Axicabtagene ciloleucel (DLBCL and HGBL, second line 1)

Addendum to Project A24-71 (dossier assessment)[1]

ADDENDUM

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Abbreviation	Meaning
ACT	appropriate comparator therapy
CAR	chimeric antigen receptor
CD	Cluster-of-Differentiation
CR	complete response
DLBCL	diffuse large B-cell lymphoma
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)
mEFS	modified event-free survival
PR	partial response
RCT	randomized controlled trial
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
R-GDP	rituximab, gemcitabine, dexamethasone, cisplatin
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
RR	relative risk
SCT	stem cell transplantation
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 12 November 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-71 (Axicabtagene ciloleucel – Benefit assessment according to §35a Social Code Book V [SGB V]) [1].

The commission comprised the assessment of the analyses and information on the ZUMA-7 study subsequently submitted by the pharmaceutical company in the commenting procedure [2], taking into account the information in the dossier [3]. The subsequently submitted analyses and data include analyses of modified event-free survival (mEFS)1.1/1.2 and mEFS2.1/2.2, data on the median disease duration, data on patients who died before treatment, data on the time until completion of autologous stem cell transplantation (SCT) treatment and the observation period for mEFS2.

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

The aim of benefit assessment A24-71 [1] was 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 (Cluster-of-Differentiation 20 [CD20]) that had relapsed within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and who are candidates for high-dose therapy. The ACT was induction therapy choosing from R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin), R-ICE (rituximab, ifosfamide, carboplatin, etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) followed by high-dose therapy with autologous or allogeneic SCT in case of response to induction therapy.

The randomized controlled trial (RCT) ZUMA-7 presented by the company was used for the benefit assessment and is described in dossier assessment A24-71 [1]. As part of the commenting procedure, the company submitted new analyses on the mEFS as well as some missing information on the patient population and on treatment and observation durations. The new analyses and data are assessed and presented below in accordance with the commission[b].

2.1 Analyses subsequently submitted for mEFS1 and mEFS2

With its dossier, the company submitted analyses on mEFS1 and mEFS2 for the outcome “failure of the curative treatment approach” (for a detailed description of these analyses, see [1]), which were used for the benefit assessment. As part of the comments, the company has now submitted revised analyses on mEFS1 and mEFS2 (referred to by the company as mEFS1.1/2.1 and mEFS1.2/2.2). Compared to the analyses already used in the dossier assessment, the analyses subsequently submitted do not provide any additional information and are also incomplete, as no subgroup analyses and Kaplan-Meier curves are available. The analyses submitted by the company in the commenting procedure are described below; a supplementary presentation is provided in Appendix A.

mEFS1.1/2.1

The analyses on the composite outcome of mEFS1 and mEFS2 presented by the company in the dossier also include the component "failure to achieve a complete response [CR] by Day 150 according to blinded central review (or, if applicable, by Month 9)". The company also already argued in its dossier that a response to chimeric antigen receptor (CAR)-T cell therapy could still occur after Month 9 and that 4 patients in the intervention arm still achieved CR after Month 9 [3]. For its analyses mEFS1.1 and mEFS2.1 presented in the context of the commenting procedure, the company therefore extended the component on “failure to achieve CR” to "failure to achieve CR after blinded central review on Day 150 (or, if applicable, up to Month 18)". As a result, the 4 patients named above were no longer included as events

in the analysis. In addition, 1 patient who had progression according to blinded central review but later achieved a CR without starting a new therapy was also no longer included as an event in the analyses.

Assessment of the mEFS1.1/2.1

The extension of the component of failure to achieve a CR by 9 months in order to include a late CR to treatment with axicabtagene-ciloleucel is comprehensible. In these patients, the curative treatment approach had not failed, but the CR was only achieved at a later stage. As explained by the company, this change in the operationalization means that 4 patients without subsequent therapy in the intervention arm of the ZUMA-7 study with a late CR were no longer included as an event in the analysis. This operationalization is appropriate in the present data situation. In contrast, it is viewed critically not to classify patients with a progression event based on the central review as an event or to make the event dependent on the further course of the disease, since according to the present operationalization a qualifying event for the composite outcome has demonstrably occurred.

An effect in favour of axicabtagene ciloleucel is shown for both the analysis of mEFS1.1 and of mEFS2.1, but according to the Institute's General Methods [4] to a considerable extent for mEFS1.1 compared to a minor extent for mEFS2.1. A sensitivity analysis for mEFS1 based on the Institute's calculations, in which the 1 patient with progression of the disease is still counted as an event, however, also shows only a minor effect (104 [58%] vs. 133 [74%] EFS events in the intervention vs. comparator arm, relative risk (RR) [95% CI]; p-value: 0.78 [0.67; 0.91]; 0.001).

mEFS1.2/2.2

The analyses mEFS1 and mEFS2 presented by the company in its dossier each include the component "failure to achieve CR or partial response (PR) by Day 50 in the comparator arm (after blinded central review)" [3]. Since this component only represents a qualifying event in the comparator arm and failure of the curative treatment approach can therefore be achieved inherently earlier than in the intervention arm, the time-to-event analyses for mEFS1 and mEFS2 were assessed as not interpretable in the dossier assessment [1]. To address this aspect, the company removed the component "failure to achieve CR or PR according to blinded central review by Day 50 in the comparator arm" from the analyses mEFS1.2 and mEFS2.2 presented with its comments. The company's approach has no impact on the interpretability of the time-to-event analyses. This is explained below. The analyses mEFS1.2 and mEFS2.2 are shown as supplementary information in the Appendix (see Table 3).

Assessment of the mEFS1.2/2.2

It makes sense to record the component "failure to achieve a CR or PR by Day 50" in the comparator arm as a qualifying event in the outcome of EFS, as it is at this point that the

decision is made whether to continue or discontinue the treatment approach. High-dose therapy and autologous SCT is only continued if the patients in the comparator arm respond to their induction therapy (at least PR). In the comparator arm, a non-response to induction therapy therefore always represents a failure of the curative treatment approach. This occurs regardless of whether the component "failure to achieve CR or PR by Day 50" in the comparator arm is explicitly included in the analysis as a qualifying event or not.

This is also clear from the company's subsequently submitted analyses mEFS1.2/2.2. The 34 patients in the comparator arm who showed non-response by Day 50 in the analyses mEFS1.1/2.1 are now largely (29 of 34 events, corresponding to 85%) included in the respective analyses with the qualifying event "commencement of new lymphoma therapy". It can be assumed that this will only slightly change the time to event, as the new lymphoma therapy is usually started shortly after the non-response by Day 50. This is also reflected in the median time to event, which differs only insignificantly between the analyses mEFS1.1 and mEFS1.2 or mEFS2.1 and mEFS2.2 (see Appendix A). In contrast, the failure of the curative treatment approach in the intervention arm can only be determined much later, for example if the patient has not yet achieved CR by Day 150 (or, if applicable, by Month 18).

Thus, the time-to-event analyses are still inherently biased in favour of the intervention arm, even in the operationalizations now presented. In the present data situation, the relevant effect measure for determining the added benefit for the outcome of failure of the curative treatment approach is still the RR.

Conclusion on the subsequently submitted analyses of the mEFS

In summary, the analyses on mEFS presented by the company with the comments did not change the assessments of dossier assessment A24-71. The subsequently submitted analyses mEFS1.1 and mEFS2.1 confirm the minor added benefit of axicabtagene ciloleucel compared with the ACT in the outcome of failure of the curative treatment approach. The time-to-event analyses are still inherently biased in favour of the intervention arm and therefore still cannot be interpreted.

2.2 Information on patient population, treatment and observation periods

Information on the median disease duration

In the dossier assessment, it was noted that the company did not provide any information on the median disease duration of the patients in the ZUMA-7 study. As part of the comments, the company subsequently submitted information on the median disease duration, defined as the time in months from the first diagnosis of the disease to the time point of randomization. The median disease duration was 7.5 months in the intervention arm and 7.4 months in the comparator arm. The median disease duration was comparable between

the treatment arms. The subsequently submitted data have no consequences for the benefit assessment.

Information on patients who died before treatment

It was noted in the dossier assessment that 8 patients in the intervention arm had died before treatment with axicabtagene ciloleucel and that the reasons for this are unclear. As part of the comments, the company subsequently submitted the reasons for the patients' death. According to these, 2 patients already died before leukapheresis. 3 patients died of disease progression and 1 patient died of sepsis, 1 of respiratory failure due to human respiratory syncytial virus (RSV) infection and 1 of torsade de pointes tachycardia. The subsequently submitted data have no consequences for the benefit assessment.

Information on the time until completion of the autologous SCT

In the dossier assessment, it was pointed out that no information on the time to completion of treatment with autologous SCT is available for the comparator arm. In the comments, the company describes that a total of 62 of the 179 patients in the comparator arm had received protocol-compliant high-dose therapy and autologous SCT by the data cut-off of 25 January 2023. In these patients, the median time between the first administration of induction chemotherapy and receipt of autologous SCT was 89.5 days. The subsequently submitted data have no consequences for the benefit assessment.

Observation period for mEFS2

It was noted in the dossier assessment that the follow-up observation for failure of the curative treatment approach was only presented for the mEFS1 analysis. Within the framework of the comments, the company declares that the median observation period for the mEFS2, defined as the time from randomization to the time of the event or to the time of censoring, was 8.3 months in the intervention arm and 2.1 months in the comparator arm (data cut-off: 18 March 2021). The subsequently submitted data have no consequences for the benefit assessment.

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 A23-71.

Table 1 below shows the result of the benefit assessment of axicabtagene ciloleucel, taking into account dossier assessment A24-71 and the present addendum.

Table 1: 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 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 analyses on the outcome of failure of the curative treatment approach presented with the comments

Table 2: Results (mEFS1.1 and mEFS2.1) – 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 (mEFS1.1)					
Event rate[a]	180	– 103 (57)	179	– 133 (74)	RR: 0.77 [0.66; 0.89]; < 0.001[b]
Death from any cause	180	– 12 (7)	179	– 7 (4)	
Progression according to blinded central assessment	180	– 81 (45)	179	– 71[c] (40)	
Failure to achieve CR or PR according to the blinded central review by Day 50 in the comparator arm	180	–	179	– 34[c] (19)	
Failure to achieve CR by Day 150 according to blinded central review (or, if applicable, up to Month 18)	180	– 4 (2)	179	– 1 (1)	
Commencement of new lymphoma therapy due to SD/PD according to the investigator	180	– 6 (3)	179	– 20 (11)	
Event-free survival	180	10.2 [5.1; 21.5] 103 (57)	179	2.1 [1.7; 2.8] 133 (74)	0.39 [0.30; 0.51]; ND

Table 2: Results (mEFS1.1 and mEFS2.1) – 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 (mEFS2.1)					
Event rate[a]	180	– 101 (56)	179	– 125 (70)	RR: 0.80 [0.68; 0.94]; 0.008[b]
Death from any cause	180	– 15 (8)	179	– 18 (10)	
Progression according to blinded central assessment	180	– 81 (45)	179	– 71[c] (40)	
Failure to achieve CR or PR according to the blinded central review by Day 50 in the comparator arm	180	–	179	– 34[c] (19)	
Failure to achieve CR on Day 150 according to blinded central review (or, if applicable, up to Month 18)	180	– 4 (2)	179	– 1 (1)	
Initiation of a new lymphoma therapy with previous SD according to blinded central review	180	– 1 (1)	179	– 1 (1)	
Event-free survival	180	12.6 [5.3; 28.6] 101 (56)	179	2.8 [2.1; 3.9] 125 (70)	0.44 [0.34; 0.58]; 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 (unconditional exact test, CSZ method according to [5]).
c. Deviating information on the number of events of the analyses mEFS1 and mEFS2 [1]: 72 (40%) patients with progression according to blinded central review and 33 (18%) patients with failure to achieve CR or PR by Day 50 in the comparator arm.

CI: confidence interval; EFS: event-free survival; HDCT: high-dose chemotherapy; HR: hazard ratio; mEFS: modified event-free survival; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; PD: progressive disease; PR: partial response; RCT: randomized controlled trial; SCT: stem cell transplantation; SD: stable disease

Table 3: Results (mEFS1.2 and mEFS2.2) – 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 (mEFS1.2)					
Event rate[a]	180	– 103 (57)	179	– 133 (74)	RR: 0.77 [0.66; 0.89]; < 0.001[b]
Death from any cause	180	– 12 (7)	179	– 8 (4)	
Progression according to blinded central assessment	180	– 81 (45)	179	– 74 (41)	
Failure to achieve CR by Day 150 according to blinded central review (or, if applicable, up to Month 18)	180	– 4 (2)	179	– 2 (1)	
Commencement of new lymphoma therapy due to SD/PD according to the investigator	180	– 6 (3)	179	– 49 (27)	
Event-free survival	180	10.2 [5.1; 21.5] 103 (57)	179	2.5 [1.8; 3.3] 133 (74)	0.40 [0.31; 0.53]; ND

Table 3: Results (mEFS1.2 and mEFS2.2) – 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 (mEFS2.2)					
Event rate[a]	180	– 101 (56)	179	– 125 (70)	RR: 0.80 [0.68; 0.94]; 0.008[b]
Death from any cause	180	– 15 (8)	179	– 19 (11)	
Progression according to blinded central assessment	180	– 81 (45)	179	– 74 (41)	
Failure to achieve CR on Day 150 according to blinded central review (or, if applicable, up to Month 18)	180	– 4 (2)	179	– 2 (1)	
Initiation of a new lymphoma therapy with previous SD according to blinded central review	180	– 1 (1)	179	– 30 (17)	
Event-free survival	180	12.6 [5.3; 28.6] 101 (56)	179	3.3 [2.3; 4.6] 125 (70)	0.45 [0.35; 0.59]; 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 (unconditional exact test, CSZ method according to [5]).

CI: confidence interval; EFS: event-free survival; HDCT: high-dose chemotherapy; HR: hazard ratio; mEFS: modified event-free survival; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; PD: progressive disease; PR: partial response; RCT: randomized controlled trial; SCT: stem cell transplantation; SD: stable disease