Axicabtagene ciloleucel (DLBCL and HGBL, second line)

Addendum to Project A23-66 (dossier assessment)[1]

ADDENDUM

Project: A23-106 Version: 1.0 Status: 1 December 2023

[1] Translation of the addendum *Axicabtagen-Ciloleucel (DLBCL und HGBL, Zweitlinie) – Addendum zum Projekt A23-66 (Dossierbewertung)*. 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) – Addendum to Project A23-66

Commissioning agency

Federal Joint Committee

Commission awarded on

7 November 2023

Internal Project No.

A23-106

Address of publisher

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Keywords

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CAR	chimeric antigen receptor
CI	confidence interval
CR	complete response
CSR	clinical study report
DLBCL	diffuse large B-cell lymphoma
EFS	event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HDCT	high-dose chemotherapy
HGBL	high-grade B-cell lymphoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD	progressive disease
pola-BR	polatuzumab in combination with bendamustine and rituximab
PR	partial response
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
R-GDP	rituximab, gemcitabine, dexamethasone, cisplatin
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
RCT	randomized controlled trial
SCT	stem cell transplantation
SD	stable disease
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 7 November 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-66 (Axicabtagene ciloleucel – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses of the ZUMA-7 study [2] presented by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure, taking into account the information in the company's dossier [3]. The following data are to be assessed: the subsequently submitted data from the clinical study report (CSR) at the second data cut-off [4], the information on subsequent therapies, the data on event-free survival (EFS) (including investigator assessment vs. central review for the individual data cut-offs, reasons for commencement of new lymphoma therapy without disease assessment, best response by Day 50 according to central review, and sensitivity analyses by the company), and the time to first improvement in patient-reported outcomes (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30], visual analogue scale [VAS] of the EQ-5D). In addition, a conclusion should be drawn on the quantification of the added benefit based on the subsequent change of the appropriate induction therapy to R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin), R-ICE (rituximab, ifosfamide, carboplatin, etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin).

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

2 Assessment

For the benefit assessment of axicabtagene ciloleucel, the randomized controlled trial (RCT) ZUMA-7 was used for research question 1 of dossier assessment A23-66 (adults 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 for whom high-dose therapy is an option). This study investigated the comparison of axicabtagene ciloleucel versus induction therapy followed by high-dose chemotherapy (HDCT) with autologous stem cell transplantation (SCT) in case of response to induction therapy (hereafter referred to as "induction + HDCT + autologous SCT").

For the ZUMA-7 study, the company presented results of the second data cut-off from 25 January 2023 in Module 4 A of its dossier and used them for its assessment. This approach is appropriate, but no CSR was available for the second data cut-off. The CSR on the second data cut-off was subsequently submitted with the company's comments and taken into account for the assessment in the present addendum. In comparison with the dossier, the CSR does not provide any additional data relevant to the assessment. However, it was possible to take the missing data on the qualifying events in the outcome of EFS for the second data cut-off described in dossier assessment A23-66 from the CSR, and they are presented as supplementary information (see Table 3).

In the commenting procedure, the company also presented further analyses and information on the outcome of EFS/failure of the curative treatment approach, on symptoms, health status and health-related quality of life, and on outcomes in the side effects category, as well as information on observation periods and subsequent therapies. These are described in more detail in the following sections.

IQWiG was also commissioned by the G-BA to quantify the added benefit based on the subsequent change of the induction therapy component of the appropriate comparator therapy (ACT) to R-GDP, R-ICE or R-DHAP. The present addendum therefore assesses the added benefit of axicabtagene ciloleucel compared with the ACT based on this change.

2.1 Outcomes included

Interpretation of the results of the overall survival outcome

For dossier assessment A23-66, the results of the outcome of overall survival were not interpretable due to missing information on subsequent therapies at the second data cut-off and a high risk of bias at study level with an effect with only minor extent. It was also noted that the subsequent therapies potentially not (yet) indicated may have a relevant influence on the observed effect in the overall survival outcome (see also below). The company's comments now included information on the subsequent therapies for this data cut-off.

Information on subsequent therapies

Table 1 shows the subsequent therapies patients received after discontinuing the study medication.

Table 1: 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)
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)

Table 1: 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**
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 relation to the patients in whom, according to the investigator, an EFS event other than death had occurred by the second data cut-off (94 patients in the intervention arm versus 137 patients in the comparator arm, see Table 3), this means that 94% of these patients in the intervention arm and 93% in the comparator arm received at least one subsequent antineoplastic therapy.

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 [5]. 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, it was not clear from the information in the company's dossier whether starting 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 (see section on the outcome of failure of the curative treatment approach). Starting a subsequent therapy without the curative approach having failed (e.g. at the patient's request) can cause bias in overall survival of the comparator arm, as already described in the dossier assessment. 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 (see below), but then potentially received subsequent therapy with CAR T therapy instead of HDCT + autologous SCT for no stated reason. 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.

Conclusion on overall survival taking into account the subsequently submitted information on subsequent therapies

The subsequent therapies used in the study appear to be adequate overall. The fact that subsequent therapies were potentially not (yet) indicated for a relevant proportion of patients in the comparator arm can cause a risk of bias on overall survival of the comparator arm in addition to the aspects described in the dossier assessment. There are no changes with regard to the other aspects described in dossier assessment A23-66, which led to a lack of interpretability of the results on the outcome of overall survival.

Overall, the results for the outcome of overall survival are still not interpretable. The results are presented as supplementary information in Table 3 in Appendix A.

EFS is unsuitable for representing failure of the curative treatment approach

The available data on the outcome of EFS are still not suitable to represent failure of the curative treatment approach and are therefore not used for the benefit assessment. This is justified below.

Relevant data cut-off

In its comments, 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 present addendum. For the analysis of EFS according to the investigator, results are available for the second data cut-off, but these are not used for the assessment, as the analysis according to the investigator shows discrepancies compared with the blinded central review at the time of the first data cut-off (see following section).

Overall, the lack of EFS per blinded central review for the second data cut-off is of secondary importance, as, according to the investigator, only few additional events occurred between the first and second data cut-off.

Discrepancies between blinded central review and investigator as well as response by Day 50

As described in dossier assessment A23-66, there is a clear discrepancy between investigator assessment and blinded central review in the comparator arm, but not in the intervention arm, with regard to the respective qualifying events for the outcome of EFS. This applies in particular to the respective proportion of disease progression and new lymphoma therapy as qualifying event. For example, in the comparator arm of the ZUMA-7 study, at the first data cut-off, according to the investigator, 98 (70%) of qualifying events were attributed to disease progression and 37 (26%) to commencement of new lymphoma therapy, whereas according

to blinded central review, 75 (52%) of events were disease progression and 63 (44%) were commencement of new lymphoma therapy (see Table 3 in Appendix A).

For commencement of new lymphoma therapy, it could not be inferred from the company's dossier whether this per se represented a failure of the curative treatment approach (defined as death from any cause, disease progression, failure to achieve complete response [CR] or partial response [PR] at the time of the treatment decision on HDCT and autologous SCT in the comparator arm or failure to achieve CR after completion of treatment). With its subsequent submission in the context of the commenting procedure, the company now presented information on the reasons for the 63 events of commencement of new lymphoma therapy in the comparator arm according to blinded central review [6]:

- 10 patients: commencement of new lymphoma therapy without disease assessment after study start, including
  - 5 patients who did not receive treatment as part of the study at their own request,
  - 1 patient with a negative disease biopsy,
  - 3 patients starting new lymphoma therapy due to toxicity/intolerance to the initial induction therapy,
  - 1 patient with progressive disease (PD) according to the investigator, but later classified as undefined per blinded central review (no usable response)
- 4 patients: new lymphoma therapy in the form of external radiotherapy during a response to treatment as part of the study
- 2 Patients: other reasons
- 47 patients: commencement of new lymphoma therapy in stable disease (SD) or PD according to the investigator
  - 26 patients with PD according to the investigator; according to the company, the majority of these patients had SD per central review
  - 21 patients with SD according to the investigator

In the 10 patients who started new lymphoma therapy without disease assessment after the start of the study, no event was identified that would indicate failure of the curative treatment approach in this line of treatment. With regard to the 3 patients thereof who started new lymphoma therapy due to toxicity/intolerance to the initial induction therapy, it should also be noted that a change of induction regimen does not indicate a failure of the curative treatment approach. With regard to the 4 patients who received external radiotherapy during a response to treatment as part of the study, it is unclear at what point this took place. In the case of consolidation radiotherapy prior to completion of treatment as part of the study, this

is regarded as part of the treatment strategy and therefore not as failure of the curative treatment approach. For the 2 patients who started new lymphoma therapy for other reasons, there is no information that these reasons represent a failure of the curative treatment approach. In a total of 16 of the corresponding 63 patients in the comparator arm, new lymphoma therapy was thus started for reasons that did not or did not necessarily represent failure of the curative treatment approach. Accordingly, these patients are no longer included as EFS events in the following sensitivity analyses.

With regard to the total of 47 patients in the comparator arm who started new lymphoma therapy in SD or PD according to the investigator, it is unclear for how many of these patients a corresponding event and thus failure of the curative treatment approach was or would have been determined in the blinded central review. One reason for this is that, according to the company, the majority of the 26 patients with PD per investigator assessment were found to have SD per blinded central review, but the company did not clarify what majority means in this context and what this means for the remaining patients [6]. Besides, the company provided information on the blinded central review of best response by Day 50 (time of treatment decision in the comparator arm) in its comments [2]. These data show that no blinded central review of response by Day 50 was performed in 32 patients in the comparator arm (see Table 5). It is unclear how many of these 32 patients were found to have SD or PD by the investigator or how many of these cases would also have been found to have SD or PD by the blinded central review.

It should also be noted that a total of 87 patients (43 with CR and 44 with PR, see Table 5) achieved response to induction therapy by Day 50 per blinded central review, but only 64 patients continued with HDCT and subsequent autologous SCT (see Table 10 of dossier assessment A23-66). Accordingly, 23 patients in the comparator arm with response at Day 50 did not have HDCT and subsequent autologous SCT, although this was planned according to the study design. The reasons for this are unclear. It is also unclear whether these patients received new lymphoma therapy and were therefore included as EFS events in the company's analyses.

In order to address the uncertainties described, 2 sensitivity analyses were conducted, each of which assumed a minimum or maximum possible number of occurred qualifying events that reflect failure of the curative treatment approach. These are described below and are shown in Table 4. The company's analyses are shown in Table 3.

Sensitivity analysis 1: minimum possible number of occurred qualifying events that mean failure of the curative treatment approach

The data on best response at Day 50 according to central review show that SD at Day 50 was found in 26 (15%) of the patients in the comparator arm (see Table 5). It is therefore assumed

for the comparator arm that the curative treatment approach failed at least in these patients and in those with disease progression, death or SD as best response by Day 150 according to blinded central review. Based on this assumption, a sensitivity analysis was performed for the outcome of EFS per central review, which, for the comparator arm, takes into account the determination of SD as best response at Day 50 instead of commencement of new lymphoma therapy (see Table 4). For the comparator arm, this sensitivity analysis does not take into account those patients for whom no blinded central review of response at Day 50 was performed, and thus represents a minimum assumption regarding the possible number of events that occurred.

In the intervention arm, unlike in the comparator arm, SD at Day 50 does not represent the failure of the curative treatment approach, as an improvement in response after Day 50 was still possible due to axicabtagene ciloleucel. As part of the sensitivity analysis, it is therefore assumed for the intervention arm that commencement of new lymphoma therapy is a better reflection of the failure of the curative treatment approach than the determination of SD as best response at Day 50. However, 2 patients in the intervention arm were excluded from the sensitivity analysis, for whom the company stated in its comments that they received new lymphoma therapy without prior disease assessment [2]. This approach is therefore based on assumptions, but appears to be the best approximation in the present data situation, as both the number of corresponding qualifying events and the deviations between blinded central review and investigator in the intervention arm are small overall.

This sensitivity analysis (minimum assumption) shows no statistically significant difference between treatment groups for the outcome of failure of the curative treatment approach (see Table 4).

Sensitivity analysis 2: maximum possible number of occurred qualifying events that mean failure of the curative treatment approach

In order to represent the maximum possible number of occurred qualifying events that mean failure of the curative treatment approach, commencement of new lymphoma therapy in SD or PD according to the investigator was rated as event for the outcome of EFS per central review. In its subsequent submission, the company presented corresponding data only for the comparator arm [6]. This sensitivity analysis also assumes that in the intervention arm, commencement of new lymphoma therapy represents the failure of the curative treatment approach, with the exception of the 2 cases described in the previous section.

For the outcome of failure of the curative treatment approach, this sensitivity analysis (maximum assumption) shows a statistically significant difference in favour of axicabtagene ciloleucel compared with induction + HDCT + autologous SCT (upper limit of the confidence interval [CI_u] = 0.96; see Table 4).

Missing information on failure to achieve complete response after completion of therapy

As described in dossier assessment A23-66, for a comprehensive representation of failure of the curative approach, it is necessary to record the failure to achieve CR after completion of treatment as a separate qualifying event. However, there is still no corresponding information available, which is why this event could not be taken into account in the 2 sensitivity analyses carried out. This uncertainty therefore also continues to exist.

Sensitivity analysis by the company: commencement of new lymphoma therapy due to efficacy concerns as a qualifying event

With its subsequent submission, the company presented a sensitivity analysis for the outcome of EFS per blinded central review [6]. According to the company, this sensitivity analysis only considered commencement of new lymphoma therapy due to efficacy concerns, instead of commencement of new lymphoma therapy for any reason, to be a qualifying event for the outcome of EFS. The company stated that, in the context of this sensitivity analysis, EFS is defined as disease progression, death from any cause, or residual disease leading to commencement of new lymphoma therapy; however, it did not provide any information on the number of patients with the respective qualifying events.

The operationalization of the EFS outcome in this sensitivity analysis is not suitable for representing the failure of the curative treatment approach. For commencement of new lymphoma therapy as a component of the EFS outcome, it is unclear whether this event per se represents failure of the curative treatment approach. As can be seen from dossier assessments A23-48 and A23-66, this uncertainty exists regardless of whether this is commencement of new lymphoma therapy due to efficacy concerns or for any reason [1,7]. In addition, the company did not describe the reasons for starting new lymphoma therapy for all patients it excluded from this sensitivity analysis. In total, it excluded 4 patients in the intervention arm and 8 patients in the comparator arm from its sensitivity analysis. However, the company should have excluded at least those 10 patients in the comparator arm who started new lymphoma therapy without disease assessment after the start of the study and in whom commencement of new lymphoma therapy could therefore not be attributed to the presence of residual disease (see above).

Conclusion on the outcome of failure of the curative treatment approach

In summary, there are still discrepancies between blinded central review and investigator assessment at the first data cut-off. The component of new lymphoma therapy does not adequately reflect failure of the curative approach, as it has been shown that events were also included that do not or do not necessarily represent failure of the curative treatment approach. The sensitivity analyses excluding these events, which were carried out specifically for this purpose, show no more than effects of minor extent, which are also subject to major

uncertainty. In addition, there is a lack of data that records the failure to achieve CR after completion of treatment as a separate qualifying event.

Overall, the results for the outcome of failure of the curative treatment approach are still not interpretable.

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

With its comments, the company presented additional analyses on the outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30), which, however, are not suitable for the benefit assessment. Firstly, these analyses continue to refer to the first data cut-off and not, as requested in the benefit assessment, to the second data cut-off; secondly, the analyses presented do not include an effect estimate, but only the median time to event. Irrespective of these aspects, 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. 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 still not suitable for the benefit assessment.

Outcomes on side effects

The analyses presented by the company on outcomes in the outcome category of side effects are still not suitable for the benefit assessment. One reason for is that they are based on an incomplete analysis population. Secondly, as described in Section I 3.2 of dossier assessment A23-66, a notably longer observation period is assumed for the side effects outcomes in the intervention arm than in the comparator arm. However, despite the potentially clear difference in observation periods, the company did not present any time-to-event analyses. Corresponding analyses were also not presented during the commenting procedure, without this being justified by the company. The data on the observation periods for the side effects outcomes presented by the company in the commenting procedure are not plausible and do not change this assessment (see Table 6). Based on the analyses available in the company's dossier, greater harm cannot be excluded for the side effects outcomes.

Final assessment and summary

There are still serious deficiencies in the data presented by the company. For the outcomes of overall survival and in the sensitivity analyses on the failure of the curative treatment

approach, effects of no more than minor extent were shown, which were also subject to major uncertainty. On the harm side, no suitable data are available for the assessment of axicabtagene ciloleucel versus the ACT of induction + HDCT + autologous SCT. Therefore, it is still impossible to weigh benefits versus harm.

2.2 Results

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

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of axicabtagene ciloleucel from dossier assessment A23-66. This also applies under the condition of the subsequent change of the induction therapy component of the ACT to R-GDP, R-ICE or R-DHAP for research question 1 of the dossier assessment (adults with DLBCL or HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and for whom high-dose therapy is an option).

Table 2 below shows the result of the benefit assessment of axicabtagene ciloleucel, taking into account dossier assessment A23-66 and the present addendum.

Table 2: Axicabtagene ciloleucel – probability and extent of added benefit

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

a. It is assumed that patients are eligible for high-dose therapy with curative intent.
b. Presentation of the ACT based on the subsequent change of the induction therapy component to R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin), R-ICE (rituximab, ifosfamide, carboplatin, etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin). Presented is the ACT analogous to the assessment procedure for lisocabtagene maraleucel in the analogous therapeutic indication [8].
c. In the line of treatment, allogeneic stem cell transplantation is an option in patients who have a very high risk of relapse or in whom sufficient stem cell collection for autologous stem cell transplantation was not possible.
d. Patients are assumed to be not eligible for high-dose therapy and to generally continue antineoplastic treatment after first-line immunotherapy.
e. A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
f. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of the corresponding patient groups. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
g. The approval of pola-BR and tafasitamab + lenalidomide relates exclusively to DLBCL (approval of 2020/2021). With the updated WHO classification of 2022, HGBL was newly listed as a definite entity. Prior to this update, aggressive lymphomas with MYC and BCL2/6 rearrangements were classified as DLBCL, so that HGBL was not specified separately in the therapeutic indication at the time of approval of pola-BR and tafasitamab + lenalidomide. Therefore, specifying these treatment options for both DLBCL and HGBL is considered appropriate.

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

The G-BA decides on the added benefit.

3 References

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

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Appendix A Supplementary presentation of the results on mortality and morbidity

A.1 Analyses by the company

Table 3: Results (mortality, morbidity), analyses by the company – 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[a]
ZUMA-7					
Mortality					
Overall survival	180	NA [28.6; NC] 82 (46)	179	31.1 [17.1; NC] 95 (53)	0.73 [0.54; 0.98]; 0.017
Morbidity					
Data cut-off 1 (18 March 2021)					
EFS per central review (sensitivity analysis by company)					
Event rate[b]	180	– 104 (58)	179	– 136 (76)	RR 0.76 [0.65; 0.88]; 0.001[c]
Disease progression	180	ND	179	ND	
Death from any cause	180	ND	179	ND	
Residual disease leading to commencement of new lymphoma therapy	180	ND	179	ND	
Event-free survival (EFS)	180	11.2 [5.0; 21.5] 104 (58)	179	2.0 [1.7; 2.7] 136 (76)	0.40 [0.31; 0.53]; < 0.001
EFS per central review (company dossier)					
Event rate[b]	180	– 108 (60)	179	– 144 (80)	RR: 0.75 [0.65; 0.86]; < 0.001[c]
Disease progression	180	– 82 (46)	179	– 75 (42)	
SD as best response until Day 150	180	– 4 (2)	179	– 0 (0)	
Commencement of new lymphoma therapy	180	– 11 (6)	179	– 63 (35)	
Death from any cause	180	– 11 (6)	179	– 6 (3)	
Event-free survival (EFS)	180	8.3 [4.5; 15.8] 108 (60)	179	2.0 [1.6; 2.8] 144 (80)	0.40 [0.31; 0.51]; < 0.001

Table 3: Results (mortality, morbidity), analyses by the company – 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[a]
EFS according to investigator (company dossier)					
Event rate[b]	180	– 103 (57)	179	– 140 (78)	RR: 0.73 [0.63; 0.85]; < 0.001[c]
Disease progression	180	– 85 (47)	179	– 98 (55)	
SD as best response until Day 150	180	– 2 (1)	179	– 0 (0)	
Commencement of new lymphoma therapy	180	– 5 (3)	179	– 37 (21)	
Death from any cause	180	– 11 (6)	179	– 5 (3)	
Event-free survival (EFS)	180	10.8 [5.0; 28.6] 103 (57)	179	2.3 [1.7; 3.1] 140 (78)	0.40 [0.31; 0.53]; ND
Data cut-off 2 (25 January 2023)					
EFS according to investigator (company dossier)					
Event rate[b]	180	– 109 (61)	179	– 143 (80)	RR 0.76 [0.66; 0.87]; 0.001[c]
Disease progression	180	– 86 (48)	179	– 100 (56)	
SD as best response until Day 150	180	– 2 (1)	179	– 0 (0)	
Commencement of new lymphoma therapy	180	– 6 (3)	179	– 37 (21)	
Death from any cause	180	– 15 (8)	179	– 6 (3)	
Event-free survival (EFS)	180	10.8 [5.0; 25.5] 109 (61)	179	2.3 [1.7; 3.1] 143 (80)	0.42 [0.33; 0.55]; < 0.001

a. Effect and CI: stratified Cox proportional hazards model; p-value: one-sided, stratified log-rank test. In each case stratified by response to first-line therapy (primary refractory vs. relapse ≤ 6 months after first-line therapy vs. relapse > 6 and ≤ 12 months after first-line therapy) and sAAIPI (0 or 1 vs. 2 or 3).
b. Individual components – if available – 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 [9]).

Table 3: Results (mortality, morbidity), analyses by the company – 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[a]
CI: confidence interval; CSZ: convexity, symmetry, z-score; EFS: event-free survival; HDCT: high-dose chemotherapy; HR: hazard ratio; CI: confidence interval; n: number of patients with event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; sAAIPI: second-line age-adjusted International Prognostic Index; SCT: stem cell transplantation; SD: stable disease					

A.2 Kaplan-Meier curves for the analyses by the company

A.2.1 Overall survival

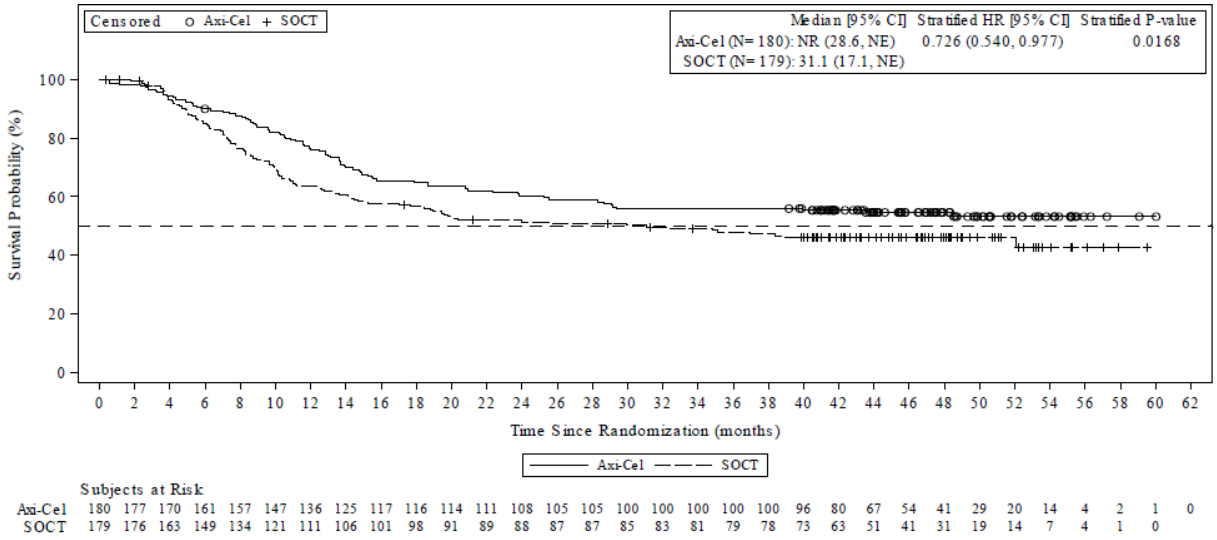

Figure 1: Kaplan-Meier curves for the outcome of overall survival of the ZUMA 7 study, second data cut-off (25 January 2023), total population

A.2.2 Event-free survival (EFS)

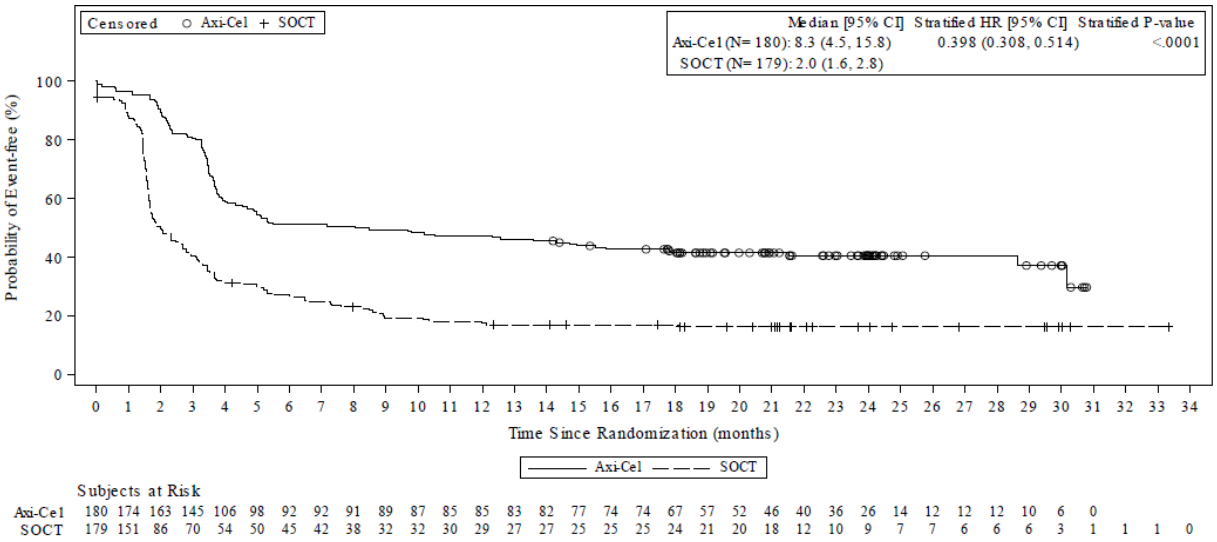

Figure 2: Kaplan-Meier curves for the outcome of event-free survival (EFS) per central review in the ZUMA-7 study, first data cut-off (18 March 2021), total population

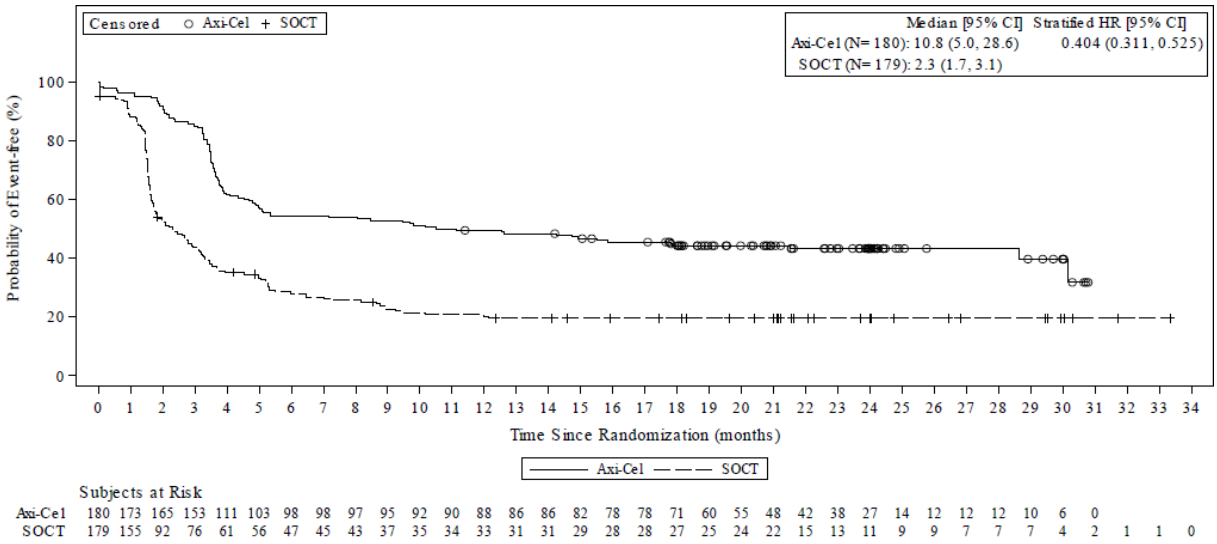

Figure 3: Kaplan-Meier curves for the outcome of event-free survival (EFS) per investigator assessment in the ZUMA-7 study, first data cut-off (18 March 2021), total population

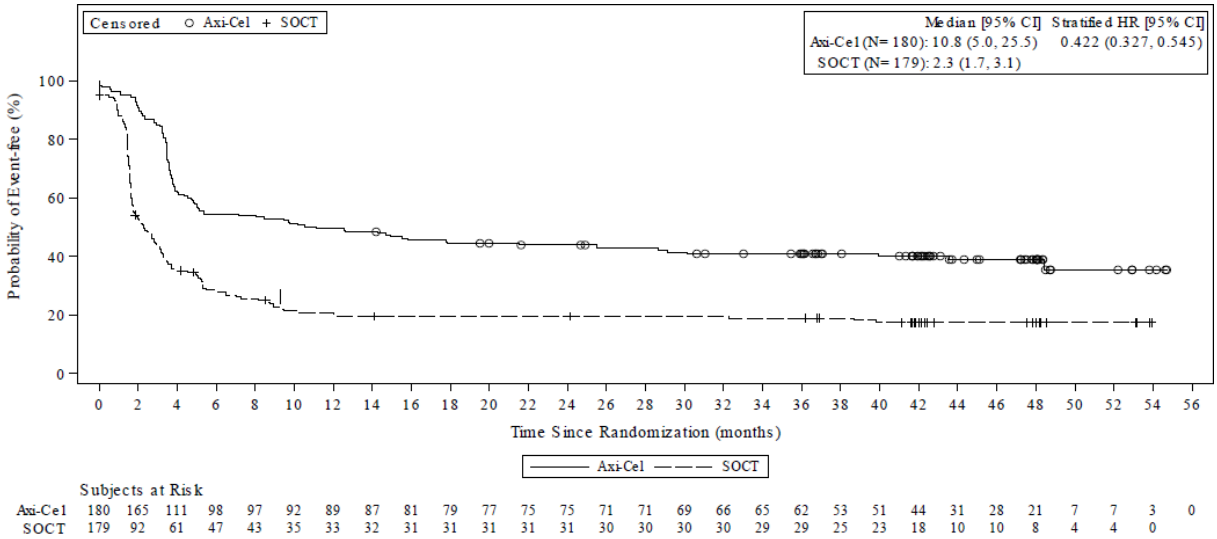

Figure 4: Kaplan-Meier curves for the outcome of event-free survival (EFS) per investigator assessment in the ZUMA-7 study, second data cut-off (25 January 2023), total population

A.3 Sensitivity analyses by IQWiG

Table 4: Results (morbidity), sensitivity analyses by IQWiG – 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					
Morbidity					
Data cut-off 1 (18 March 2021)					
Failure of the curative treatment approach (sensitivity analysis 1 IQWiG)					
Event rate[a]	180	– 106 (59)[b]	179	– 107 (60)[b]	RR 0.99 [0.83; 1.17]; 0.912[c]
Disease progression	180	– 82 (46)	179	– 75 (42)	
SD per central review as best response until Day 150	180	– 4 (2)	179	– 0 (0)	
Commencement of new lymphoma therapy	180	– 9 (5)[b, e]	179	– –	
SD per central review as best response as of Day 50[d]	180	– –	179	– 26 (15)	
Death from any cause	180	– 11 (6)	179	– 6 (3)	
Event-free survival (EFS)	180	ND 106 (59)[b]	179	ND 107 (60)[b]	ND
Failure of the curative treatment approach (sensitivity analysis 2 IQWiG)					
Event rate[a]	180	– 106 (59)[b]	179	– 128 (72)[b]	RR 0.82 [0.71; 0.96]; 0.012[c]
Disease progression	180	– 82 (46)	179	– 75 (42)	
SD as best response until Day 150	180	– 4 (2)	179	– 0 (0)	
Commencement of new lymphoma therapy	180	– 9 (5)[b, e]	179	– –	

Table 4: Results (morbidity), sensitivity analyses by IQWiG – 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
Commencement of new lymphoma therapy in SD per investigator assessment		– –		– 21 (12[b])	
Commencement of new lymphoma therapy in PD per investigator assessment		– –		– 26 (15[b])	
Death from any cause	180	– 11 (6)	179	– 6 (3)	
Event-free survival (EFS)	180	ND 106 (59)[b]	179	ND 128 (72)[b]	ND

a. Individual components – if available – 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.
b. Institute's calculation.
c. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [9]).
d. It is assumed that a new lymphoma therapy was started in SD as best response at Day 50, and that there is therefore no overlap between these patients and those with SD as best response until Day 150.
e. In the intervention arm, 2 patients received a new lymphoma therapy without prior disease assessment (for one patient, treatment with axicabtagene ciloleucel was deemed unsuitable due to cardiac lymphoma and one patient did not receive axicabtagene ciloleucel due to grade 2 increased alanine aminotransferase). These 2 patients were not included in the present analysis, as these situations do not represent failure of the curative treatment approach.

CI: confidence interval; CSZ: convexity, symmetry, z-score; EFS: event-free survival; HDCT: high-dose chemotherapy; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; ND: no data; PD: progressive disease; RCT: randomized controlled trial; sAAIPI: second-line age-adjusted International Prognostic Index; SCT: stem cell transplantation; SD: stable disease

Appendix B Best response at Day 50 per central review

Table 5: Best response at Day 50 per central review – RCT, direct comparison: axicabtagene ciloleucel vs. induction + HDCT + autologous SCT

Study	Axicabtagene ciloleucel N = 180	Induction + HDCT + autologous SCT N = 179
ZUMA-7		
Data cut-off 1 (18 March 2021)		
Best response at Day 50 per central review[a], n (%)		
CR	87 (48)	43 (24)
PR	55 (31)	44 (25)
SD	13 (7)	26 (15)
PD	17 (9)	29 (16)
Not evaluable[b]	0	1 (1)
Undefined/no disease[c]	0	4 (2)
Not evaluated	8 (4)	32 (18)

a. Response at Day 50 was defined as follows: For patients who had a disease assessment at the Day 50 visit (after central review), as the best response measured at Day 50; for patients who had a disease assessment between Days 43 and 71 (since randomization) but not at Day 50, as the best response measured then. The response was based on the Lugano classification [10].
b. Not evaluable is defined as follows according to the CSR: A disease assessment was performed, but no conclusion was possible.
c. Undefined/no disease is defined as follows according to the CSR: According to central review, no disease was detected in these patients at the start of the study or at a subsequent recording, whereas disease was detected by an investigator.

CR: complete response; CSR: clinical study report; HDCT: high-dose chemotherapy; n: number of patients in the category; N: number of randomized patients; PD: progressive disease; PR: partial response; RCT: randomized controlled trial; SCT: stem cell transplantation; SD: stable disease

Appendix C Information on the course of the study

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

Study Duration of the study phase Outcome category	Axicabtagene ciloleucel N = 180	Induction + HDCT + autologous SCT N = 179
ZUMA-7		
Treatment duration[a] [days]		
Median [Q1; Q3]	26.0 [16; 52]	ND
Mean (SD)	26.9 (6.1)	ND
Observation period [months], median [95% CI]		
Overall survival [b]	47.0 [45.4; 48.3]	45.8 [44.2; 47.8]
Failure of the curative approach or EFS per investigator assessment[b]	42.6 [42.0; 47.2]	42.0 [41.6; 42.8]
Symptoms, health-related quality of life (EORTC QLQ-C30)[c, d]	13.7 [ND; ND]	3.5 [ND; ND]
Health status (EQ-5D VAS)[c, d]	12.7 [ND; ND]	3.5 [ND; ND]
Side effects[e]	–[f]	–[f]

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 follow-up observation periods for the outcomes of overall survival and failure of the curative approach or EFS (according to the investigator) were calculated using the reverse Kaplan-Meier method. This differs from the methods used in Module 4 to calculate the observation period for overall survival at the same data cut-off (25 January 2023) (date of death or last known day alive – day of randomization + 1): median in months [Q1; Q3]: axicabtagene ciloleucel: 41.1 [12.6; 47.5], induction + HDCT + autologous SCT: 21.2 [7.8; 45.4].
c. No information on the methods for calculating the observation period in the company's documents.
d. 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).
e. Data refer to the safety analysis set (axicabtagene ciloleucel: N = 170, induction + HDCT + autologous SCT: N = 168).
f. The observation periods of 40.6 months in the intervention arm and 22.4 months in the comparator arm provided in the company's comments are not plausible, as follow-up observation of all outcomes in the side effects category with the exception of targeted SAEs (defined as corresponding neurological or haematological events, infections, autoimmune disorders and secondary malignancies) was planned for a maximum of up to 5 months after randomization or the commencement of new lymphoma therapy, whichever occurred first. As described in dossier assessment A23-66, a notably longer observation period in the intervention arm than in the comparator arm is assumed regardless of this.

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