outcomes were only observed until Month 5 or commencement of new lymphoma therapy, with new lymphoma therapy relatively early in the course of the study being notably more frequent in the comparator arm than in the intervention arm.

Information on subsequent therapies

Information on subsequent therapies is not available for the relevant second data cut-off. For the consequences of this missing data, see Section I 3.2.1.

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ZUMA-7	Yes	Yes	No	No	Yes	No[a]	High[b]

a. There are uncertainties in the separation of study conduct and study monitoring, which is why study protocol amendments were potentially data-driven; see previous and following text sections.
b. Due to additional aspects.

HDCT: high-dose chemotherapy; RCT: randomized controlled trial; SCT: stem cell transplantation

The ZUMA-7 study has a high risk of bias across outcomes. This is due to uncertainties in the conduct of the study. As described above, the EMA found that there was no sufficiently secure separation between study conduct and study monitoring [12], so that the described changes

to the triggers for the analyses were potentially data-driven. This risk of bias affects all data cut-offs and outcomes. The risk of bias across outcomes is therefore rated as high.

Transferability of the study results to the German health care context

The company stated that the ZUMA-7 study was fully transferable to the German health care context, as it was conducted in Germany (6 patients) and other Western industrialized countries (Europe and North America) with comparable medical care standards, and the majority of patients were of white family origin (approx. 83%).

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - failure of the curative treatment approach
  - symptoms, recorded using the EORTC QLQ-C30
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - serious cytokine release syndrome
  - severe cytokine release syndrome
  - neurological toxicity
  - severe neurological toxicity
  - severe infections
  - further specific AEs, if any

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

Table 13 shows the outcomes for which data were available in the included ZUMA-7 study.

Table 13: Matrix of outcomes – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study	Outcomes													
	Overall survival	Failure of the curative approach[a]	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Cytokine release syndrome[c] (SAEs)	Severe cytokine release syndrome[b, c]	Neurological toxicity[d]	Severe neurological toxicity[b, e]	Severe infections[b, f]	Other specific AEs
ZUMA-7	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]

a. Operationalized as event rate and event-free survival; includes the events of death, disease progression, failure to respond (CR or PR not achieved) by Week 150 after randomization, commencement of new lymphoma therapy, whichever occurs first; see text below for explanation.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized via PT collection of the company.
d. Operationalized as AEs of the SOC nervous system disorders.
e. Operationalized as severe AEs of the SOC nervous system disorders.
f. Operationalized as severe AEs of the SOC infections and infestations.
g. No suitable data/analyses available; see body of text for reasons.

ACT: appropriate comparator therapy; AE: adverse event; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HDCT: high-dose chemotherapy; PR: partial response; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SCT: stem cell transplantation; VAS: visual analogue scale

Unsuitability of the data presented

The data submitted by the company are unsuitable for the benefit assessment. This is explained below for all relevant outcomes. The results are also not presented as requested in the G-BA's commission, as they cannot be interpreted independently of the research question (see Section I 2).

Overall survival

Three aspects are decisive for the lack of interpretability of the results for the outcome of overall survival. Firstly, due to the uncertainties in the study conduct described in Section I 3.1.2 and the potentially data-driven changes to the study protocol, there is already a high risk of bias across outcomes and thus also a high outcome-specific risk of bias for the outcome of overall survival. Secondly, information on the subsequent therapies administered is missing for the relevant second data cut-off. In the present therapeutic indication, failure of the curative treatment approach means transition to the third (still potentially curative) line of therapy, for which, according to the S3 guideline, CAR T-cell therapies are the principal option in the comparator arm [15]. Due to the lack of information on subsequent therapies, it is not possible to adequately clarify whether the subsequent therapies administered at the second data cut-off are in line with S3 guideline recommendations. Furthermore, although the effect observed at the second data cut-off for the outcome of overall survival is statistically significant (hazard ratio: 0.726; 95% confidence interval: [0.540; 0.977]), the effect shown based on the upper limit of the confidence interval is of only minor extent. Taking into account the high risk of bias, the lack of information on subsequent therapies at the second data cut-off, and the minor extent of the effect, it remains unclear whether there is an actual advantage of axicabtagene ciloleucel in the outcome of overall survival. The results can therefore not be interpreted in the present data situation without further information.

Failure of the curative treatment approach

In the present therapeutic indication, curative therapy is possible in principle. Failure to achieve remission or occurrence of a relapse after achieving remission means that the curative treatment approach in this line of therapy has failed. In the present treatment situation, failure of the curative treatment approach in the current line of therapy is a patient-relevant event because, albeit possible in principle, cure is less likely to be achieved in a subsequent line of therapy. Failure of the curative treatment approach is therefore considered a patient-relevant outcome in this assessment. In the present data situation, with a sufficiently long observation period and specification of the median observation period (see Section I 3.1.2), an alternative option is to consider the counter-event, i.e. cure, as outcome.

In the ZUMA-7 study, failure of the curative treatment approach was not directly recorded as an outcome. As an approximation, the present assessment is to consider the events that were recorded as part of the primary outcome of the ZUMA-7 study, i.e. the composite outcome of EFS, as operationalization for the outcome. The proportion of patients with event as well as the time to the occurrence of an event are potentially relevant for the assessment.

In the ZUMA-7 study, EFS was defined as time from randomization to the first occurrence of one of the following events:

- death from any cause
- disease progression
- stable disease (SD) as best response until Day 150 after randomization
- commencement of new lymphoma therapy

The data presented on the outcome of EFS are not suitable for benefit assessment; this is explained below.

Missing data on the second data cut-off

Although EFS per blinded central review is the primary outcome of the ZUMA-7 study, the results of this analysis for the for the second data cut-off with an additional observation period of approx. 2 years are missing without justification. For the current data cut-off, the company only presented data for the outcome of EFS as assessed by the investigator; information on the qualifying events for the second data cut-off was completely missing. This approach is not appropriate. In principle, complete analyses should be presented for all data cut-offs listed by the company for all relevant outcomes recorded.

Component of new lymphoma therapy does not adequately reflect failure of the curative approach

For commencement of new lymphoma therapy as a component of the composite EFS outcome, it remains unclear whether this event per se represents a failure of the curative treatment approach. Commencement of new lymphoma therapy as a component of the composite EFS outcome includes both events that reflect failure of the curative approach (e.g. lack of response to induction therapy at Day 50 in the comparator arm) and those that potentially do not, e.g. commencement of new lymphoma therapy despite response (CR or PR) to induction therapy at Day 50. It is unclear how many such events were included in the outcome of EFS, as the reasons for starting new lymphoma therapy are missing in the company's documents. It is therefore not clear whether the commencement of new lymphoma therapy actually regularly represents the failure of the curative approach or whether there were potentially other reasons for these events. The study documents show that 10 patients in the comparator arm did not receive a disease assessment after baseline and nevertheless started new lymphoma therapy. It is likely that these patients had not yet started induction therapy at all (see also Table 10). These patients were counted as events in the EFS outcome (commencement of new lymphoma therapy without disease assessment after baseline = EFS event on Day 0), although the curative treatment approach with induction + HDCT + autologous SCT had potentially not started and therefore had not failed.

The uncertainty in the component of new lymphoma therapy in the present data situation is particularly problematic because the observed differences between the intervention and

comparator arms, both according to the blinded central review and according to the investigator, are almost exclusively attributable to differences in this component. In the other components (death, disease progression and SD as best response until Day 150 after randomization), however, no relevant differences were shown between the treatment arms (see I Appendix C of the full dossier assessment). It is therefore not ensured that the EFS outcome reflects failure of the curative treatment approach.

Discrepancies between blinded central review and investigator

In the analysis of the EFS outcome as assessed by the investigator, only few events were added between the first and second data cut-off (see I Appendix C of the full dossier assessment). At the first data cut-off, however, there is a clear discrepancy between the assessment according to the investigator and the blinded central review in the assessment of the qualifying event. For example, in the comparator arm of the ZUMA-7 study, at the first data cut-off, according to the investigator, 70% of qualifying events were attributed to disease progression and about 26% to new lymphoma therapy, whereas according to blinded central review, 52% of events were disease progression and 44% were new lymphoma therapies. In the intervention arm, however, there was no relevant difference in the distribution of qualifying events between the 2 analyses; besides, new lymphoma therapy as a qualifying event occurred only sporadically. In addition, the median time to event in the intervention arm was about 2.5 months shorter according to blinded central review than according to investigator assessment. Particularly in view of the clear differences in qualifying events in the comparator arm with consistent results in the intervention arm, a systematic error due to a lack of blinding of the outcome assessors cannot be ruled out. In addition to the already high risk of bias across outcomes, the results for the EFS outcome according to the investigator therefore have a high outcome-specific risk of bias. As the analysis of the EFS according to the investigator is not sufficiently robust in comparison with the blinded central review at the first data cut-of, and the described deviations were not addressed by the company in the dossier, the analysis according to the investigator cannot be used for the benefit assessment of the second data cut-off.

It should be noted that there was no relevant difference between blinded central review and investigator assessment in the effect estimation for the EFS outcome at the first data cut-off. This is due to the fact that it can be assumed that, after detecting a progression event, the investigator usually initiated subsequent therapy (based on the incomplete information in the company’s dossier) and the blinded central review had to determine an event even without objectifiable progression due to the newly initiated lymphoma therapy (as the component of new lymphoma therapy in the EFS outcome). The agreement of the effect estimate between both analyses is therefore not due to consistent results of the 2 assessments, but is inherently caused by the operationalization of the outcome. It should also be noted that there can also

be a relevant influence from the potentially not (yet) indicated subsequent therapies on the results for overall survival.

Sensitivity analyses – PR after completion of the therapy sequence

For a comprehensive representation of failure of the curative approach, it is also necessary to represent the failure to achieve CR after completion of treatment as a separate qualifying event. However, failure to achieve CR after completion of treatment was not recorded in the EFS outcome in the ZUMA-7 study. The company did not provide any information on the response rates of patients at the individual time points of recording, which is why sensitivity analyses cannot be conducted, as described in the benefit assessment on lisocabtagene maraleucel (A23-48 [17]). Since the data presented by the company are not suitable for the benefit assessment, this has no consequences for the assessment in the present data situation.

Conclusion on failure of the curative treatment approach

In summary, relevant data are missing for the second data cut-off, there are unexplained discrepancies between blinded central review and investigator assessment for the first data cut-off, and the component of new lymphoma therapy does not reflect failure of the curative approach with sufficient certainty. The analyses on the EFS outcome presented by the company are therefore unsuitable for the benefit assessment. An operationalization analogous to the procedure presented in dossier assessment A23-48 [17] would be required.

Symptoms, health status, and health-related quality of life

Missing data

In Module 4 A, the company presented analyses on symptoms recorded using the EORTC QLQ-C30, on health status recorded using the EQ-5D VAS, and on health-related quality of life recorded using the EORTC QLQ-C30, exclusively for the first data cut-off from 18 March 2021. The company did not provide a reason for the lack of analyses for the second data cut-off. The approach of the company is not appropriate. Since data on symptoms, health status and health-related quality of life were recorded for 24 months after randomization and there were only approx. 17 months between the inclusion of the last patient and the first data cut-off, there may have been further recordings until the relevant second data cut-off.

High differential proportion of patients missing from the analysis

The data quality of the patient-reported outcomes recorded in the ZUMA-7 study is inadequate. On the one hand, a relevant proportion of randomized patients were not included in the analyses (about 8% in the intervention arm versus 27% in the comparator arm), with a difference of about 19 percentage points in the proportion of included patients between the treatment arms. Due to the difference between the treatment arms, it cannot be assumed that the patients were missing from the analyses by chance. The structural equality of the

treatment groups originally established by the randomization is no longer given in the present case (for the size of the effects and potential interpretability of the results, see below). On the other hand, the proportion of missing values increased strongly over the course of the study and differentially between the treatment arms, so that, already at the recording on Day 100, only < 50% of the randomized patients in the comparator arm were included in the analyses.

Responder analyses presented are unsuitable for the benefit assessment

Irrespective of the inadequate data quality, the analyses for the patient-reported outcomes are not suitable for the benefit assessment. In Module 4 A, the company presented responder analyses for the outcomes of symptoms, health status and health-related quality of life for the time to definitive improvement by at least 10 (EORTC QLQ-C30, scale range 0 to 100) or 15 (EQ-5D VAS, scale range 0 to 100) points. An improvement was only rated as definitive improvement if a patient had reached or exceeded the threshold value for improvement and had not deteriorated below this threshold value at any later point in time. In the present data situation, these analyses are not suitable for the benefit assessment, since due to the differentially increasing missing values (see above), notable differences in the observation periods in the treatment arms are assumed (outcome-specific observation periods are not available, see Table 8). Definitive improvement cannot be meaningfully interpreted in this case. In addition, it can be assumed that the analysis also included patients who had improved once at the last time point of recording and for whom no confirmatory value was available. It is unclear how many patients in each of the treatment arms were affected. In the present situation with potentially different observation periods, analyses of first deterioration or improvement would be required, as described by the G-BA [18]. Said analyses are not available in the company's dossier.

The company additionally presented analyses using a mixed-effects model with repeated measures (MMRM). On the one hand, however, it did not present an effect estimate for the entire observation period, but only for individual time points of recording (e.g. Day 100). On the other, due to the strong and differential increase in missing values described above, neither an analysis over the entire observation period nor at individual points in time during the course of the study can be meaningfully interpreted.

Conclusion on symptoms, health status, and health-related quality of life

In summary, analyses of the patient-reported outcomes are missing for the second data cut-off, the data quality (patients not included and high proportion of missing values in the analyses) is inadequate, and, in addition, the company did not present any suitable analyses. The outcomes of symptoms, health status and health-related quality of life recorded in the ZUMA-7 study are therefore not suitable for the benefit assessment.

Outcomes on side effects

Missing data

In Module 4 A, the company did not present any analyses of the Standardized Medical Dictionary for Regulatory Activities Queries (SMQs) prespecified in the ZUMA-7 study. In addition, effect estimates and p-values for the outcome of discontinuation due to AEs are missing. The information in the dossier shows that there were only few discontinuations due to AEs (see Table 15 of the full dossier assessment). As these were treatment discontinuations, only events could be recorded that occurred until the infusion of axicabtagene ciloleucel in the intervention arm or until the autologous SCT in the comparator arm. AEs that would lead to treatment discontinuation could still have occurred after the infusion of axicabtagene ciloleucel or after autologous SCT, but could no longer be recorded. In the present data constellation, the missing effect estimate and p-value for the outcome of discontinuation due to AEs therefore have no consequences for the assessment.

Analysis population not appropriate

To analyse the AE outcomes, the company used the safety analysis set (axicabtagene ciloleucel: n = 170, induction + HDCT + autologous SCT: n = 168). In the intervention arm, this only includes patients who received an axicabtagene ciloleucel infusion. In addition, AEs in these patients that occurred during the preparatory processes, i.e. leukapheresis, bridging therapy and lymphodepletion (and were also recorded according to the study protocol), were not included in the analysis. In the comparator arm, however, all patients who received a dose of induction chemotherapy were included in the analyses. The approach of the company is not appropriate. For the benefit assessment, analyses are necessary in which the patients' entire treatment sequence is taken into account. This is particularly problematic because 8 patients in the intervention arm who, according to the company, discontinued the study and had not previously received treatment with axicabtagene ciloleucel died (potential SAEs that are not taken into account in the analyses). In the present data situation, this may have a relevant impact on the observed effects in the AE outcomes.

Presented analyses of AEs, SAEs and severe AEs not suitable

For AEs, SAEs, and severe AEs, the company presented analyses using the relative risk. However, information on the outcome-specific observation period for the AEs is missing (see Table 11), which means that it remains unclear whether the relative risk is a suitable effect measure. Since AEs were recorded from randomization to Day 150 or until commencement of new lymphoma therapy, and since many patients, particularly in the comparator arm, received new lymphoma therapy early in the course of the study, a notably longer observation period can be assumed in the intervention arm than in the comparator arm. In this case, analyses using time-to-event analyses are necessary, which the company did not present, however.

Note on the outcome of cytokine release syndrome

In the ZUMA-7 study, both the diagnosis of cytokine release syndrome and the underlying symptoms were documented using Preferred Terms (PTs). However, this recording was only conducted in the intervention arm. This approach is not appropriate, as it does not allow a comparison between the intervention and comparator arms. The data recorded by the company on the outcome of cytokine release syndrome are therefore not suitable for the benefit assessment.

Conclusion on outcomes in the outcome category of side effects

The analyses presented by the company on outcomes in the outcome category of side effects are unsuitable because they are based on an incomplete analysis population and because no time-to-event analyses were presented in the presence of potentially marked differences in observation periods.

Final assessment and summary

There are serious deficiencies in the data presented by the company. Some of the deficiencies on outcomes described above can potentially be addressed by the company (e.g. analysis population and time-to-event analyses for AE outcomes and incompleteness of the data presented). Other deficiencies (e.g. the insufficient data quality for the patient-reported outcomes, the inconsistent results in the EFS outcome, high risk of bias across outcomes, and insufficient bridging therapies), however, are due to the study conduct and can therefore no longer be remedied.

In summary, there are no suitable data for the assessment of axicabtagene ciloleucel versus the ACT induction + HDCT + autologous SCT for the relevant research question, neither on the benefit nor on the harm side. Therefore, it is impossible to weigh benefits versus harm.

I 3.2.2 Results

For the assessment of the added benefit of axicabtagene ciloleucel in adult patients with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom high-dose therapy is an option, no suitable data are available for comparison with the ACT. There is no hint of an added benefit of axicabtagene ciloleucel in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

For the assessment of the added benefit of axicabtagene ciloleucel in adult patients with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom high-dose therapy is an option, no suitable data are available. An added benefit of axicabtagene ciloleucel in comparison with the ACT is therefore not proven for these patients.

I 4 Research question 2: patients for whom high-dose therapy is not an option

I 4.1 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 5 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

The check of completeness of the study pool identified no RCT directly comparing axicabtagene ciloleucel versus the ACT of the G-BA.

The company conducted an information retrieval for other investigations with axicabtagene ciloleucel and presented data from the single-arm ALYCANTE study in its dossier [19,20]. In this study, 62 patients with relapsed or refractory DLBCL after first-line therapy, for whom autologous stem cell transplantation was not an option, were treated with axicabtagene ciloleucel. The company conducted no information retrieval on other investigations with the ACT. The evidence of the single-arm ALYCANTE study presented by the company did not investigate a comparison with the G-BA's ACT and is therefore not suitable for the benefit assessment.

I 4.2 Results on added benefit

For the assessment of the added benefit of axicabtagene ciloleucel in adult patients with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom high-dose therapy is not an option, no data are available for comparison with the ACT. There is no hint of an added benefit of axicabtagene ciloleucel in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

For the assessment of the added benefit of axicabtagene ciloleucel in adult patients with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-

line chemoimmunotherapy, and for whom high-dose therapy is not an option, the company presented no suitable data. An added benefit of axicabtagene ciloleucel in comparison with the ACT is therefore not proven for these patients.

I 5 Probability and extent of added benefit

Table 14 summarizes the result of the assessment of the added benefit of axicabtagene ciloleucel in comparison with the ACT.

Table 14: Axicabtagene ciloleucel – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom			
1	high-dose therapy is an option[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy	Added benefit not proven
2	high-dose therapy is not an option[d]	Treatment of physician's choice[e], taking into account ▪ pola-BR[f] ▪ tafasitamab + lenalidomide[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research question 2). Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
c. In the line of treatment, allogeneic stem cell transplantation is an option in patients who have a very high risk of relapse or in whom sufficient stem cell collection for autologous stem cell transplantation was not possible.
d. Patients are assumed to be not eligible for high-dose therapy and to generally continue antineoplastic treatment after first-line immunotherapy.
e. A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
f. The approval of pola-BR and tafasitamab + lenalidomide relates exclusively to DLBCL (approval of 2020/2021). With the updated WHO classification of 2022, HGBL was newly listed as a definite entity. Prior to this update, aggressive lymphomas with MYC and BCL2/6 rearrangements were classified as DLBCL, so that HGBL was not specified separately in the therapeutic indication at the time of approval of pola-BR and tafasitamab + lenalidomide. Therefore, specifying these treatment options for both DLBCL and HGBL is considered appropriate.

ACT: appropriate comparator therapy; BSG: Federal Social Court; DLBCL: diffuse large B-cell lymphoma; G-BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; MINE: combination therapy of mesna, ifosfamide, mitoxantrone and etoposide; pola-BR: polatuzumab in combination with bendamustine and rituximab; SGB: Social Code Book; WHO: World Health Organization

The assessment described above differs from that of the company, which derived an indication of a considerable added benefit for research question 1 on the basis of the ZUMA-7 study, and a hint of a non-quantifiable added benefit for research question 2 on the basis of the ALYCANTE study.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list. The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Kite Pharma. Fachinformation Yescarta Infusionsdispersion (Axicabtagen-Ciloleucel); Stand: Oktober. 2022.

2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

3. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

4. Kite Pharma. Clinical Study Report KTE-C19-107: A Phase 3 Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7) [unpublished]. 2021.

5. Kite Pharma. Addendum to the primary analysis clinical study report [unpublished]. 2022.

6. Kite Pharma. Summary Report of Primary Analysis of Overall Survival: A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7) [unpublished]. 2023.

7. ClinicalTrials.gov. NCT03391466 - Titel: Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma [online]. 2023 [Accessed: 03.04.2023]. URL: https://classic.ClinicalTrials.gov/show/NCT03391466.

8. EU C.T.R. 2017-002261-22 - Titel: A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7) [online]. 2017. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002261-22.

9. Elsawy M, Chavez JC, Avivi I et al. Patient-reported outcomes in ZUMA-7; a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma. Blood 2022.

10. Locke FL, Miklos DB, Jacobson CA et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med 2021.

11. Westin JR, Oluwole OO, Kersten MJ et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med 2023. https://dx.doi.org/10.1056/NEJMoa2301665.

12. European Medicines Agency. Yescarta; Assessment report [online]. 2022 [Accessed: 18.08.2023]. URL: https://www.ema.europa.eu/documents/variation-report/yescarta-h-c-004480-ii-0046-epar-assessment-report-variation_en.pdf.

13. Swerdlow SH, Campo E, Pileri SA et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127(20): 2375-2390. https://dx.doi.org/10.1182/blood-2016-01-643569.

14. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32(27): 3059-3068. https://dx.doi.org/10.1200/JCO.2013.54.8800.

15. Leitlinienprogramm Onkologie. S3-Leitlinie Diagnostik, Therapie und Nachsorge für erwachsene Patient*innen mit einem diffusen großzelligen B-Zell-Lymphom und verwandten Entitäten; Langversion 1.0 [online]. 2022 [Accessed: 07.11.2022]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/DLBCL/Version_1/LL_DLBCL_Langversion_1.0.pdf.

16. Gisselbrecht C. Use of rituximab in diffuse large B-cell lymphoma in the salvage setting. Br J Haematol 2008; 143(5): 607-621. https://dx.doi.org/10.1111/j.1365-2141.2008.07383.x.

17. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lisocabtagen maraleucel (DLBCL, HGBL, PMBCL und FL3B, Zweitlinie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 07.09.2023]. URL: https://www.iqwig.de/download/a23-48_lisocabtagen-maraleucel_nutzenbewertung-35a-sgb-v_v1-0.pdf.

18. Gemeinsamer Bundesausschuss. Antworten auf häufig gestellte Fragen zum Verfahren der Nutzenbewertung [online]. [Accessed: 31.08.2023]. URL: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/faqs/.

19. ClinicalTrials.gov. NCT04531046 - Titel: Axi-Cel as a 2nd Line Therapy in Patients With Relapsed/Refractory Aggressive B Lymphoma Ineligible to Autologous Stem Cell Transplantation [online]. 2023 [Accessed: 03.04.2023]. URL: https://classic.clinicaltrials.gov/ct2/show/NCT04531046.

20. EU C.T.R. 2020-001868-28 - Titel: Phase 2, Open Label Study Evaluating Axi-Cel as a 2nd Line Therapy in Patients with Relapsed/Refractory Aggressive B-NHL Who Are Ineligible to Autologous Stem Cell Transplantation. EU Clinical Trials Register; 2020. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=ALYCANTE.

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