Axicabtagene ciloleucel (DLBCL and HGBL, second line)

Benefit assessment according to §35a SGB V[1] (expiry of the decision)

EXTRACT

Project: A24-71 Version: 1.0 Status: 24 Sep 2024 DOI: 10.60584/A24-71_en

[1] Translation of Sections I 1 to I 4 of the dossier assessment *Axicabtagen-Ciloleucel (DLBCL und HGBL, Zweitlinie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Axicabtagene ciloleucel (DLBCL and HGBL, second line) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

28 June 2024

Internal Project No.

A24-71

DOI-URL

https://doi.org/10.60584/A24-71_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

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

Medical and scientific advice

- Ingo Schmidt-Wolf, Germany

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

Patient and family involvement

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

IQWiG thanks the respondent and the Patientenorganisation Leukämie und Lymphom SHG Ruhr-Lippe e. V. for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent and the Patientenorganisation Leukämie und Lymphom SHG Ruhr-Lippe e. V. were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Jonas Goretzko
- Nadia Abu Rajab
- Dorothee Ehlert
- Ulrich Grouven
- Ulrike Lampert
- Philip Kranz
- Prateek Mishra
- Ulrike Seay

Keywords

Axicabtagene Ciloleucel, Lymphoma – Large B-Cell – Diffuse, Benefit Assessment, NCT03391466

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[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
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
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
FACT-LymS	Functional Assessment of Cancer Therapy-Lymphoma Subscale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HDCT	high-dose chemotherapy
HGBL	high-grade B-cell lymphoma
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PR	partial response
RCT	randomized controlled trial
RR	relative risk
sAAIPI	second-line age-adjusted International Prognostic Index
SAE	serious adverse event
SCT	stem cell transplantation
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

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 28 June 2024.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. The dossier was sent to IQWiG on 30 June 2023. In this procedure, by decision of 21 December 2023, the G-BA limited its decision until 01 July 2024.

The time limit is based on the fact that the analyses on adverse events (AEs) from the ZUMA-7 study presented by the company were not suitable for the benefit assessment and it was thus impossible to weight the benefits and harms of axicabtagene ciloleucel on the basis of the data presented. For the reassessment after expiry of the decision, it was requested that analyses on all outcomes on AEs (including event time analyses) in the ZUMA-7 study be submitted based on an analysis population that not only includes patients in the intervention arm who received an infusion with axicabtagene ciloleucel, but also comprises AEs during the preparatory processes, i.e. leukapheresis, bridging therapy and lymphodepletion. In addition, results on all patient-relevant outcomes from the ZUMA-7 study were to be presented.

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, and who are candidates for high-dose therapy. Depending on the suitability of high-dose therapy for the patients, the G-BA distinguished between different treatment situations and specified different ACTs for each of them. In accordance with the G-BA's limitation of the decision, the present assessment refers exclusively to the research question presented in Table 2.

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

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 who are eligible for high-dose therapy[b]	Induction therapy with one of the following options: ▪ R-GDP ▪ R-ICE ▪ R-DHAP followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy
a. Presented is the ACT specified by the G-BA. b. Patients are presumed to be 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. DLBCL: diffuse large B-cell lymphoma; G BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide	

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

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

Study pool and study design

Study ZUMA-7

Concurring with the company, the study pool of the present benefit assessment comprises the RCT ZUMA-7, in which axicabtagene ciloleucel was compared with induction chemotherapy (induction) followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (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 (CD) 20 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).

Treatment with axicabtagene ciloleucel was in accordance with the Summary of Product Characteristics (SPC). 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, R-DHAP, R-ESHAP or R-GDP at the discretion of the investigator. Patients who achieved a partial response (PR) or complete response (CR) by the Lugano Classification after 2 to 3 cycles of induction therapy (approximately on Day 50) received subsequent HDCT and autologous SCT.

Primary outcome of the ZUMA-7 study was event-free survival (EFS). Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects.

The 2nd data cut-off from 25 January 2023 was primarily used for the benefit assessment; the 1st data cut-off from 18 March 2021 was only used for the outcome “failure of the curative treatment approach”.

The ZUMA-7 study has several limitations. For example, relevant changes were made to the study protocol during the course of the study, although it is not sufficiently ensured that this was done without knowledge of the data. In the European Public Assessment Report (EPAR), also the European Medicines Agency (EMA) points out that, for example, biostatisticians had continuous access to the study data during its implementation, and that no clearly defined firewall was in place to ensure that the study conduct and the monitoring of the study were separated from each other.

In both arms of the ZUMA-7 study, the investigator assessed the response to the therapy on Day 50. In the comparator arm of the ZUMA-7 study, the treatment approach was only continued in the case of PR or CR. It was already described in dossier assessment A23-66 and addendum A23-106 that there was a clear discrepancy between the investigator's assessment and the blinded central review in the comparator arm, but not in the intervention arm. The company has now presented data showing the deviation between the investigator's assessment and the central review at Day 50. The assessments deviated for 28 (19%) patients for whom both an assessment by the investigator and a central assessment were available on

Day 50. This suggests a systematic bias due to the lack of blinding of the outcome recorders, which affects the further treatment of the patients and the observation for outcomes in the side effects category during the course of the study.

In addition, in the ZUMA-7 study, the bridging therapy after leukapheresis and before the infusion of axicabtagene ciloleucel was limited to corticosteroids. 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.

Risk of bias

The risk of bias across outcomes was rated as high for the study. This is due to the fact that there are uncertainties in the conduct of the study and the assessments by the unblinded investigators in the comparator arm differ greatly from the central blinded assessment. The outcome-specific risk of bias was also rated as high for the results of all patient-relevant outcomes. Based on the ZUMA-7 study, at most hints, e.g. of an added benefit, can therefore be derived.

Results

Mortality

Overall survival

No suitable data are available for the outcome of overall survival. There is no hint of an added benefit of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Morbidity

Failure of the curative treatment approach

For the outcome of failure of the curative treatment approach, a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. In summary, there is a hint of an added benefit of axicabtagene ciloleucel compared to induction + HDCT + autologous SCT for this outcome.

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 EQ-5D visual analogue scale [EQ-5D VAS])

Suitable data are neither available for symptoms (recorded using the EORTC QLQ-C30 and the Functional Assessment of Cancer Therapy-Lymphoma Subscale [FACT-LymS]) nor for health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for health-related quality of life (recorded using EORTC QLQ-C30). There is no hint of an added benefit of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Severe AEs

No statistically significant difference between treatment groups was shown for the outcome of severe AEs. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No information on the effect estimate is available for the outcome "discontinuation due to AEs". However, only very few events occurred in both study arms, so that a statistically significant difference between the study arms can be ruled out. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Specific AEs

Cytokine release syndrome, secondary malignancies

No suitable data are available for the outcomes of cytokine release syndrome and secondary malignancies. In each case, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Severe neurological toxicity (severe AEs [Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3])

For the outcome of severe neurological toxicity, a statistically significant difference was shown to the disadvantage of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of greater harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Severe infections (severe AEs [CTCAE grade ≥ 3])

No statistically significant difference between treatment groups was shown for the outcome of severe infections. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Ear and labyrinth disorders, mucosal inflammation, hiccups (AEs)

For each of the outcomes of ear and labyrinth disorders, mucosal inflammation and hiccup, a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. In each case, there is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Hypoxia (AEs)

For the outcome of hypoxia, a statistically significant difference was shown to the disadvantage of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of greater harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Cough (AEs)

For the outcome of cough, a statistically significant difference was shown to the disadvantage of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. However, there is an effect modification by the characteristic of second-line age-adjusted International Prognostic Index (sAAIPI). For patients with sAAIPI 2 to 3, there is a hint of greater harm from axicabtagene ciloleucel versus induction + HDCT + autologous SCT. For patients with sAAIPI 0 to 1, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven for patients with sAAIPI 0 to 1.

Febrile neutropenia (SAEs)

For the outcome of febrile neutropenia (SAEs), a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Gastrointestinal disorders (severe AEs [CTCAE grade ≥ 3])

For the outcome of gastrointestinal disorders (severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Thrombocytopenia (severe AEs [CTCAE grade ≥ 3])

For the outcome of thrombocytopenia (severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. However, there was an effect modification by the characteristic of age. For patients < 65 years of age, there is a hint of lesser harm from axicabtagene ciloleucel versus induction + HDCT + autologous SCT. For patients ≥ 65 years of age, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven for patients ≥ 65 years of age.

Neutropenia, general disorders and administration site conditions, psychiatric disorders, hypotension (in each case severe AEs [CTCAE grade ≥ 3])

For the outcomes of neutropenia, general disorders and administration site conditions, psychiatric disorders and hypotension (severe AEs [CTCAE grade ≥ 3] in each case), there is a statistically significant difference to the disadvantage of axicabtagene ciloleucel compared to induction + HDCT + autologous SCT. In each case, there is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

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

On the basis of the results presented, the probability and extent of added benefit of the drug axicabtagene ciloleucel in comparison with the ACT is assessed as follows:

In the overall assessment, there are both positive and negative effects of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

In terms of positive effects, there is a hint of minor added benefit for the outcome of failure of the curative treatment approach. In the category of serious/severe side effects, there are hints of both greater harm and lesser harm, some of which are considerable. In the category of non-serious/non-severe side effects, there are also hints of both greater and lesser harm of up to considerable extent. Overall, the positive and negative effects in terms of side effects are balanced and do not challenge the positive effect in terms of morbidity.

[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 {Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2023 #2;Skipka, 2016 #11}.

In summary, for patients with DLBCL or HGBL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and who are eligible for high-dose therapy, there is a hint of minor added benefit of axicabtagene ciloleucel compared with the ACT "induction + HDCT + autologous SCT".

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

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

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 who are eligible for high-dose therapy[b]	Induction therapy with one of the following options: ▪ R-GDP ▪ R-ICE ▪ R-DHAP followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy	Hint of minor added benefit

a. Presented is the ACT specified by the G-BA.
b. Patients are presumed to be 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.

DLBCL: diffuse large B-cell lymphoma; G BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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, and who are candidates for high-dose therapy.

The G-BA has defined 2 research questions depending on the suitability of high-dose therapy for the patients. In accordance with the G-BA's limitation of the decision, this assessment relates exclusively to the issue of patients for whom high-dose therapy is an option [1].

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

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

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 who are eligible for high-dose therapy[b]	Induction therapy with one of the following options: ▪ R-GDP ▪ R-ICE ▪ R-DHAP followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy
a. Presented is the ACT specified by the G-BA. b. Patients are presumed to be 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. DLBCL: diffuse large B-cell lymphoma; G BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide	

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

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on axicabtagene ciloleucel (status: 3 April 2024)
- bibliographical literature search on axicabtagene ciloleucel (last search on 3 April 2024)
- search in trial registries/trial results databases for studies on axicabtagene ciloleucel (last search on 3 April 2024)
- search on the G-BA website for axicabtagene ciloleucel (last search on 3 April 2024)

To check the completeness of the study pool:

- search in trial registries for studies on axicabtagene ciloleucel (last search on 11 July 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: 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 [2-4]	Yes [5,6]	Yes [7-13]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
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

The study pool of the present benefit assessment comprises the RCT ZUMA-7. The study pool corresponds to that of the company.

I 3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: 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 HGBLb with refractory or relapsed diseasec < 12 months after first-line therapyd ▪ 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 01/2018–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 8.
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 body of text).

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 **non-permitted 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 **non-permitted concomitant treatment** ▪ other lymphoma therapies, such as immunotherapy, targeted drugs (e.g. CD19-targeted therapy), radiotherapy (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 a partial or complete response to induction therapy, HDCT (e.g. BEAM or CBV with or without total body irradiation) and autologous SCT were initiated according to 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		

ZUMA-7 is an ongoing, open-label, multicentre RCT comparing axicabtagene ciloleucel versus induction chemotherapy (induction) followed by HDCT and autologous SCT in adult patients with DLBCL or HGBL according to the 2016 WHO classification [14].

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 after first-line therapy) and sAAIPI (0 to 1 versus 2 to 3).

Axicabtagene ciloleucel treatment was administered in compliance with the SPC [15]. Leukapheresis was performed within 5 days of randomization. Lymphodepleting chemotherapy 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 [16] 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 (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [AWMF])[17]. The R-ESHAP regimen administered in the ZUMA-7 study is not explicitly listed in the S3 guideline and is not part of the G-BA's ACT. However, it was only used in 3% of patients in the study, so the use of R-ESHAP 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.

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 primarily relevant data cut-off for the benefit assessment because the follow-up period was almost 2 years longer. For the outcome "failure of the curative treatment approach", however, the 1st data cut-off is used (for explanation see Section I 4.1).

Limitations of the study

Potentially data-driven changes to the study protocol

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 reduced 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.

Despite the subsequent explanations of the company in the context of the commenting procedure [18] on project A23-66, it cannot be excluded with sufficient certainty that the triggers for the analyses of the study were changed in a data-driven manner. This uncertainty is taken into account in the risk of bias across outcomes.

Deviations between the investigator's assessment and the central blinded assessment

In both arms of the ZUMA-7 study, the investigator assessed the response to the therapy on Day 50. In the comparator arm of the ZUMA-7 study, the treatment approach was only continued in the case of PR or CR. If no PR or CR was detected, the therapy approach was considered to have failed and a follow-up treatment was initiated. The unblinded assessment of the investigator was therefore decisive for the further treatment of the patients and the observation in the outcome category of side effects. A blinded central review only took place after a delay.

It was already described in dossier assessment A23-66 [12] and the related addendum A23-106 [11] that there was a clear discrepancy between the investigator's assessment and the blinded central review in the comparator arm, but not in the intervention arm. The company has now presented data showing the deviation between the investigator's assessment and the central review at Day 50. For 28 (19%) patients for whom an assessment by both the investigator and the central review was available at Day 50, the assessments differed (19 patients without objective response according to the investigator but response according to the central review; 9 patients with objective response according to the investigator but not according to the central review). This suggests a systematic bias due to the lack of blinding of the outcome recorders, which affects the further treatment of the patients and the observation for outcomes in the side effects category during the course of the study. This is taken into account in the risk of bias across outcomes.

Bridging therapies

The 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) [17]. In general, these are chemoimmunotherapies, but targeted substances or radiotherapy are also possible. According to the current National Comprehensive Cancer Network (NCCN) guideline for the treatment of B-cell lymphomas, various chemotherapy regimens (including R-DHAP, R-GDP, R-ICE) are described as recommended bridging therapy options before CAR-T cell therapy for the second line of treatment [19]. 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 also considered inappropriate against the background of current guideline recommendations and does not adequately reflect the health care context. This therefore represents another relevant limitation of the ZUMA-7 study.

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 or failure of the curative treatment approach	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 patient characteristics of 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)

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
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)
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 [10]. 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
Study ZUMA-7		
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]
Response (PR/CR) at Day 50 per central review, n (%)	142 (79)	87 (49)
Response (PR/CR) at Day 50 according to the investigator, n (%)	ND	80 (45)[e]
HDCT, n (%)	–	64 (36)[e]
Autologous SCT, n (%)	–	62 (35)[e]

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).
e. Includes the following patients: 77 patients who had a response (PR/CR) according to the investigator within the Day 50 assessment window (day 43 - 71); of these patients, 62 received HDCT and 60 received autologous SCT. In addition, 3 patients with a response according to the investigator whose assessment was outside the Day 50 time window; 2 of them received HDCT followed by autologous SCT.

AE: adverse event; CR: complete response; 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; ND: no data; PR: partial response; 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

In the intervention arm, 94% of the patients received axicabtagene ciloleucel infusion. 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.

It should be noted that a total of 87 patients achieved response to induction therapy by Day 50 according to the blinded central review (43 with CR and 44 with PR, see Table 10), but only 64 patients continued with HDCT, and 62 patients with subsequent autologous SCT. The investigator's assessment of the response on Day 50 was decisive for the continuation of the treatment approach. The company cited disease progression in the period between the assessment on Day 50 and the planned SCT as the main reason for the non-performance of autologous SCT despite the patients' response.

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/outcome**	**Axicabtagene ciloleucel** **N = 180**	**Induction + HDCT + autologous SCT** **N = 179**
ZUMA-7		
Treatment duration[a] [days]		
Median [Q1; Q3]	26.0 [16; 52]	N D
Mean (SD)	26.9 (6.1)	N D
Observation period [months]		
Overall survival[b]		
Median [95% CI]	47.0 [45.4; 48.3]	45.8 [44.2; 47.8]
Failure of the curative approach or EFS (mEFS1)[c]		
Median [Q1; Q3]	5.5 [3.4; 21.0]	1.8 [1.4; 5.5]
Mean (SD)	11.9 (9.7)	5.7 (7.8)
Failure of the curative treatment approach or EFS according to the central review (mEFS2)c	N D	N D
Symptoms, health-related quality of life (EORTC QLQ-C30), median[d, e]	13.7 [N D; N D]	3.5 [N D; N D]
Health status (EQ-5D VAS), median[d, e,]	12.7 [N D; N D]	3.5 [N D; N D]
Side effects[f]		
Median [Q1; Q3]	4.8 [4.0; 4.8]	3.4 [2.2; 4.8]
Mean (SD)	4.3 (1.0)	3.4 (1.4)

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 observation periods for the outcome of overall survival were calculated using the reverse Kaplan-Meier method.
c. The observation period for the mEFS1 is the time from randomization to the time of the event or to the time of censoring.
d. No information on the methods for calculating the observation period in the company's documents.
e. Data refer to the first data cut-off (from 18 March 2021) and only to patients for whom a value was available at baseline (axicabtagene ciloleucel: N = 165, induction + HDCT + autologous SCT: N = 131).
f. Data refer to the modified safety analysis set (axicabtagene-ciloleucel: N = 178, induction + HDCT + autologous SCT: N = 168), which includes all patients in the intervention arm who started the prepared processes (leukapheresis, bridging therapy and lymphodepletion) before infusion with axicabtagene ciloleucel or patients in the comparator arm who received at least 1 dose of induction chemotherapy.

EFS: event-free survival; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life 5 Dimensions; HDCT: high-dose chemotherapy; N D: no data; mEFS: modified EFS; N: number of randomized patients; 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

The median treatment duration in the intervention arm, defined as the time from leukapheresis to infusion of axicabtagene ciloleucel, was 26 Days. For the comparator arm,

the dossier provides no information on the time to completion of treatment with autologous SCT.

The median observation period for overall survival was about 47 months in the intervention arm and thus comparable to the comparator arm (approx. 46 months). In the dossier, the company only states the follow-up for "failure of the curative treatment approach" or "EFS" for the newly presented mEFS1 analysis, defined as the time from randomization to the time of the event or to the time of censoring. The median observation period of mEFS1 was about 6 months in the intervention arm and about 2 months in the comparator arm.

The observation periods for the other outcomes were all shortened and differed between the study arms.

Subsequent therapies

Table 12 shows the subsequent therapies patients received after discontinuing the study medication.

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (ZUMA 7) (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy n (%)**	
	axicabtagene ciloleucel **N = 180**	**induction + HDCT + autologous SCT** **N = 179**
ZUMA-7		
Total	88 (49)	128 (72)
Chemo(immuno)therapy (including anti-CD20 therapy and pola-BR)	71 (39)	76 (42)
Autologous CD19 CAR T therapy	12 (7)	99 (55)
Antibody-drug conjugates (except Pola-BR)	15 (8)	14 (8)
BTK inhibitor	11 (6)	7 (4)
Immunomodulatory agents	14 (8)	18 (10)
Radiation therapy alone	16 (9)	28 (16)
HDT + autologous SCT	13 (7)	7 (4)
Allogeneic SCT	14 (8)	7 (4)
Other cellular therapies	2 (1)	5 (3)
Allogeneic CD19 CAR T therapy	1 (1)	1 (1)
Autologous CD19/CD22 bispecific CAR T therapy	0 (0)	1 (1)
CAR NK anti-CD16	1 (1)	0 (0)
CD22-CAR-T	0 (0)	2 (1)
Cord blood NK	0 (0)	1 (1)

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (ZUMA 7) (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy n (%)**	
	axicabtagene ciloleucel N = 180	**induction + HDCT + autologous SCT N = 179**
Other therapies (not including any anti-CD20)	43 (24)	42 (23)
4-1BB agonist	0 (0)	1 (1)
Anti-CCR4 and checkpoint inhibitor	1 (1)	0 (0)
BCL2 inhibitor	6 (3)	2 (1)
BET inhibitor	0 (0)	1 (1)
Bispecific T-cell engager	10 (6)	7 (4)
Checkpoint inhibitor	18 (10)	12 (7)
CRL4-CRBN E3 ubiquitin ligase inhibitor	1 (1)	0 (0)
DHODH inhibitor	1 (1)	0 (0)
EED inhibitor	1 (1)	0 (0)
Heat shock protein 90 inhibitor	0 (0)	1 (1)
Immunotherapy (not otherwise specified)	0 (0)	1 (1)
Investigational product on clinical study (not otherwise specified)	3 (2)	2 (1)
IRAK4 kinase inhibitor	0 (0)	1 (1)
Monoclonal antibody anti-CD19	1 (1)	3 (2)
Monoclonal antibody anti-CD27	4 (2)	2 (1)
MALT-1 inhibitor	0 (0)	1 (1)
mRNA and checkpoint inhibitor	1 (1)	0 (0)
mTOR inhibitor and asparaginase	0 (0)	1 (1)
Nuclear export inhibitor	2 (1)	1 (1)
PDH-KGDH inhibitor	1 (1)	0 (0)
PI3K and HDAC inhibitor	1 (1)	0 (0)
PI3K inhibitor	1 (1)	1 (1)
Recombinant fusion CD47	0 (0)	1 (1)
Steroids	8 (4)	16 (9)
Surgery	2 (1)	2 (1)

4-1BB: tumour necrosis factor receptor superfamily member 9; BCL2: apoptosis regulator Bcl-2; BET: bromodomain and extra-terminal domain; CAR: chimeric antigen receptor; CCR4: C-C chemokine receptor type 4; CD: cluster of differentiation; CRBN: cereblon; CRL4: cullin-RING E3 ubiquitin ligase 4; DHODH: dihydroorotate dehydrogenase; EED: polycomb protein EED; HDAC: histone deacetylase; HDT: high-dose therapy; IRAK4: interleukin-1 receptor-associated kinase 4; KGDH: α-ketoglutarate dehydrogenase; MALT-1: mucosa-associated lymphoid tissue lymphoma translocation protein 1; mRNA: messenger ribonucleic acid; mTOR: mammalian target of rapamycin; n: number of patients with subsequent therapy; N: number of analysed patients; NK: natural killer cell; PDH: pyruvate dehydrogenase; PI3K: phosphoinositide 3-kinase; Pola-BR: polatuzumab in combination with bendamustine and rituximab; RCT: randomized controlled trial; SCT: stem cell transplantation

In the ZUMA-7 study, subsequent therapies were permitted without restrictions in both study arms. Overall, 88 (49%) patients in the intervention arm and 128 (72%) patients in the comparator arm received at least one subsequent therapy as of the second data cut-off.

In the intervention arm, 71 (81%) of patients with subsequent therapy received chemo(immuno)therapy (including anti-CD20 therapy and polatuzumab in combination with bendamustine and rituximab [pola-BR]). High-dose therapy followed by autologous SCT was used in 13 (15 %) of the patients with subsequent therapy in the intervention arm. The subsequent therapies used in the intervention arm appear appropriate overall.

In the comparator arm, 99 (77%) of patients with subsequent therapy received autologous CD19 CAR T therapy. A relevant proportion of patients thus received subsequent therapy in accordance with the guideline recommendation, which provides for anti-CD19 therapy with CAR T-cells for the treatment of ≥ 2nd relapse with primary curative intent, if this has not already been carried out in second-line therapy [17]. It cannot be inferred from the company's information whether other patients in the comparator arm would have benefited from CAR T therapy as subsequent therapy.

Overall, the subsequent therapies used in the ZUMA-7 study are assumed to be appropriate. However, as described in dossier assessment A23-66 [12], it is still not certain that the start of a subsequent therapy was actually indicated for all patients in the ZUMA-7 study. The company's subsequent submission in the context of the commenting procedure now shows that subsequent therapies were potentially not (yet) indicated for a relevant proportion of patients in the comparator arm, as the curative approach had not failed at this time. This applied to 16 of 63 patients (25%) in the comparator arm who had a new lymphoma therapy as a qualifying EFS event according to the blinded central review [11]. In addition, there might be patients for whom, deviating from the investigator's assessment, the central review revealed no failure of the curative treatment approach (see above). For these, it is unclear whether the start of subsequent therapy was already indicated. Starting a subsequent therapy without the curative approach having failed can cause bias in overall survival of the comparator arm. This is justified below.

If the patients received a subsequent therapy although the therapy with induction + HDCT + autologous SCT in the second line of therapy had not failed, the patients in the comparator arm were still in the second line of therapy. For these patients, the ZUMA-7 study therefore does not answer the research question of axicabtagene ciloleucel versus induction + HDCT + autologous SCT with adequate subsequent therapy after failure of the curative treatment approach, but rather that of axicabtagene ciloleucel at an early time point in the second line versus CAR T therapy at a later time point in the second line. One reason for the later time point is that, if treatment was discontinued without a failed curative treatment approach with induction + HDCT + autologous SCT in the second line, there may have been a relevant waiting

time for the potentially curative treatment with CAR T therapy. Besides, a relevant proportion of patients achieved a sufficient response to induction chemotherapy, but then potentially received subsequent therapy with CAR T therapy instead of HDCT + autologous SCT. Accordingly, leukapheresis and the subsequent production of CAR T therapy were not only delayed for the second line of therapy, but were also carried out after successful induction chemotherapy, which does not correspond to the standard of care. It is unclear how these aspects affect overall survival. Consequences for the interpretability of overall survival are described in Section I 4.1.

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: 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
a. For reasons, see body of text below.							
HDCT: high-dose chemotherapy; RCT: randomized controlled trial; SCT: stem cell transplantation							

The risk of bias across outcomes was rated as high for the study. This is due to uncertainties in the conduct of the study and potentially data-driven changes to the study protocol. In addition, the assessments by the unblinded investigators in the comparator arm differed strongly from the central blinded review (see above and Section I 4.1). Since the decision on the continuation of treatment was based on the assessment of progression by the investigators, it can be assumed that this resulted in an increased risk of bias for all outcomes. This potential bias affects all data cut-offs and outcomes.

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 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Failure of the curative treatment approach
  - Symptoms, recorded using the EORTC QLQ-C30
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - Recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Cytokine release syndrome
  - Severe neurological toxicity
  - Severe infections
  - Secondary malignancies
  - Other specific AEs, if any

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

Table 14 shows the outcomes for which data were available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

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

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC nervous system disorders.
c. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC infections and infestations.
d. The following events were considered: ear and labyrinth disorders (SOC, AEs), mucosal inflammation (PT, AEs), cough (PT, AEs), hiccups (PT, AEs), hypoxia (PT, AEs), febrile neutropenia (PT, SAEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), psychiatric disorders (SOC, severe AEs), hypotension (PT, severe AEs)
e. No suitable data/analyses available; see body of text for reasons.

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

Notes on outcomes

Overall survival is not interpretable

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 3.2, the potentially data-driven changes to the study protocol and the investigator's assessment deviating from the central review, 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, it is unclear whether the subsequent therapies administered in the comparator arm were actually already indicated (for an explanation, see Section I 3.2). In its dossier, the company itself now

notes that a bias in the results due to a subsequent therapy that has not yet been indicated cannot be ruled out. Furthermore, although the effect observed at the second data cut-off for the outcome of overall survival is statistically significant (hazard ratio: (HR) 0.73; 95% confidence interval: [0.54; 0.98]), 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 potentially not yet indicated subsequent therapies and the minor extent of the effect, it remains unclear whether there is actually an advantage for axicabtagene ciloleucel in the outcome of overall survival.

Overall, the results for the outcome of overall survival are thus not interpretable. The results are presented as supplementary information in I Appendix D of the full dossier assessment.

Failure of the curative treatment approach

In the present therapeutic indication, curative therapy is possible in principle. Failure to achieve remission or occurrence of relapse after achieving remission means that the curative treatment approach in this line of therapy has failed. In the present treatment situation, failure of the curative treatment approach in the current line of therapy is a patient-relevant event because, albeit possible in principle, cure is less likely to 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, 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. 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. The primary outcome of the ZUMA-7 study is not suitable for depicting the failure of the curative treatment approach, as it includes the component “commencement of a new lymphoma therapy”, which does not reliably report a failure of the curative treatment approach (see also dossier assessment A23-66). However, events that were recorded in the composite outcome EFS and reliably reflect the failure of the curative treatment approach can be considered approximately for the present benefit assessment. This involves various uncertainties, which are approximately addressed by the company in the context of 2 new operationalizations of the outcome of EFS (mEFS1 and mEFS2). The company’s analyses were jointly used for the benefit assessment. The limitations of the operationalization of the EFS presented for the previous benefit assessment are first described below. In particular, the differences between the investigator's assessment and the blinded central review are addressed. The operationalizations of the EFS that are now available are explained below.

Discrepancies between the investigator's assessment and the blinded central review

As described in Section I 3.2, there are relevant differences between the blinded central review and the investigator's assessment with regard to the assessment of the response to therapy in the comparator arm at Day 50. At this point, the investigator's assessment was decisive for the continuation of therapy in the comparator arm or the switch to a new lymphoma therapy. In the comparator arm, the original EFS analyses at the first data cut-off showed that, according to the investigator, 98 (70%) of the qualifying events were attributed to disease progression and 37 (26%) to the start of new lymphoma therapy, while 75 (52%) of the events were disease progression and 63 (44%) were the start of new lymphoma therapy according to the blinded central review [12]. In the intervention arm, however, the distribution of qualifying events did not differ significantly between the two analyses. Therefore, a systematic bias due to a lack of blinding of the outcome recorders cannot be ruled out. Against this background, analyses based on the blinded central review appear to be generally more suitable for the benefit assessment in the present data situation. However, the problem here is that a central review on Day 50 is not available for all patients, which means that the number of EFS events in a review based on this assessment is potentially underestimated. This affected 32 (18%) patients in the comparator arm. The company has now submitted the reasons for the lack of information on the central review on Day 50. For 11 of the 32 patients, there was no blinded central review because they did not start treatment. In these patients, the curative treatment approach did not fail and they are therefore not included as an event in the analyses. In the majority of the remaining 21 patients, events occurred that reflect a failure of the curative treatment approach (SD or PD on Day 50 according to the central review, but outside the Day 50 time window from Days 43 to 71).

In order to consider both the central review and the treatment-decisive assessment by the investigator, the company has now presented 2 new operationalizations of the EFS (named mEFS1 and mEFS2 by the company) in the dossier. The mEFS2 only includes the assessments of the blinded central review, while the mEFS1 also includes the investigators' assessments.

<u>mEFS1</u>

The mEFS1 is defined as the time between the day of randomization and the time of occurrence of the first of the following events:

- Death due to any cause
- Progression of the disease (according to the blinded central review)
- Failure to achieve CR or PR by Day 50 in the comparator arm (after blinded central review)

- Failure to achieve CR at Day 150 according to blinded central review (or, if applicable, up to and including month 9)
- Initiation of new lymphoma therapy due to stable disease (SD) or PD according to the investigator

mEFS2

The mEFS2 is defined as the time between the day of randomization and the time of occurrence of the first of the following events:

- Death due to any cause
- Progression of the disease (according to the blinded central review)
- Failure to achieve CR or PR by Day 50 in the comparator arm (after blinded central review)
- Failure to achieve CR at Day 150 according to blinded central review (or, if applicable, up to and including month 9)
- Initiation of a new lymphoma therapy with previous SD according to blinded central review

The two operationalizations are consistent in 4 out of 5 included components. The only difference between mEFS1 and mEFS2 was in the component "commencement of new lymphoma therapy" (SD or PD according to investigator vs. previous SD according to blinded central review).

The components “death from any cause” and “progression of the underlying disease” according to central review are considered suitable for reflecting the failure of the curative treatment approach. In the comparator arm, a decision was made on Day 50 of the study as to whether the treatment strategy would be continued or not. Patients who had not achieved PR or CR did neither receive HDCT nor subsequent autologous SCT. The therapeutic approach has failed in this case. The component “failure to achieve CR or PR by Day 50 in the comparator arm (according to the blinded central review) is therefore considered adequate.

Recording the failure to achieve a CR at Day 150 (or, if applicable, up to and including month 9) after randomization as an event is considered to be adequate to reflect the failure of the curative treatment approach in this therapeutic indication. The present analyses only consider the assessment at Month 9 if a central review took place at this time. The company also argues that a response to CAR-T cell therapy could still occur after Month 9 and that 4 patients in the intervention arm still achieved CR after Month 9. However, in the analyses on the failure of the curative treatment approach presented in the dossier and used for the benefit assessment, these patients are counted as events.

Classification of the present operationalizations

As described above, the start of a new lymphoma therapy does not always indicate the failure of the curative treatment approach. The operationalizations of the mEFS1 and mEFS2 that have now been presented each include events that comprehensibly justify the initiation of a new lymphoma therapy. For example, the mEFS1 takes into account that the investigator has diagnosed SD or PD. In the mEFS2, however, the new lymphoma therapy is only counted as an event if it was preceded by SD after a blinded central review. This concerns only 1 event per study arm (see Table 16). In principle, the two operationalizations are therefore suitable for depicting the failure of the curative treatment approach.

The mEFS1 operationalization includes events based on the investigator's assessment of SD or PD. Events in this component are subject to a high degree of uncertainty, as the investigators' assessment differs significantly from the central review (high risk of bias). To address the uncertainty regarding the potential systematic bias due to the lack of blinding of the outcome recorders, only events according to the central blinded review are included in the mEFS2. Even though there is no central review on Day 50 for 32 patients, it is assumed that the majority of these patients experienced qualifying events that reflect the failure of the curative treatment approach (e.g. PD) and that these are taken into account in the mEFS2. Overall, the joint consideration of both operationalizations, taking into account the respective weaknesses described, allows conclusions to be drawn about the failure of the curative treatment approach. Therefore, both operationalizations are considered for the benefit assessment and used together to derive the added benefit.

Relevant data cut-off

In its comments on A23-66, the company clarified that EFS per blinded central review was no longer recorded at the second data cut-off. For this outcome, the results of the first data cut-off thus cover the longest available observation period and are considered for the benefit assessment. Overall, the lack of EFS per blinded central review for the second data cut-off is of secondary importance, as only few additional events occurred between the first and second data cut-off.

Notes on the time-to-event analyses

The company specifies event time analyses and HR as effect measures for its new analyses. In the present case, however, the time-to-event analyses are inherently biased by the outcome operationalizations, as the component "failure to achieve CR or PR by Day 50" is only included in the analysis in the comparator arm and failure can therefore be achieved significantly earlier than in the intervention arm. The HR is therefore not interpretable in this case and is not shown. The Kaplan-Meier curves are not shown for the same reason. The relevant effect measure for determining the added benefit for the outcome of failure of the curative treatment approach is the relative risk (RR).

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

The analyses of the outcomes on symptoms, health status and health-related quality of life recorded in the ZUMA-7 study are not suitable for the benefit assessment, as was already described in dossier assessment A23-66 and in addendum A23-106. On the one hand, there is a high differential proportion of patients missing from the analysis, and on the other, the proportion of missing values increased strongly over the course of the study and differentially between the treatment arms, so that, already at the Day 100 recording, only < 50 % of the randomized patients in the comparator arm were taken into account in the analyses.

For these reasons, the results on the outcomes of symptoms, health status and health-related quality of life are not suitable for the benefit assessment.

Side effects

The company presented analyses on all AE outcomes (including time-to-event analysis) for a modified safety analysis set. In the intervention arm, this includes all patients from the time of leukapheresis and in the comparator arm all patients who have received at least one dose of the induction chemotherapy. This approach is appropriate. The analyses presented by the company without the disease-related events of the System Organ Class (SOC) neoplasms benign, malignant and unspecified (incl cysts and polyps) were used for the overall rates of AEs, SAEs and severe AEs.

Cytokine release syndrome

In the ZUMA-7 study, both the diagnosis of cytokine release syndrome and the underlying symptoms were documented using 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.

Secondary malignancies

In the ZUMA-7 study, the outcome of secondary malignancies was recorded as an AE of particular interest. The study documents show that the events recorded in the SOC “neoplasms benign, malignant and unspecified” (incl cysts and polyps) should be checked for those suggesting secondary malignancies. There is insufficient information on the criteria to be used for this review. It is also unclear which events were included in the analyses. These can therefore not be used for the benefit assessment. Furthermore, it is unclear whether the observation period in the ZUMA-7 study (see Table 11) is sufficient to fully reflect the occurrence of secondary malignancies.

Discontinuation due to AEs

In Module 4 A of the dossier, the company presents analyses without effect estimates on the outcome "discontinuation due to AEs" for the modified safety analysis set. It becomes clear that there were only a few discontinuations due to AEs (see Table 16). 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 estimates therefore have no consequences for the assessment.

I 4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study		Outcomes												
	Study level	Overall survival	Failure of the curative treatment approach	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Cytokine release syndrome	Severe neurological toxicity[a, b]	Severe infections[a, c]	Secondary malignancies	Further specific AEs[d]
ZUMA-7	H	–[e]	H[f]	–[e]	–[e]	–[e]	H[f]	H[f]	H[f]	–[e]	H[f]	H[f]	–[e]	H[f]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC nervous system disorders.
c. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC infections and infestations.
d. The following events were considered: ear and labyrinth disorders (SOC, AEs), mucosal inflammation (PT, AEs), cough (PT, AEs), hiccups (PT, AEs), hypoxia (PT, AEs), febrile neutropenia (PT, SAEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), psychiatric disorders (SOC, severe AEs), hypotension (PT, severe AEs).
e. No usable data/analyses available; see Section I 4.1 for the reasoning.
f. High risk of bias across outcomes.

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; H: high; L: low; 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

The outcome-specific risk of bias was rated as high for the results of all patient-relevant outcomes. This is due to the high risk of bias across outcomes (see Section I 3.2). Based on the ZUMA-7 study, at most hints, e.g. of an added benefit, can therefore be derived.

I 4.3 Results

Table 16 summarizes the results for the comparison of axicabtagene ciloleucel versus induction + HDCT + autologous SCT in patients with DLBCL or HGBL, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy, and who are eligible for high-dose therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses (if available) are presented in I Appendix B, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs in I Appendix C of the full dossier assessment.

Table 16: Results (morbidity, side effects) – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study **outcome category** **outcome**	**Axicabtagene ciloleucel**		**Induction + HDCT + autologous SCT**		**Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value**
ZUMA-7					
Mortality					
Overall survival	No suitable data[a]				
Morbidity					
Data cut-off 1 (18 March 2021)					
Failure of the curative treatment approach (mEFS1)					
Event rate[b]	180	– 108 (60)	179	– 133 (74)	RR[c] 0.81 [0.70; 0.94]; 0.004
Death due to any cause	180	– 12 (7)	179	– 7 (4)	
Progression according to blinded central assessment	180	– 82 (46)	179	– 72 (40)	
Failure to achieve CR or PR according to the blinded central review by Day 50 in the comparator arm	180	–	179	– 33 (18)	
Failure to achieve CR by Day 150 according to blinded central review (or, if applicable, up to Month 9)	180	– 8 (4)	179	– 1 (1)	
Commencement of a new lymphoma therapy due to SD/PD according to the investigator	180	– 6 (3)	179	– 20 (11)	

Table 16: Results (morbidity, side effects) – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study **outcome category** **outcome**	**Axicabtagene ciloleucel**		**Induction + HDCT + autologous SCT**		**Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value**
Failure of the curative treatment approach (mEFS2)					
Event rate[b]	180	– 106 (59)	179	– 125 (70)	RRc 0.84 [0.72; 0.99]; 0.033
Death due to any cause	180	– 15 (8)	179	– 18 (10)	
Disease progression according to blinded central review	180	– 82 (46)	179	– 72 (40)	
Failure to achieve CR or PR according to the blinded central review by Day 50 in the comparator arm	180	–	179	– 33 (18)	
Failure to achieve CR on Day 150 according to blinded central review (or, if applicable, up to Month 9)	180	– 8 (4)	179	– 1 (1)	
Initiation of a new lymphoma therapy with previous SD according to blinded central review	180	– 1 (1)	179	– 1 (1)	
Symptoms (EORTC QLQ-C30)	No suitable data[a]				
Health status (EQ-5D VAS)	No suitable data[a]				
Health-related quality of life					
EORTC QLQ-C30	No suitable data[a]				

Table 16: Results (morbidity, side effects) – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study outcome category outcome	Axicabtagene ciloleucel		Induction + HDCT + autologous SCT		Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Side effects					
Data cut-off 2 (25 January 2023)					
AEs (supplementary information)	178	0.5 [0.3; 0.6] 178 (100)	168	0.1 [0.1; 0.1] 168 (100)	–
SAEs	178	3.6 [1.4; 9.3] 106 (60)	168	4.9 [3.3; 8.6] 75 (45)	1.07 [0.79; 1.45]; 0.677
Severe AEs[d]	178	0.9 [0.8; 1.0] 164 (92)	168	0.5 [0.4; 0.5] 139 (83)	0.93 [0.74; 1.17]; 0.508
Discontinuation due to AEs	178	ND 4 (2.2)	168	ND 2 (1.2)	ND
Cytokine release syndrome	No suitable data[a]				
Severe neurological toxicity[d, e]	178	NA 41 (23)	168	32.2 [NC; NC] 15 (9)	2.70 [1.47; 4.97]; < 0.001
Severe infections[d, f]	178	10.9 [5.7; 27.1] 37 (21)	168	19.9 [NC; NC] 20 (12)	1.08 [0.61; 1.93]; 0.790
Secondary malignancies	No suitable data[a]				
Ear and labyrinth disorders (SOC, AEs)	178	NA 5 (3)	168	NA 18 (11)	0.23 [0.09; 0.63]; 0.002
Mucosal inflammation (PT, AEs)	178	NA 1 (1)	168	7.0 [4.9; NC] 16 (10)	0.04 [0.01; 0.32]; < 0.001
Cough (PT, AEs)	178	NA 47 (26)	168	NA 18 (11)	2.46 [1.43; 4.24]; < 0.001
Hiccups (PT, AEs)	178	NA 9 (5)	168	NA 21 (13)	0.36 [0.16; 0.78]; 0.007
Hypoxia (PT, AEs)	178	NA 38 (21)	168	NA 13 (8)	2.80 [1.49; 5.26]; < 0.001
Febrile neutropenia (PT, SAEs)	178	28.3 [12.1; NC] 6 (3)	168	NA 22 (13)	0.09 [0.03; 0.32]; < 0.001
Neutropenia (PT, severe AEs)	178	NA [3.1; NC] 74 (42)	168	NA 28 (17)	2.71 [1.75; 4.19]; < 0.001
Thrombocytopenia (PT, severe AEs)	178	NA 14 (8)	168	NA 37 (22)	0.29 [0.16; 0.55]; < 0.001

Table 16: Results (morbidity, side effects) – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study outcome category outcome	Axicabtagene ciloleucel		Induction + HDCT + autologous SCT		Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Gastrointestinal disorders (SOC, severe AEs)	178	12.0 [NC; NC] 21 (12)	168	5.0 [5.0; NC] 30 (18)	0.53 [0.30; 0.94]; 0.026
General disorders and administration site conditions (SOC, severe AEs)	178	6.0 [NC; NC] 30 (17)	168	7.1 [4.9; NC] 13 (8)	2.20 [1.12; 4.31]; 0.018
Psychiatric disorders (SOC, severe AEs)	178	27.6 [NC; NC] 18 (10)	168	NA 2 (1)	7.87 [1.82; 34.10]; 0.001
Hypotension (PT, severe AEs)	178	NA 21 (12)	168	NA 5 (3)	3.88 [1.46; 10.31]; 0.003

a. No suitable data available; see Section I 4.1 for reasons.
b. Individual components are shown in the lines below; since only the qualifying events are included in the event rate (total), the effect estimates of the individual components are not shown.
c. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [20]).
d. Operationalized as CTCAE grade ≥ 3.
e. Operationalized as nervous system disorders (SOC, severe AEs).
f. Operationalized as infections and infestations (SOC, severe AEs).

AE: adverse event; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; HDCT: high-dose chemotherapy; HR: hazard ratio; MEFS: modified EFS; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PD: progressive disease; 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; SD: stable disease; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

No suitable data are available for the outcome of overall survival (see Section I 4.1 for reasons). There is no hint of an added benefit of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Morbidity

Failure of the curative treatment approach

For the outcome "failure of the curative treatment approach", there was a statistically significant difference in favour of axicabtagene ciloleucel for both the operationalization mEFS1 and the operationalization mEFS2. In summary, there is a hint of an added benefit of axicabtagene ciloleucel compared to induction + HDCT + autologous SCT for this outcome.

Symptoms (recorded using EORTC QLQ-C30), health status (recorded using EQ-5D VAS)

No suitable data are available for symptoms (recorded using EORTC QLQ-C30) and health status (recorded using EQ-5D VAS), (for reasons, see Section I 4.1). There is no hint of an added benefit of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Health-related quality of life

No usable data are available for health-related quality of life (recorded using the EORTC QLQ-C30) (for reasons, see Section I 4.1). There is no hint of an added benefit of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Severe AEs

No statistically significant difference between treatment groups was shown for the outcome of severe AEs. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No information on the effect estimate is available for the outcome "discontinuation due to AEs". However, only very few events occurred in both study arms, so that a statistically significant difference between the study arms can be ruled out. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Specific AEs

Cytokine release syndrome, secondary malignancies

No suitable data are available for the outcomes of cytokine release syndrome and secondary malignancies (see Section I 4.1 for reasons). In each case, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Severe neurological toxicity (severe AEs [CTCAE grade ≥ 3])

For the outcome of severe neurological toxicity, a statistically significant difference was shown to the disadvantage of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of greater harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Severe infections (severe AEs [CTCAE grade ≥ 3])

No statistically significant difference between treatment groups was shown for the outcome of severe infections. There is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Ear and labyrinth disorders, mucosal inflammation, hiccups (AEs)

For each of the outcomes of ear and labyrinth disorders, mucosal inflammation and hiccup, a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. In each case, there is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Hypoxia (AEs)

For the outcome of hypoxia, a statistically significant difference was shown to the disadvantage of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of greater harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Cough (AEs)

For the outcome of cough, a statistically significant difference was shown to the disadvantage of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. However, there is an effect modification by the characteristic of sAAIPI. For patients with sAAIPI 2 to 3, there is a hint of greater harm from axicabtagene ciloleucel versus induction + HDCT + autologous SCT. For patients with sAAIPI 0 to 1, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven for patients with sAAIPI 0 to 1 (see Section I 4.4).

Febrile neutropenia (SAEs)

For the outcome of febrile neutropenia (SAEs), a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Gastrointestinal disorders (severe AEs [CTCAE grade ≥ 3])

For the outcome of gastrointestinal disorders (severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. There is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

Thrombocytopenia (severe AEs [CTCAE grade ≥ 3])

For the outcome of thrombocytopenia (severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was shown in favour of axicabtagene ciloleucel versus induction + HDCT + autologous SCT. However, there was an effect modification by the characteristic of age. For patients < 65 years of age, there is a hint of lesser harm from axicabtagene ciloleucel versus induction + HDCT + autologous SCT. For patients ≥ 65 years of age, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven for patients ≥ 65 years of age (see Section I 4.4).

Neutropenia, general disorders and administration site conditions, psychiatric disorders, hypotension (in each case severe AEs [CTCAE grade ≥ 3])

For the outcomes of neutropenia, general disorders and administration site conditions, psychiatric disorders and hypotension (severe AEs [CTCAE grade ≥ 3] in each case), there is a statistically significant difference to the disadvantage of axicabtagene ciloleucel compared to induction + HDCT + autologous SCT. In each case, there is a hint of lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- sAAIPI recorded via interactive voice/web response system (0 to 1 vs. 2 to 3)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 17. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B of the full dossier assessment.

Table 17: Subgroups (side effects) – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Study outcome characteristic subgroup	**Axicabtagene ciloleucel**		**Induction + HDCT + autologous SCT**		**Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT**	
	N	**median time to event in months [95 % CI] patients with event n (%)**	**N**	**median time to event in months [95 % CI] patients with event n (%)**	**HR [95% CI]**	**p-value**
ZUMA-7						
Side effects						
Cough (PT, AEs)						
sAAIPI (IXRS)						
0 to 1	98	NA 22 (22)	93	NA 14 (15)	1.36 [0.69; 2.66]	0.369
2 to 3	80	NA 25 (31)	75	NA 4 (5)	6.54 [2.28; 18.81]	< 0.001
Total					Interaction[b]:	0.019
Thrombocytopenia (PT, severe AEs[a])						
Age						
< 65	127	NA 6 (5)	113	NA 27 (24)	0.15 [0.06; 0.37]	< 0.001
≥ 65	51	NA 8 (16)	55	NA 10 (18)	0.80 [0.32; 2.04]	0.643
Total					Interaction[b]:	0.016

a. Operationalized as CTCAE grade ≥ 3.
b. From non-stratified Cox regression model with the covariates treatment and subgroup variable as well as the interaction of treatment and subgroup variable.

AE: adverse event; CI: confidence interval; HR: hazard ratio; IXRS: interactive voice/web response system; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; sAAIPI: second-line age-adjusted International Prognostic Index

Side effects

Specific AEs

Cough (PT, AEs)

There is a statistically significant effect modification by the characteristic of sAAIPI for the outcome of cough (PT, AEs). For patients with sAAIPI 2 to 3, there is a statistically significant difference to the disadvantage of axicabtagene ciloleucel. For patients with sAAIPI 2 to 3, there is a hint of greater harm from axicabtagene ciloleucel versus induction + HDCT + autologous SCT. However, no statistically significant difference between treatment groups was shown for patients with sAAIPI 0 to 1. For patients with sAAIPI 0 to 1, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven for these patients.

Thrombocytopenia (PT, severe AEs)

There is a statistically significant effect modification by the characteristic of age for the outcome of thrombocytopenia (PT, severe AEs). For patients < 65 years of age, a statistically significant difference was shown in favour of axicabtagene ciloleucel. For patients < 65 years of age, there is a hint of lesser harm from axicabtagene ciloleucel versus induction + HDCT + autologous SCT. However, no statistically significant difference between treatment groups was shown for patients ≥ 65 years. For patients ≥ 65 years of age, there is no hint of greater or lesser harm from axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [21].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 18).

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

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

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

Table 18: Extent of the added benefit at outcome level: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	No suitable data[c]	Lesser/added benefit not proven
Morbidity		
Failure of the curative treatment approach		Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
mEFS1 (event rate)	60% vs. 74% RR: 0.81 [0.70; 0.94]; p = 0.004 probability: “hint”	
mEFS2 (event rate)	59% vs. 70% RR: 0.84 [0.72; 0.99]; p = 0.033 probability: “hint”	
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[c]	Lesser/added benefit not proven
Side effects		
SAEs	3.6 vs. 4.9 months HR: 1.07 [0.79; 1.45]; p = 0.677	Greater/lesser harm not proven
Severe AEs	0.9 vs. 0.5 months HR: 0.93 [0.74; 1.17]; p = 0.508	Greater/lesser harm not proven
Discontinuation due to AEs	N D vs. N D 2.2% vs. 1.2% HR: ND	Greater/lesser harm not proven
Cytokine release syndrome	No suitable data[c]	Greater/lesser harm not proven

Table 18: Extent of the added benefit at outcome level: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Severe neurological toxicity	NA vs. 32.2 months HR: 2.70 [1.47; 4.97] HR: 0.37 [0.20; 0.68][d]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
Severe infections	10.9 vs. 19.9 months HR: 1.08 [0.61; 1.93]; p = 0.790	Greater/lesser harm not proven
Secondary malignancies	No suitable data[c]	Greater/lesser harm not proven
Ear and labyrinth disorders (AE)	NA vs. NA HR: 0.23 [0.09; 0.63]; p = 0.002 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Mucosal inflammation (AEs)	NA vs. 7.0 months HR: 0.04 [0.01; 0.32]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Cough (AEs) sAAIPI (IXRS) 0 to 1	NA vs. NA HR: 1.36 [0.69; 2.66]; p = 0.369	Greater/lesser harm not proven
2 to 3	NA vs. NA HR: 6.54 [2.28; 18.81] HR: 0.15 [0.05; 0.44][d]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: “considerable”
Hiccups (AEs)	NA vs. NA HR: 0.36 [0.16; 0.78]; p = 0.007 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Hypoxia (AEs)	NA vs. NA HR: 2.80 [1.49; 5.26] HR: 0.36 [0.19; 0.67][d]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: “considerable”

Table 18: Extent of the added benefit at outcome level: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Febrile neutropenia (SAEs)	28.3 vs. NA months HR: 0.09 [0.03; 0.32]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"
Neutropenia (severe AEs)	NA vs. NA HR: 2.71 [1.75; 4.19] HR: 0.37 [0.24; 0.57][d]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_o < 0.75, risk ≥ 5% greater harm, extent: “major”
Thrombocytopenia (severe AEs) Age		
< 65 years	NA vs. NA HR: 0.15 [0.06; 0.37]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_o < 0.75, risk ≥ 5% lesser harm, extent: "major"
≥ 65 years	NA vs. NA HR: 0.80 [0.32; 2.04]; p = 0.643	Greater/lesser harm not proven
Gastrointestinal disorders (severe AEs)	12.0 vs. 5.0 months HR: 0.53 [0.30; 0.94]; p = 0.026 probability: “hint”	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 lesser harm, extent: “minor”
General disorders and administration site conditions (severe AEs)	6.0 vs. 7.1 months HR: 2.20 [1.12; 4.31] HR: 0.45 [0.23; 0.89][d]; p = 0.018 probability: “hint”	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent: "considerable"
Psychiatric disorders (severe AEs)	27.6 vs. NA months HR: 7.87 [1.82; 34.10] HR: 0.13 [0.03; 0.55][d]; p = 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”

Table 18: Extent of the added benefit at outcome level: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Axicabtagene ciloleucel vs. induction + HDCT + autologous SCT** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Hypotension (severe AEs)	NA vs. NA HR: 3.88 [1.46; 10.31] HR: 0.26 [0.10; 0.68][d]; p = 0.003 probability: “hint”	Outcome category: serious/severe side effects CI_o < 0.75, risk ≥ 5% greater harm, extent: “major”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. See Section I 4.1 for reasons.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; IXRS: interactive voice/web response system; mEFS: modified event-free survival; RR: relative risk; sAAIPI: second-line age-adjusted International Prognostic Index; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Morbidity ▪ failure of the curative treatment approach: hint of an added benefit – extent: “minor”	
Outcomes with shortened observation period	
Serious/severe side effects ▪ febrile neutropenia (SAEs): hint of lesser harm – extent: "major" ▪ thrombocytopenia (severe AEs): ▫ age < 65 years: hint of lesser harm – extent: “major” ▪ gastrointestinal disorders (severe AEs): hint of lesser harm – extent: “minor”	Serious/severe side effects ▪ severe neurological toxicity, neutropenia (severe AEs), psychiatric disorders (severe AEs), hypotension (severe AEs): hint of greater harm, extent: “major” ▪ general disorders and administration site conditions (severe AEs): hint of greater harm – extent: "considerable"
Non-serious/non-severe side effects ▪ ear and labyrinth disorders (AEs), mucosal inflammation (AEs), hiccups (AEs): hint of lesser harm – extent: “considerable”	Non-serious/non-severe side effects ▪ cough (AEs): ▫ sAAIPI 2 to 3; hint of greater harm, extent: “considerable” ▪ hypoxia (AEs): hint of greater harm - extent: “considerable”
The data presented for the outcome "overall survival" cannot be interpreted. No suitable data are available for the outcomes of symptoms, health status and health-related quality of life.	
AE: adverse event; HDCT: high-dose chemotherapy; sAAIPI: second-line age-adjusted International Prognostic Index; SAE: serious adverse event; SCT: stem cell transplantation	

In the overall assessment, there are both positive and negative effects of axicabtagene ciloleucel in comparison with induction + HDCT + autologous SCT.

In terms of positive effects, there is a hint of minor added benefit for the outcome of failure of the curative treatment approach. In the category of serious/severe side effects, there are hints of both greater harm and lesser harm, some of which are considerable. In the category of non-serious/non-severe side effects, there are also hints of both greater and lesser harm of up to considerable extent. Overall, the positive and negative effects in terms of side effects are balanced and do not challenge the positive effect in the outcome category of morbidity.

In summary, for patients with DLBCL or HGBL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and who are eligible for high-dose therapy, there is a hint of minor added benefit of axicabtagene ciloleucel compared with the ACT “induction + HDCT + autologous SCT”.

Table 20 summarizes the result of the assessment of added benefit for axicabtagene ciloleucel in comparison with the ACT.

Table 20: Axicabtagene ciloleucel – probability and extent of added benefit

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 who are eligible for high-dose therapy[b]	Induction therapy with one of the following options: ▪ R-GDP ▪ R-ICE ▪ R-DHAP followed by high-dose therapy with autologous or allogeneic stem cell transplantation[c] if there is a response to induction therapy	Hint of minor added benefit

a. Presented is the ACT specified by the G-BA.
b. Patients are presumed to be 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.

DLBCL: diffuse large B-cell lymphoma; G BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References

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

Please see full dossier assessment for full reference list.

1. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V); Axicabtagen-Ciloleucel (Neues Anwendungsgebiet: Diffus großzelliges B-Zell-Lymphom, hochmalignes B-Zell-Lymphom, nach 1 Vortherapie, Rezidiv innerhalb von 12 Monaten oder refraktär) [online]. 2023 [Accessed: 19.08.2024]. URL: https://www.g-ba.de/downloads/40-268-10124/2023-12-21_AM-RL-XII_Axicabtagene-Ciloleucel_D-890_TrG.pdf.

2. 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.

3. Kite Pharma. Primary Overall Survival Analysis; Addendum to ZUMA-7 Primary Analysis Clinical Study Report [unpublished]. 2023.

4. Kite Pharma. Erratum to Study KTE-C19-107 (ZUMA-7); primary EFS Analysis Clinical Study Report and primary OS Analysis Clinical Study Report Addendum [unpublished]. 2024.

5. Kite. Study of Effectiveness of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Patients With Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7) [online]. 2024 [Accessed: 16.07.2024]. URL: https://clinicaltrials.gov/study/NCT03391466.

6. Kite Pharma. 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]. [Accessed: 16.07.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002261-22.

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

8. 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.

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

10. 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.

11. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Axicabtagen-Ciloleucel (DLBCL und HGBL, Zweitlinie); Addendum to project A23-66 (dossier assessment) [online]. 2023 [Accessed: 04.01.2024]. URL: https://doi.org/10.60584/A23-106.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Axicabtagen-Ciloleucel (DLBCL und HGBL, Zweitlinie); Nutzenbewertung gemäß § 35a SGB V; dossier assessment [online]. 2023 [Accessed: 10.10.2023]. URL: https://www.iqwig.de/download/a23-66_axicabtagen-ciloleucel_nutzenbewertung-35a-sgb-v_v1-0.pdf.

13. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Axicabtagen-Ciloleucel (Neues Anwendungsgebiet: Diffus großzelliges B-Zell-Lymphom, hochmalignes B-Zell-Lymphom, nach 1 Vortherapie, Rezidiv innerhalb von 12 Monaten oder refraktär) [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/901/#nutzenbewertung.

14. 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://doi.org/10.1182/blood-2016-01-643569.

15. Kite Pharma. Yescarta [online]. 2024 [Accessed: 19.08.2024]. URL: https://www.fachinfo.de.

16. 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://doi.org/10.1200/JCO.2013.54.8800.

17. 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.

18. Gilead Sciences. Stellungnahme zum IQWiG-Bericht Nr. 1645: Axicabtagen-Ciloleucel (DLBCL und HGBL, Zweitlinie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/901/#beschluesse in the document "Zusammenfassende Dokumentation"].

19. National Comprehensive Cancer Network. NCCN Guidelines B-Cell Lymphomas; Version 2.2024 [online]. 2024 [Accessed: 18.06.2024]. URL: https://www.nccn.org/.

20. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

21. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwg.de/methoden/allgemeine-methoden_version-7-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-71.html.