Lisocabtagene maraleucel (DLBCL, HGBL, PMBCL and FL3B, second line)

Addendum to Project A23-48 (dossier assessment)[1]

ADDENDUM

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

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

IQWiG employees involved in the addendum

- Philip Böhler
- Katharina Hirsch
- Kirsten Janke
- Daniela Preukschat

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BOR	best overall response
CR	complete response
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
FACT-LymS	Functional Assessment of Cancer Therapy-Lymphoma Subscale
FL3B	follicular lymphoma grade 3B
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)
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	Preferred Term
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
R-GDP	rituximab, dexamethasone, gemcitabine, cisplatin
R-ICE	rituximab, ifosfamide, etoposide, carboplatin
RCT	randomized controlled trial
sAAIPI	age-adjusted International Prognostic Index
SAE	serious adverse event
SCT	stem cell transplantation
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 10 October 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-48 (Lisocabtagene maraleucel – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses of the TRANSFORM study [2,3] 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 [4]. The following analyses subsequently submitted are to be assessed: analyses of the outcome of event-free survival (EFS) with consideration of failure to achieve complete response (CR) at Month 18 as a qualifying event, and analyses of the effect estimates of the specific adverse events (AEs). 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, cisplatin, dexamethasone), 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 lisocabtagene maraleucel, the randomized controlled trial (RCT) TRANSFORM was used for research question 1 of dossier assessment A23-48 (adults with diffuse large B-cell lymphoma [DLBCL], high-grade B-cell lymphoma [HGBL], primary mediastinal B-cell lymphoma [PMBCL] or follicular lymphoma grade 3B [FL3B], who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and who are eligible for high-dose therapy). This study investigated the comparison of lisocabtagene maraleucel 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").

The dossier assessment considered failure of curative treatment as a patient-relevant outcome. In the TRANSFORM study, failure of curative treatment was not directly recorded as an outcome, however. As an approximation, the dossier assessment therefore considered the events that were recorded as part of the primary outcome of the TRANSFORM study, i.e. the composite outcome of EFS, as operationalization for the outcome. However, the operationalization for the EFS available in the dossier may not have included all events that are necessary to fully reflect failure of curative treatment. In addition, the company's dossier provided no information on statistical significance for some outcomes of the side effects category, although the company could have calculated p-values using the log-rank test. Furthermore, only few Kaplan-Meier curves were available for these outcomes.

In the commenting procedure, the company presented supplementary analyses on the outcome of failure of curative treatment and on outcomes in the side effects category. 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 lisocabtagene maraleucel compared with the ACT based on this change.

Failure of curative treatment: consideration of failure to achieve complete response after completion of treatment as event

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

- death from any cause
- disease progression
- failure to achieve CR or partial response (PR) by Week 9 after randomization
- start of new antineoplastic therapy due to efficacy concerns

However, as described in the dossier assessment, this operationalization may not include all events that are necessary to fully reflect failure of curative treatment. In addition to progression events and failure to achieve CR or PR by Week 9 after randomization, failure to achieve CR after completion of treatment also means failure of curative treatment. In the TRANSFORM study, the first assessment of response after the end of treatment in both study arms took place at Week 18, at which point the presence of PR also meant failure of curative treatment. In the EFS outcome, failure to achieve CR at Week 18 should therefore also have been recorded as an independent qualifying event, in addition to the other events already included.

Despite this uncertainty, the EFS and the proportion of patients with event (hereinafter referred to as "event rate") were used in the dossier assessment to reflect the outcome of failure of curative treatment. In order to address the existing uncertainty regarding the failure to achieve CR by Week 18, a sensitivity analysis was performed for the event rate and taken into account for the assessment of the outcome. This analysis rated the presence of PR as best overall response (BOR) by Week 18 as additional event for the event rate, based on the assumption that none of the additionally considered patients subsequently experienced progression within the observation period of the study. However, as described in the dossier assessment, it can be assumed that this was the case for at least some of the patients with PR as best response by Week 18, and that such patients were counted multiple times as event in the sensitivity analysis for the outcome. It remained unclear for the dossier assessment how many patients with event were affected, however.

Furthermore, it remained unclear how the patients with PR as BOR by Week 18 were distributed among the subgroups relevant to the assessment. For the subgroup of patients < 65 years of age, it was nevertheless assumed that even taking into account failure to achieve CR by Week 18 after randomization, there was a statistically significant difference in favour of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT. In contrast, for patients ≥ 65 years of age, no conclusion on the comparison of lisocabtagene maraleucel with induction + HDCT + autologous SCT for the outcome of failure of curative treatment was possible in the present data situation due to the uncertainty.

In the commenting procedure, the company presented analyses for EFS and event rate (including subgroup analyses) in which the failure to achieve CR up to 18 weeks after randomization was taken into account as an additional qualifying event. These analyses are suitable as an operationalization of the outcome of failure of curative treatment and are used below for the assessment.

Side effects: completeness of the available analyses

As described in dossier assessment A23-48, in Module 4 B of the dossier the company presented only proportions of patients with event for some outcomes in the side effects category for which events occurred in only one study arm. The company provided no information on statistical significance for these outcomes, although it could have calculated p-values using the log-rank test. In addition, only few Kaplan-Meier curves were available for these outcomes.

In the commenting procedure, the company presented p-values and Kaplan-Meier curves for these outcomes in the side effects category. The p-values are used below for the assessment. However, effect estimates could not be calculated for these outcomes using the Cox proportional hazards model presented by the company. If the superordinate System Organ Class (SOC) of a specific AE mainly comprised events of the relevant Preferred Term (PT), the available results of the SOC are therefore considered as an approximation for the assessment below. This was possible for (serious) cytokine release syndrome (PT, AE/serious AE [SAE]) and acute kidney injury (PT, SAE). The Kaplan-Meier curves are presented in Appendix A.2.

2.1 Results

2.1.1 Risk of bias

With regard to the risk of bias across outcomes and the outcome-specific risk of bias, there are no changes compared with dossier assessment A23-48.

As described in Section I 4.2 of dossier assessment A23-48, due to the size of the effect and the early occurrence of the events in the course of the study, before there was a critical extent of censorings, there is a high certainty of results of the results for the outcome of cytokine release syndrome despite the high risk of bias. The Kaplan-Meier curves on the outcome subsequently submitted by the company with its comments (see Figure 3 in Appendix A.2) confirm this assessment, which was made in dossier assessment A23-48 on the basis of the approximate consideration of the superordinate SOC immune system disorders (AE).

Summary assessment of the certainty of conclusions

In dossier assessment A23-48, there was an uncertainty for the TRANSFORM study resulting from the fact that the ACT was not fully implemented in the comparator arm of the study. In the present specific data constellation, the study could nevertheless be interpreted for research question 1 of the assessment, but the certainty of conclusions of the study results for this research question was reduced, as described in Section I 3.2 of the dossier assessment. Therefore, based on the TRANSFORM study, no more than hints, e.g. of an added benefit, could be derived for research question 1 of the dossier assessment. In addition, no conclusions on the extent of the added benefit could be derived from the results of the study for this reason.

In the present addendum, the added benefit is assessed based on the subsequent change of the induction therapy component of the ACT to R-GDP, R-ICE or R-DHAP. On this condition, at most indications, e.g. of an added benefit, as well as conclusions on the extent of the added benefit, can be derived on the basis of the TRANSFORM study for research question 1.

2.1.2 Results

Table 1 summarizes the results for the comparison of lisocabtagene maraleucel versus induction + HDCT + autologous SCT in adults with DLBCL, HGBL, PMBCL or FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and wo are eligible for high-dose therapy. Where necessary, calculations conducted by the Institute are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on time-to-event analyses submitted by the company in the commenting procedure are presented in Appendix A.

Table 1: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Outcome category Outcome	Lisocabtagene maraleucel		Induction + HDCT + autologous SCT		Lisocabtagene maraleucel 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]
TRANSFORM					
Mortality					
Overall survival	92	NA [29.5; NC] 28 (30.4)	92	29.9 [17.9; NC] 38 (41.3)	0.72 [0.44; 1.18]; 0.197
Morbidity					
Failure of curative treatment					
Event rate[b]	92	– 50 (54.3)	92	– 76 (82.6)	RR: 0.67 [0.55;0.82]; < 0.001[c]
Death	92	– 4 (4.3)	92	– 2 (2.2)	–
PD after achieving CR or PR	92	– 31 (33.7)	92	– 47 (51.1)	–
Failure to achieve CR or PR by 9 weeks after randomization	92	– 4 (4.3)	92	– 17 (18.5)	–
Start of NAT due to efficacy concerns	92	– 3 (3.3)	92	– 5 (5.4)	–
Failure to achieve CR by 18 weeks after randomization	92	– 8 (8.7)	92	– 5 (5.4)	–
Event-free survival (EFS)	92	11.7 [6.0; NC] 50 (54.3)	92	2.4 [2.2; 4.5] 76 (82.6)	0.37 [0.26; 0.53]; < 0.001
Symptoms (EORTC QLQ-C30, FACT-LymS)	No suitable data[d]				
Health status (EQ-5D VAS)	No suitable data[d]				
Health-related quality of life					
EORTC QLQ-C30	No suitable data[d]				

Table 1: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Outcome category Outcome	Lisocabtagene maraleucel		Induction + HDCT + autologous SCT		Lisocabtagene maraleucel 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]
Side effects					
AEs (supplementary information)	92	0.1 [0.1; 0.3] 92 (100)	91	0.1 [0.1; 0.1] 90 (98.9)	–
SAEs	92	4.4 [2.2; NC] 44 (47.8)	91	3.1 [2.8; NC] 45 (49.5)	0.89 [0.58; 1.36]; 0.594
Severe AEs[e]	92	0.6 [0.4; 0.9] 85 (92.4)	91	0.5 [0.4; 0.8] 81 (89.0)	1.17 [0.86; 1.61]; 0.322
Discontinuation due to AEs	92	NA 0 (0)	91	NA 4 (4.4)	NC; 0.054[f]
Cytokine release syndrome[g]	92	NA [1.48; NC] 45 (48.9)	91	NA 0 (0)	NC; < 0.001[f]
Including: serious cytokine release syndrome[h, i]	92	NA 12 (13.0)	91	NA 0 (0)	NC; < 0.001[f]
Neurological toxicity[j]	92	1.4 [1.2; NC] 54 (58.7)	91	3.3 [2.8; NC] 44 (48.4)	1.36 [0.90; 2.06]; 0.141
Including: severe neurological toxicity[k]	92	NA 10 (10.9)	91	NA 5 (5.5)	2.61 [0.71; 9.58]; 0.148
Severe infections[l]	92	NA 14 (15.2)	91	NA 19 (20.9)	0.62 [0.31; 1.27]; 0.191
Other specific AEs					
Diarrhoea (PT, AEs)	92	NA 23 (25.0)	91	3.3 [3.0; NC] 39 (42.9)	0.43 [0.26; 0.73]; 0.002

Table 1: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Outcome category Outcome	Lisocabtagene maraleucel		Induction + HDCT + autologous SCT		Lisocabtagene maraleucel 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]
Side effects					
Other specific AEs					
Mucosal inflammation (PT, AEs)	92	NA 5 (5.4)	91	NA 14 (15.4)	0.25 [0.09; 0.70]; 0.009
Gastrointestinal disorders (SOC, SAEs)	92	NA 2 (2.2)	91	NA 8 (8.8)	0.18 [0.04; 0.90]; 0.036
Acute kidney injury (PT, SAEs)[m]	92	NA 0 (0)	91	NA 5 (5.5)	NC; 0.015[f]
General disorders and administration site conditions (SOC, severe AEs[e])	92	NA 4 (4.3)	91	NA 10 (11.0)	0.30 [0.09; 0.98]; 0.046
Neutrophil count decreased (PT, severe AEs[e])	92	NA 6 (6.5)	91	NA 0 (0)	NC; 0.038[f]
Neutropenia (PT, severe AEs[e])	92	1.3 [1.15; 1.41] 75 (81.5)	91	3.0 [1.9; NC] 47 (51.6)	1.80 [1.24; 2.60]; 0.002
Lymphopenia (PT, severe AEs[e])	92	NA 24 (26.1)	91	NA 9 (9.9)	3.14 [1.41; 7.00]; 0.005
Febrile neutropenia (PT, severe AEs[e])	92	NA 11 (12.0)	91	NA 21 (23.1)	0.43 [0.20; 0.90]; 0.025
Thrombocytopenia (PT, severe AEs[e])	92	NA [1.8; NC] 46 (50.0)	91	2.2 [1.2; 2.9] 62 (68.1)	0.60 [0.41; 0.89]; 0.011

Table 1: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Outcome category Outcome	Lisocabtagene maraleucel		Induction + HDCT + autologous SCT		Lisocabtagene maraleucel 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]

a. Unless stated otherwise: effect, CI and p-value from Cox proportional hazards model, stratified by best overall response to first-line therapy (refractory [SD, PD, PR or CR with relapse < 3 months] vs. relapsed [CR with relapse ≥ 3 and < 12 months]) 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. Effect: Mantel-Haenszel method; 95% CI and p-value: normal distribution approximation, stratified by best overall response to first-line therapy (refractory [SD, PD, PR or CR with relapse < 3 months] vs. relapsed [CR with relapse ≥ 3 and < 12 months]) and sAAIPI (0 or 1 vs. 2 or 3).
d. See Section I 4.1 of dossier assessment A23-48 for the reasoning.
e. Operationalized as CTCAE grade ≥ 3.
f. p-value based on log-rank test.
g. Operationalized as AEs of the PT cytokine release syndrome. Data on the proportion of patients with event and the result of the log-rank test are available for this outcome. An effect estimate could not be calculated using the Cox proportional hazards model presented by the company. For the AEs of the superordinate SOC immune system disorders, which predominantly include the PT cytokine release syndrome, the following result is shown: 51 (55.4 %) vs. 9 (9.9 %); HR 6.96 [3.41; 14.18]; p < 0.001; for the Kaplan-Meier curve, see Figure 8 of dossier assessment A23-48.
h. Operationalized as SAEs of the PT cytokine release syndrome. The operationalization as severe AEs is not usable for this outcome due to deviation from the severity classification according to CTCAE criteria and associated discrepant results on SAEs; see Section I 4.1 of dossier assessment A23-48 for explanation.
i. Data on the proportion of patients with event and the result of the log-rank test are available for this outcome. An effect estimate could not be calculated using the Cox proportional hazards model presented by the company. For the SAEs of the superordinate SOC immune system disorders, which predominantly include the PT cytokine release syndrome, the following result is shown: 12 (13.0 %) vs. 2 (2.2 %); HR: 5.91 [1.32; 26.48]; p = 0.020; for the Kaplan-Meier curve, see Figure 10 of dossier assessment A23-48.
j. Operationalized as AEs of the SOC nervous system disorders.
k. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC nervous system disorders.
l. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC infections and infestations.
m. Data on the proportion of patients with event and the result of the log-rank test are available for this outcome. An effect estimate could not be calculated using the Cox proportional hazards model presented by the company. For the superordinate SOC renal and urinary disorders, with events predominantly comprising the PT acute kidney injury (each operationalized as SAEs), the following result is shown: 1 (1.1) vs. 7 (7.7); HR 0.11 [0.01; 0.88]; p = 0.038; for the Kaplan-Meier curve, see Figure 15 of dossier assessment A23-48.

Table 1: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Study Outcome category Outcome	Lisocabtagene maraleucel		Induction + HDCT + autologous SCT		Lisocabtagene maraleucel 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]
AE: adverse event; BOR: best overall response; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; HDCT: high-dose chemotherapy; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NAT: new antineoplastic therapy; NC: not calculable; PD: progressive disease; PR: partial response; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Cancer 30; RCT: randomized controlled trial; RR: relative risk; sAAIPI: second-line age-adjusted International Prognostic Index; 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, at most indications can be determined for the outcomes of overall survival, failure of curative treatment, severe AEs, and cytokine release syndrome, and at most hints, e.g. of an added benefit, for all other outcomes (serious AEs [SAEs], discontinuation due to AEs, and other specific AEs).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. However, there is an effect modification by the characteristic of age. For patients < 65 years of age, there is an indication of an added benefit of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT. For patients ≥ 65 years of age, there is no hint of an added benefit of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven for patients ≥ 65 years of age (see Section 2.1.3).

Morbidity

Failure of curative treatment

For the outcome of failure of curative treatment, operationalized via the event rate and the EFS, in each case including failure to achieve CR by 18 weeks after randomization, a statistically significant difference was shown in favour of lisocabtagene maraleucel compared with

induction + HDCT + autologous SCT. In contrast to dossier assessment A23-48, where no conclusion on advantages or disadvantages of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT for the outcome was possible due to the approximate consideration of the outcome and the associated uncertainty for patients ≥ 65 years of age, the data situation now available shows no effect modification for the subgroup characteristic of age (see Appendix B for the results of the subgroup analyses). The added benefit for the outcome is therefore derived on the basis of the results of the total population of the study. There is an indication of an added benefit of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT. The results of the operationalizations of event rate and EFS differ in their extent, however. In the present data situation, taking into account the differences in the proportions of patients with event and the time courses (see Appendix A.1), the overall extent of the added benefit is rated as "considerable" (see Section 2.2.1).

Irrespective of the fact that there is no effect modification by the characteristic of age for the outcome of failure of curative treatment, there are similar differences between the results for the subgroups by age as for overall survival, with a less pronounced positive effect for patients aged ≥ 65 years (see Appendix B).

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

No suitable data are available for symptoms (recorded using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and Functional Assessment of Cancer Therapy-Lymphoma Subscale [FACT-LymS]) and health status (recorded using EQ-5D visual analogue scale [VAS]), for reasons, see Section I 4.1 of dossier assessment A23-48). There is no hint of an added benefit of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30)

No usable data are available for health-related quality of life (recorded using the EORTC QLQ-C30) (for reasons, see Section I 4.1 of dossier assessment A23-48). There is no hint of an added benefit of lisocabtagene maraleucel 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 lisocabtagene maraleucel 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 found for the outcome of severe AEs. There is no hint of greater or lesser harm from lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Specific AEs

Cytokine release syndrome (AEs), serious cytokine release syndrome (SAEs)

A statistically significant difference to the disadvantage of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for the outcome of cytokine release syndrome and serious cytokine release syndrome contained therein. For cytokine release syndrome, there is an indication of greater harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT. For serious cytokine release syndrome, there is a hint of greater harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT.

Neurological toxicity (AEs), severe neurological toxicity (severe AEs)

There was no statistically significant difference between treatment groups for the outcome of neurological toxicity and for severe neurological toxicity contained therein. In each case, there is no hint of greater or lesser harm from lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Severe infections (severe AEs)

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 lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven.

Diarrhoea, mucosal inflammation (AEs)

A statistically significant difference in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for each of the specific AEs of diarrhoea and mucosal inflammation. There is a hint of lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT.

Gastrointestinal disorders (SAEs)

A statistically significant difference in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for the specific severe SAE of gastrointestinal disorders. There is a hint of lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT.

Acute kidney injury (SAEs)

A statistically significant difference in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for the specific SAE of acute kidney injury. There is a hint of lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT.

General disorders and administration site conditions (severe AEs)

A statistically significant difference in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for the specific severe AE of general disorders and administration site conditions. There is a hint of lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT.

Neutrophil count decreased, neutropenia, lymphopenia (severe AEs)

A statistically significant difference to the disadvantage of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for each of the specific severe AEs of neutrophil count decreased, neutropenia and lymphopenia. In each case, this results in a hint of greater harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT.

Febrile neutropenia (severe AEs)

A statistically significant difference in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for the specific severe AE of febrile neutropenia. However, there is an effect modification by the characteristic of second-line age-adjusted International Prognostic Index (sAAIPI). For patients with sAAIPI 0 or 1, there is a hint of lesser harm of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. For patients with sAAIPI 2 or 3, there is no hint of greater or lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm is therefore not proven for patients with sAAIPI 2 or 3 (see Section 2.1.3).

Thrombocytopenia (severe AEs)

A statistically significant difference in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for the specific severe AE of thrombocytopenia. However, there is an effect modification by the characteristic of sex. For women, there is a hint of lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT. For men, there is no hint of greater or lesser harm from lisocabtagene maraleucel in comparison

with induction + HDCT + autologous SCT; greater or lesser harm for men is therefore not proven (see Section 2.1.3).

2.1.3 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 (0 or 1 versus 2 or 3)

The methods described in Section I 4.4 of dossier assessment A23-48 are used.

The subgroup analyses subsequently submitted by the company for the outcome of failure of curative treatment showed no statistically significant interaction for the subgroup characteristics investigated. Therefore, there are no changes with regard to the relevant effect modifications compared with dossier assessment A23-48. The conclusions on the added benefit based on the subgroup results (see Table 17 of dossier assessment A23-48) are summarized below.

Mortality

Overall survival

There is a statistically significant effect modification by the characteristic of age for the outcome of overall survival. For patients < 65 years of age, a statistically significant difference between treatment groups was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. For patients < 65 years of age, there is an indication of an added benefit of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT. However, no statistically significant difference between treatment groups was shown for patients ≥ 65 years. For this subgroup, there is no hint of an added benefit of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; an added benefit for this outcome is therefore not proven for patients ≥ 65 years of age.

Side effects

Specific AEs

Febrile neutropenia (severe AEs)

There is a statistically significant effect modification by the characteristic of sAAIPI for the outcome of febrile neutropenia (severe AEs). For patients with sAAIPI 0 or 1, a statistically significant difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. For patients with sAAIPI 0 or 1, there is a hint of lesser harm of

lisocabtagene maraleucel versus induction + HDCT + autologous SCT. For patients with sAAIPI 2 or 3, however, no statistically significant difference between treatment groups was shown. For this subgroup, there is no hint of greater or lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm for this outcome is therefore not proven for patients with sAAIPI 2 or 3.

Thrombocytopenia (severe AEs)

There is a statistically significant effect modification by the characteristic of sex for the outcome of thrombocytopenia (severe AEs). For women, a statistically significant difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. There is a hint of lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT for women. For men, however, no statistically significant difference was shown between treatment groups. For this subgroup, there is no hint of greater or lesser harm of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT; greater or lesser harm for this outcome is therefore not proven for men.

2.2 Probability and extent of added benefit

Probability and extent of the added benefit for research question 1 of dossier assessment A23-48 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* [5].

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.

2.2.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.1 (see Table 2).

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 2: Extent of added benefit at outcome level: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Lisocabtagene maraleucel 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 observed over the entire study duration		
Mortality		
Overall survival Age < 65 years	NA vs. NA months HR: 0.32 [0.15; 0.68]; p = 0.003 Probability: "indication"	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: "major"
≥ 65 years	23.0 vs. 29.9 months HR: 1.40 [0.66; 2.96]; p = 0.378	Lesser/added benefit not proven
Outcomes observed over 36 months		
Morbidity		
Failure of curative treatment Event rate	54.3% vs. 82.6% RR: 0.67 [0.55; 0.82]; p < 0.001 Probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Event-free survival (EFS)	11.7 vs. 2.4 months HR: 0.37 [0.26; 0.53]; p < 0.001 Probability: "indication"	
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, FACT-LymS)	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

Table 2: Extent of added benefit at outcome level: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Lisocabtagene maraleucel 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]
Side effects		
SAEs	4.4 vs. 3.1 months HR: 0.89 [0.58; 1.36]; p = 0.594	Greater/lesser harm not proven
Severe AEs	0.6 vs. 0.5 months HR: 1.17 [0.86; 1.61]; p = 0.322	Greater/lesser harm not proven
Discontinuation due to AEs	ND vs. ND Months 0% vs. 4.4% HR: NC; p = 0.054	Greater/lesser harm not proven
Cytokine release syndrome	NA vs. NA months 48.9% vs. 0% HR: NC[d]; p < 0.001 Probability: “indication”	Outcome category: non-serious/non-severe side effects Greater harm; extent: “considerable”[d, e]
Including: serious cytokine release syndrome	NA vs. NA months 13.0% vs. 0% HR: NC[e]; p < 0.001 Probability: “hint”	
Neurological toxicity	1.4 vs. 3.3 months HR: 1.36 [0.90; 2.06]; p = 0.141	Greater/lesser harm not proven
Including: severe neurological toxicity	NA vs. NA months HR: 2.61 [0.71; 9.58]; p = 0.148	
Severe infections	NA vs. NA months HR: 0.62 [0.31; 1.27]; p = 0.191	Greater/lesser harm not proven

Table 2: Extent of added benefit at outcome level: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Lisocabtagene maraleucel 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]
Other specific AEs		
Diarrhoea (AEs)	NA vs. 3.3 months HR: 0.43 [0.26; 0.73]; 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. NA months HR: 0.25 [0.09; 0.70]; p = 0.009 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Gastrointestinal disorders (SAEs)	NA vs. NA months HR: 0.18 [0.04; 0.90]; p = 0.036 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Acute kidney injury (SAEs)	NA vs. NA months 0% vs. 5.5% HR: NC[f]; p = 0.015 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"[f]
General disorders and administration site conditions (severe AEs)	NA vs. NA months HR: 0.30 [0.09; 0.98]; p = 0.046 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Neutrophil count decreased (severe AEs)	NA vs. NA months 6.5% vs. 0% HR: NC; p = 0.038 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable"

Table 2: Extent of added benefit at outcome level: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Lisocabtagene maraleucel 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]
Neutropenia (severe AEs)	1.3 vs. 3.0 months HR: 1.80 [1.24; 2.60] HR: 0.56 [0.38; 0.81][g]; p = 0.002 Probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: “considerable”
Lymphopenia (severe AEs)	NA vs. NA months HR: 3.14 [1.41; 7.00] HR: 0.32 [0.14; 0.71][g]; p = 0.005 Probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5 % Greater harm, extent: “major”
Febrile neutropenia (severe AEs) sAAIPI 0 or 1	NA vs. NA months HR: 0.19 [0.06; 0.59]; p = 0.004 Probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5 % Lesser harm, extent: “major”
2 or 3	NA vs. NA months HR: 1.10 [0.37; 3.31]; p = 0.865	Greater/lesser harm not proven
Thrombocytopenia (severe AEs) Sex Male	1.9 vs. 2.8 months HR: 0.92 [0.56; 1.51]; p = 0.739	Greater/lesser harm not proven
Female	NA vs. 0.6 months HR: 0.34 [0.18; 0.62]; p = 0.001 Probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5 % Lesser harm, extent: “major”

Table 2: Extent of added benefit at outcome level: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Lisocabtagene maraleucel 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]**
a. Probability provided 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 of dossier assessment A23-48 for the reasoning. d. Data on the proportion of patients with event and the result of the log-rank test are available for this outcome. An effect estimate could not be calculated using the Cox proportional hazards model presented by the company. To derive the added benefit, the superordinate SOC immune system disorders (AEs), whose events predominantly include the PT cytokine release syndrome, is therefore used instead: 51 (55.4%) vs. 9 (9.9%); HR 6.96 [3.41; 14.18]; reversed direction of effect (Institute's calculation): 0.14 [0.07; 0.29]; p < 0.001. e. Data on the proportion of patients with event and the result of the log-rank test are available for this outcome. An effect estimate could not be calculated using the Cox proportional hazards model presented by the company. To derive the added benefit, the superordinate SOC immune system disorders (SAEs), whose events predominantly include the PT cytokine release syndrome, is therefore used instead: 12 (13.0%) vs. 2 (2.2%); HR 5.91 [1.32; 26.48]; reversed direction of effect (Institute's calculation): 0.17 [0.04; 0.76]; p = 0.020. f. Data on the proportion of patients with event and the result of the log-rank test are available for this outcome. An effect estimate could not be calculated using the Cox proportional hazards model presented by the company. To derive the added benefit, the superordinate SOC renal and urinary disorders (SAEs), whose events predominantly include the PT acute kidney injury, is therefore used instead: 1 (1.1%) vs. 7 (7.7%); HR: 0.11 [0.01; 0.88]; p = 0.038. g. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; HDCT: high-dose chemotherapy; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Cancer 30; RR: relative risk; sAAIPI: second-line age-adjusted International Prognostic Index; SAE: serious adverse event; SCT: stem cell transplantation; VAS: visual analogue scale		

2.2.2 Overall conclusion on added benefit

Table 3 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT

Positive effects	**Negative effects**
Outcomes observed over the entire study duration	
Mortality ▪ Overall survival ▫ Age < 65 years: indication of an added benefit – extent: “major”	–
Outcomes observed over 36 months	
Morbidity ▪ Failure of curative treatment: indication of an added benefit – extent: “considerable”	–
Outcomes with shortened observation period	
Serious/severe side effects ▪ Gastrointestinal disorders (SAEs): hint of lesser harm, extent: “minor” ▪ Acute kidney injury (SAEs): hint of lesser harm, extent: “non-quantifiable” ▪ General disorders and administration site conditions (severe AEs): hint of lesser harm, extent: “minor” ▪ Febrile neutropenia (severe AEs): ▫ sAAIPI 0 or 1: hint of lesser harm, extent: “major” ▪ Thrombocytopenia (severe AEs): ▫ Female: hint of lesser harm, extent: “major”	Serious/severe side effects ▪ Serious cytokine release syndrome: hint of greater harm, extent: “considerable” ▪ Neutrophil count decreased (severe AEs): hint of greater harm, extent: “non-quantifiable” ▪ Neutropenia (severe AEs): hint of greater harm, extent: “considerable” ▪ Lymphopenia (severe AEs): hint of greater harm, extent: “major”
Non-serious/non-severe side effects ▪ Diarrhoea, mucosal inflammation (each AEs): hint of lesser harm, extent: “considerable”	Non-serious/non-severe side effects ▪ Cytokine release syndrome: indication of greater harm, extent: “considerable”
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 lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT. These refer to the entire observation period only for overall survival. For the outcome of failure of curative treatment, the observed effects refer to the planned observation period of approximately up to 36 months after randomization (see Table 8 of dossier assessment A23-48). However, this observation period according, which was shortened as planned, has no consequences for the assessment based on the data cut-off used, at which no patient was observed for longer. For the outcomes in the side effects category, however, the observed effects relate exclusively to a shortened observation period.

On the side of the positive effects, there is an indication of considerable added benefit for the outcome of failure of curative treatment in the outcome category of morbidity. For patients aged < 65 years, this is also reflected in overall survival, for which there is an indication of major added benefit in this age group, while for patients aged ≥ 65 years, an added benefit for overall survival is not proven. Irrespective of the fact that there is no effect modification by the characteristic of age for the outcome of failure of curative treatment, the trend of these findings is also reflected in the results for the subgroup analyses for this outcome, with a less pronounced positive effect for patients aged ≥ 65 years (for subgroup results, see Appendix B). Positive effects were shown for the specific SAE of gastrointestinal disorders, among others, in the outcome category of serious/severe side effects; and for the specific AEs of diarrhoea and mucosal inflammation in the outcome category of non-serious/non-severe side effects. Negative effects were shown for cytokine release syndrome (including serious cytokine release syndrome) as well as for neutropenia and lymphopenia (both severe AEs). There were no positive or negative effects with regard to the overall rates of SAEs and severe AEs, neurological toxicity (including severe neurological toxicity) or severe infections.

In summary, based on the subsequent change of the induction therapy component of the ACT to R-GDP, R-ICE or R-DHAP, there is an indication of major added benefit of lisocabtagene maraleucel compared with the ACT for patients < 65 years of age with DLBCL, HGBL, PMBCL or FL3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and who are eligible for high-dose therapy.

For patients ≥ 65 years of age with DLBCL, HGBL, PMBCL or FL3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and who are eligible for high-dose therapy, based on the subsequent change of the induction therapy component of the ACT to R-GDP, R-ICE or R-DHAP, there is overall an indication of considerable added benefit of lisocabtagene maraleucel compared with the ACT.

2.3 Summary

Based on the subsequent change of the induction therapy component of the ACT to R-GDP, R-ICE or R-DHAP for research question 1 of dossier assessment A23-48 (adults with DLBCL, HGBL, PMBCL or FL3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and who are eligible for high-dose therapy), the data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of lisocabtagene maraleucel from dossier assessment A23-48 for this research question. For the other research questions, there is no change from dossier assessment A23-48.

The following Table 4 shows the result of the benefit assessment of lisocabtagene maraleucel under consideration of dossier assessment A23-48 and the present addendum.

Table 4: Lisocabtagene maraleucel – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT	Probability and extent of added benefit
Adults with DLBCL, HGBL, PMBCL or FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy, and			
1	who are eligible for high-dose therapy[a]	Induction therapy[b] with ▪ R-GDP (rituximab, gemcitabine, cisplatin, dexamethasone) 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	Patients ▪ < 65 years: indication of major added benefit[d] ▪ ≥ 65 years: indication of considerable added benefit[d]
2	with DLBCL or HGBL who are not eligible for high-dose therapy[e]	Treatment of physician's choice[f], taking into account ▪ pola-BR[g] ▪ tafasitamab + lenalidomide[g]	Added benefit not proven
3	with PMBCL or FL3B who are not eligible for high-dose therapy[e]	Treatment of physician's choice[f], taking into account ▪ CEOP ▪ dose-adjusted EPOCH ▪ rituximab monotherapy (only for patients with FL3B)	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, cisplatin, dexamethasone), R-ICE (rituximab, ifosfamide, carboplatin, etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin).
c. According to the G-BA, 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. Only patients who were eligible for autologous SCT were included in the TRANSFORM study. In addition, almost exclusively patients with an ECOG PS of 0 or 1 and patients with the tumour entities DLBCL, HGBL and PMBCL were included. It remains unclear whether the observed effects can be transferred to patients who are not eligible for autologous SCT, patients with ECOG PS ≥ 2, or patients with FL3B.
e. Patients are assumed to generally continue antineoplastic treatment after first-line immunotherapy.
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, the G-BA considered designating these treatment options for both DLBCL and HGBL to be appropriate.

Table 4: Lisocabtagene maraleucel – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT	Probability and extent of added benefit
ACT: appropriate comparator therapy; BSG: Federal Social Court; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; FL3B: follicular lymphoma grade 3B; G-BA: Federal Joint Committee; HGBL: high-grade B-cell lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; pola-BR: polatuzumab vedotin, bendamustine, rituximab; SGB: Social Code Book; WHO: World Health Organization			

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lisocabtagen maraleucel (DLBCL, HGBL, PMBCL und FL3B, Zweitlinie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 16.09.2023]. URL: https://www.iqwig.de/download/a23-48_lisocabtagen-maraleucel_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Bristol-Myers Squibb. Stellungnahme zum IQWiG-Bericht Nr. 1623: Lisocabtagen maraleucel (DLBCL, HGBL, PMBCL und FL3B, Zweitlinie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/960/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

3. Bristol-Myers Squibb. Lisocabtagen maraleucel (Breyanzi); Anhang zur Stellungnahme; zusätzliche Analysen [unpublished]. 2023.

4. Bristol-Myers Squibb. Lisocabtagen maraleucel (Breyanzi); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 17.10.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/960/#dossier.

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

Appendix A Kaplan-Meier curves

A.1 Failure of curative treatment

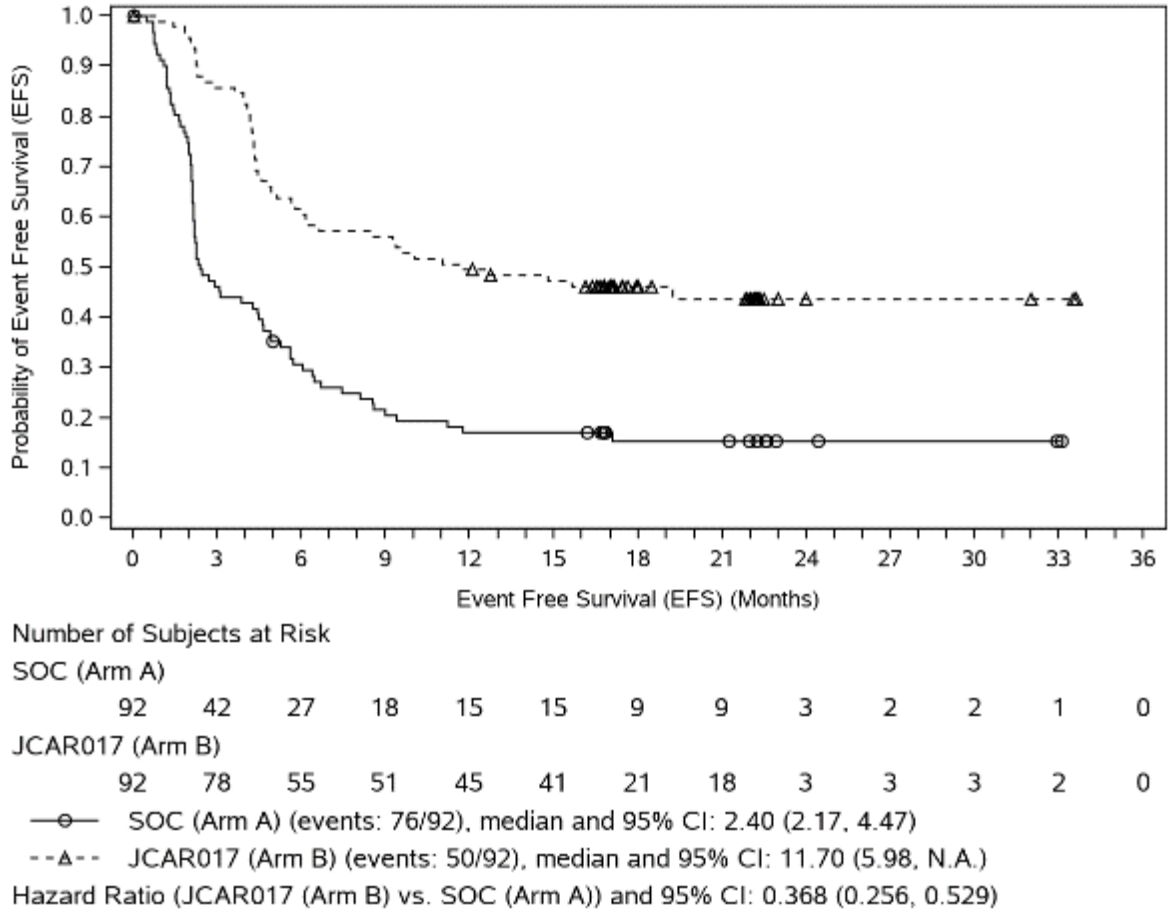

Figure 1: Kaplan-Meier curves for the outcome of failure of curative treatment (EFS including failure to achieve CR by 18 weeks after randomization) of the TRANSFORM study, 4th data cut-off (13 May 2022), total population

A.2 Side effects

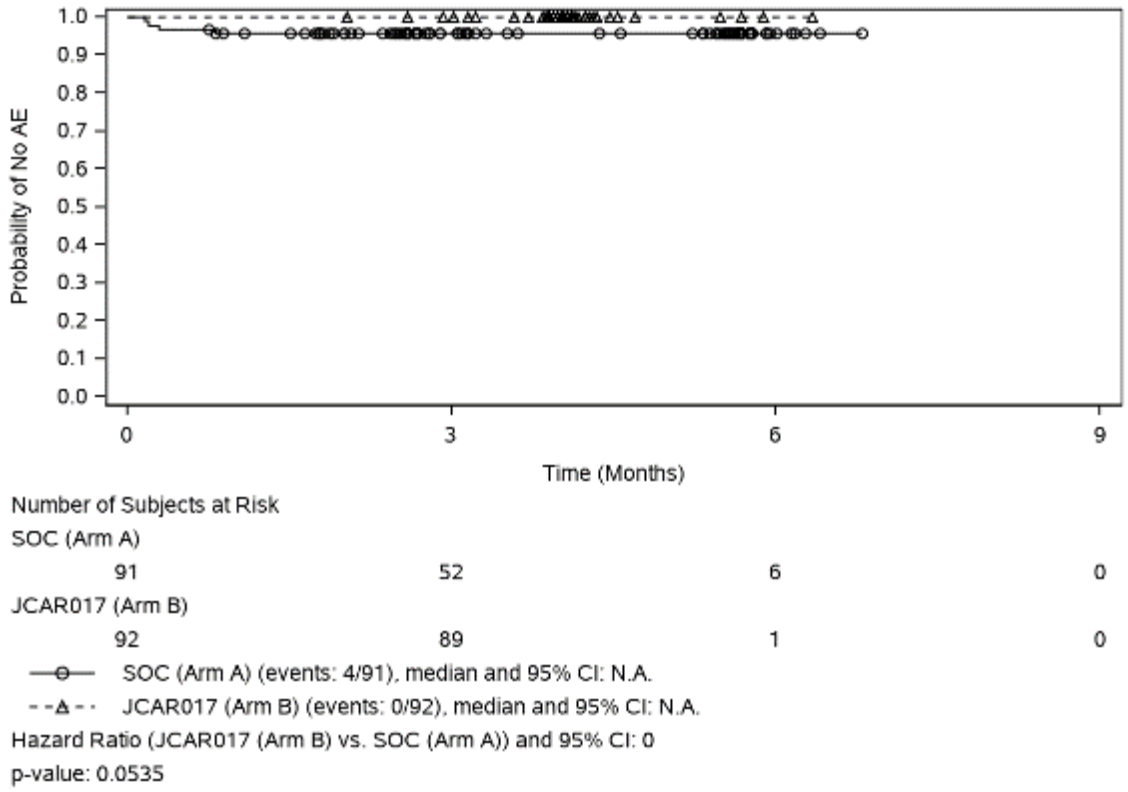

Figure 2: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the TRANSFORM study, 4th data cut-off (13 May 2022), total population

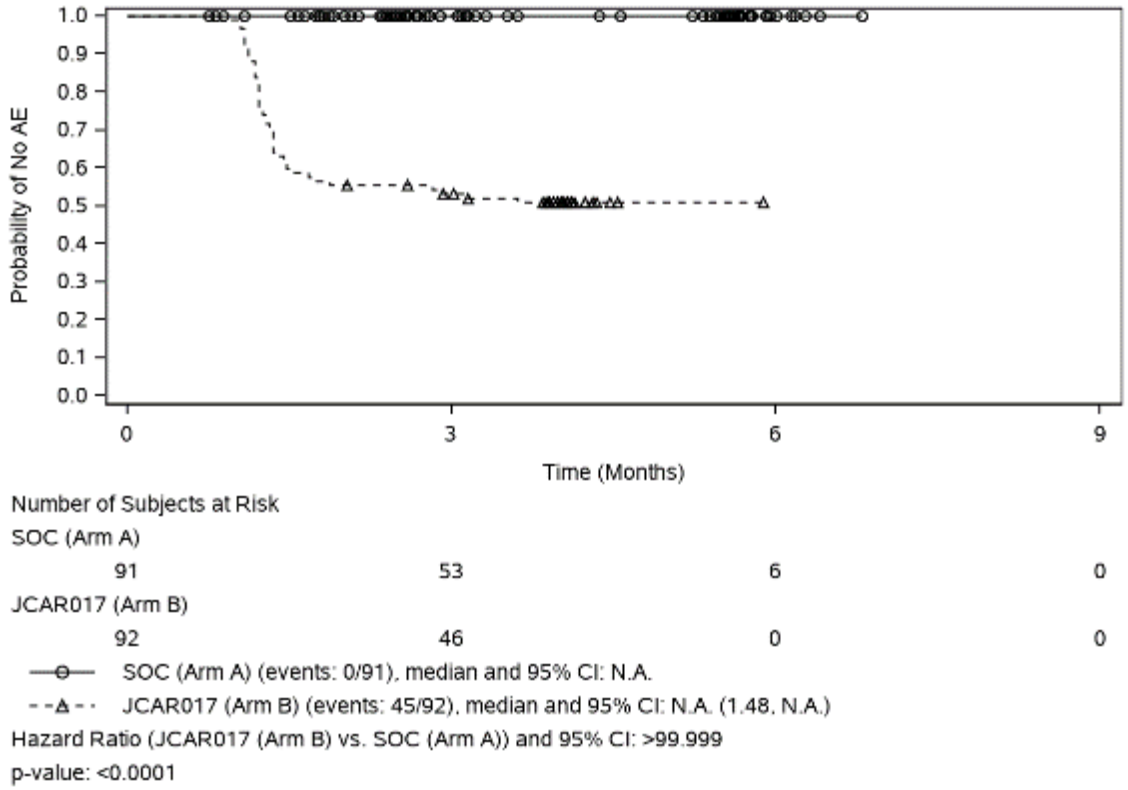

Figure 3: Kaplan-Meier curves for the outcome of cytokine release syndrome (operationalized as AEs of the PT cytokine release syndrome) of the TRANSFORM study, 4th data cut-off (13 May 2022), total population

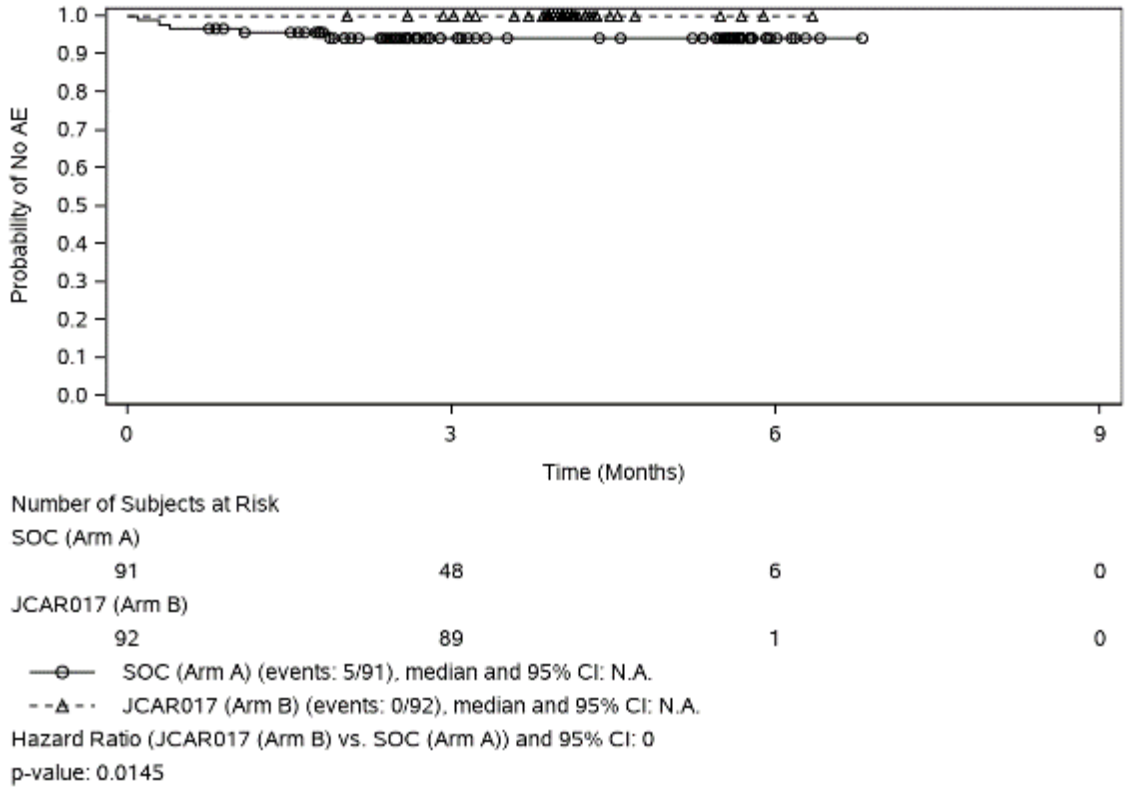

Figure 4: Kaplan-Meier curves for the outcome of acute kidney injury (PT, SAEs) of the TRANSFORM study, 4th data cut-off (13 May 2022), total population

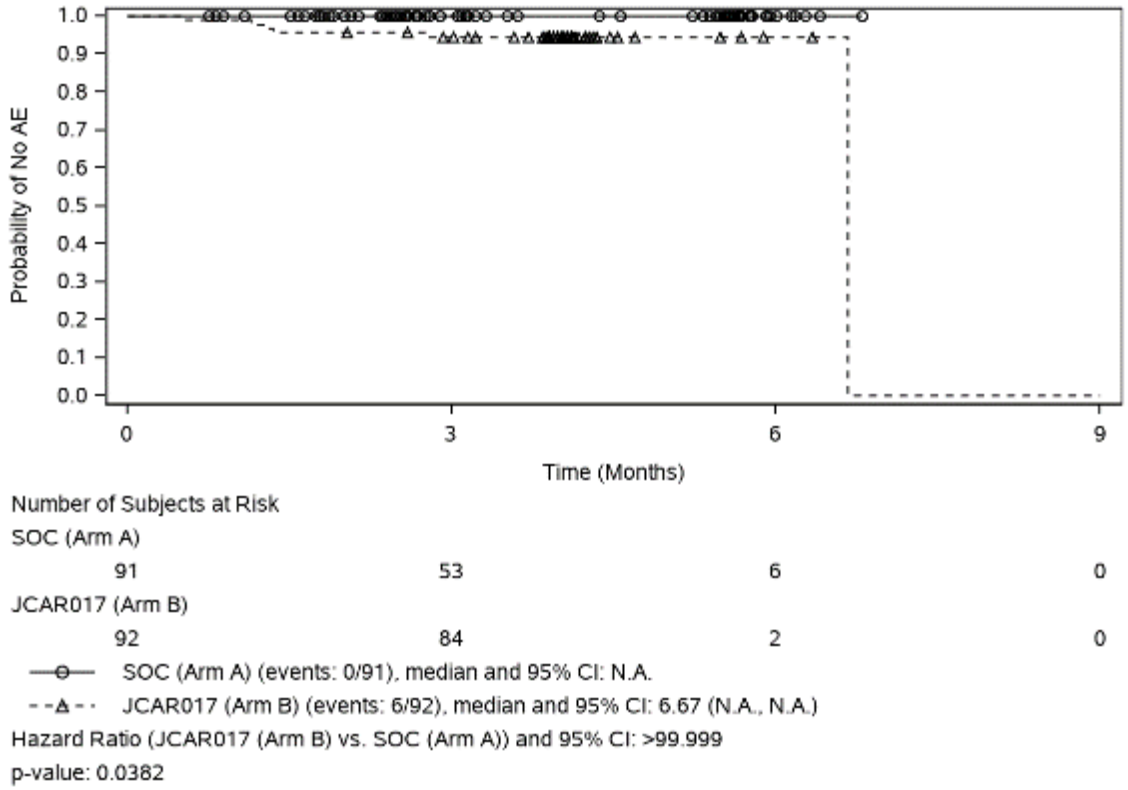

Figure 5: Kaplan-Meier curves for the outcome of neutrophil count decreased (PT, severe AEs) of the TRANSFORM study, 4th data cut-off (13 May 2022), total population

Appendix B Subgroup results for the outcome of failure of curative treatment

Table 5: Subgroups (morbidity) – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT

Study Outcome Characteristic Subgroup	Lisocabtagene maraleucel N	Lisocabtagene maraleucel Median time to event in months [95 % CI] Patients with event n (%)	Induction + HDCT + autologous SCT N	Induction + HDCT + autologous SCT Median time to event in months [95 % CI] Patients with event n (%)	Lisocabtagene maraleucel vs. induction + HDCT + autologous SCT HR [95% CI]	Lisocabtagene maraleucel vs. induction + HDCT + autologous SCT p-value
TRANSFORM						
Failure of curative treatment						
Event rate						
Age						
< 65 years	56	– 27 (48.2)	67	– 55 (82.1)	RR: 0.59 [0.44; 0.79][a]	< 0.001[a]
≥ 65 years	36	– 23 (63.9)	25	– 21 (84.0)	RR: 0.76 [0.56; 1.03][a]	0.073[a]
Total					Interaction:	0.227[b]
Event-free survival (EFS)						
Age						
< 65 years	56	19.2 [6.2; NC] 27 (48.2)	67	2.2 [2.1; 4.3] 55 (82.1)	0.32 [0.20; 0.51][c]	< 0.001[c]
≥ 65 years	36	7.7 [4.3; NC] 23 (63.9)	25	4.9 [2.3; 8.1] 21 (84.0)	0.57 [0.31; 1.03][c]	0.060[c]
Total					Interaction:	0.079[d]

a. RR: Mantel-Haenszel method; 95 % CI and p-value: normal distribution approximation.
b. p-value from Q test for heterogeneity.
c. Unstratified Cox proportional hazards model.
d. Based on Cox proportional hazards model with treatment, subgroup characteristic and interaction term (treatment x subgroup characteristic).

CI: confidence interval; HDCT: high-dose chemotherapy; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SCT: stem cell transplantation

B.1 Kaplan-Meier curves for the subgroup results of the outcome of failure of curative treatment

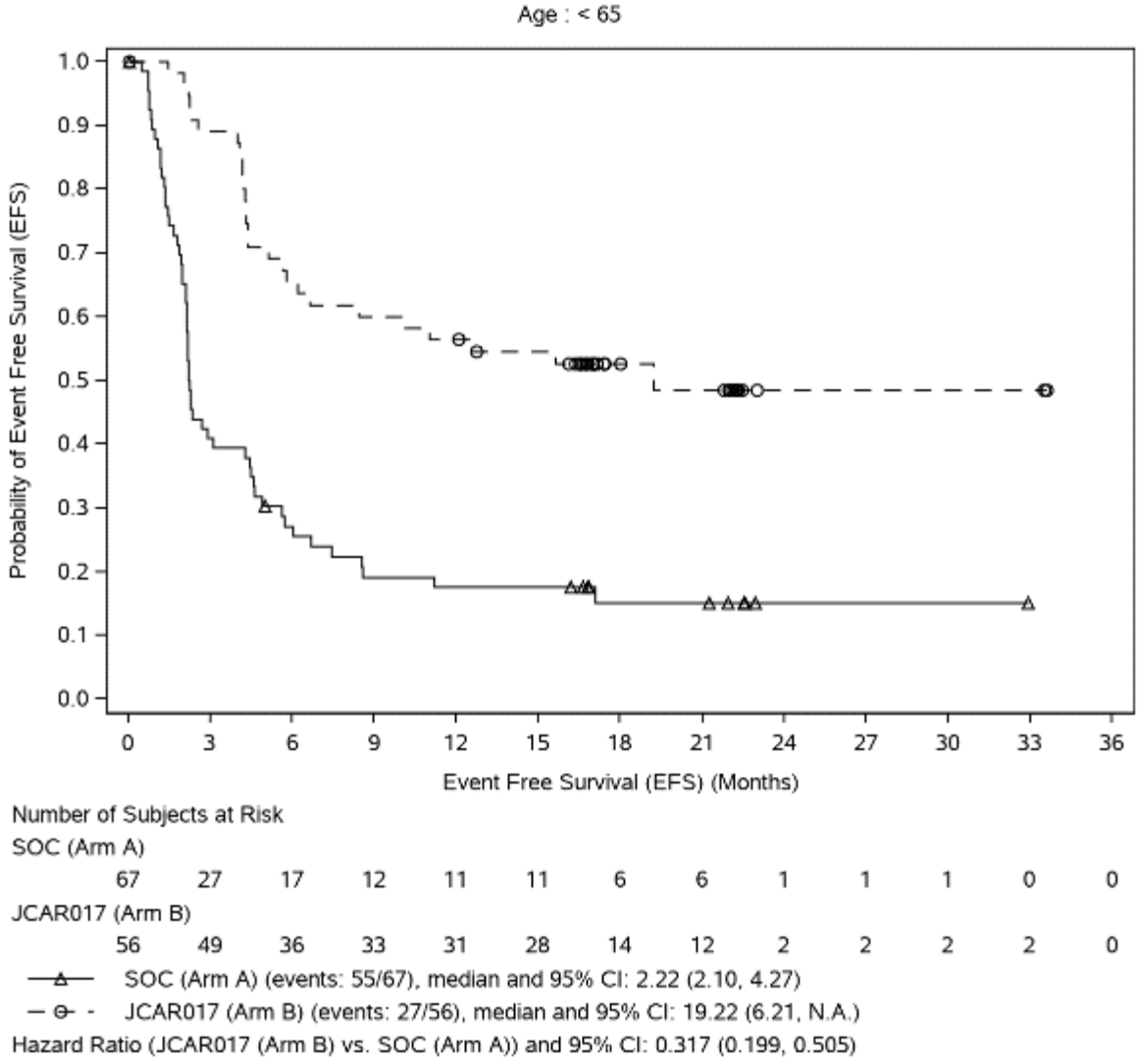

Figure 6: Kaplan-Meier curves for the outcome of failure of curative treatment (EFS including failure to achieve CR by 18 weeks after randomization) of the TRANSFORM study, 4th data cut-off (13 May 2022), subgroup < 65 years

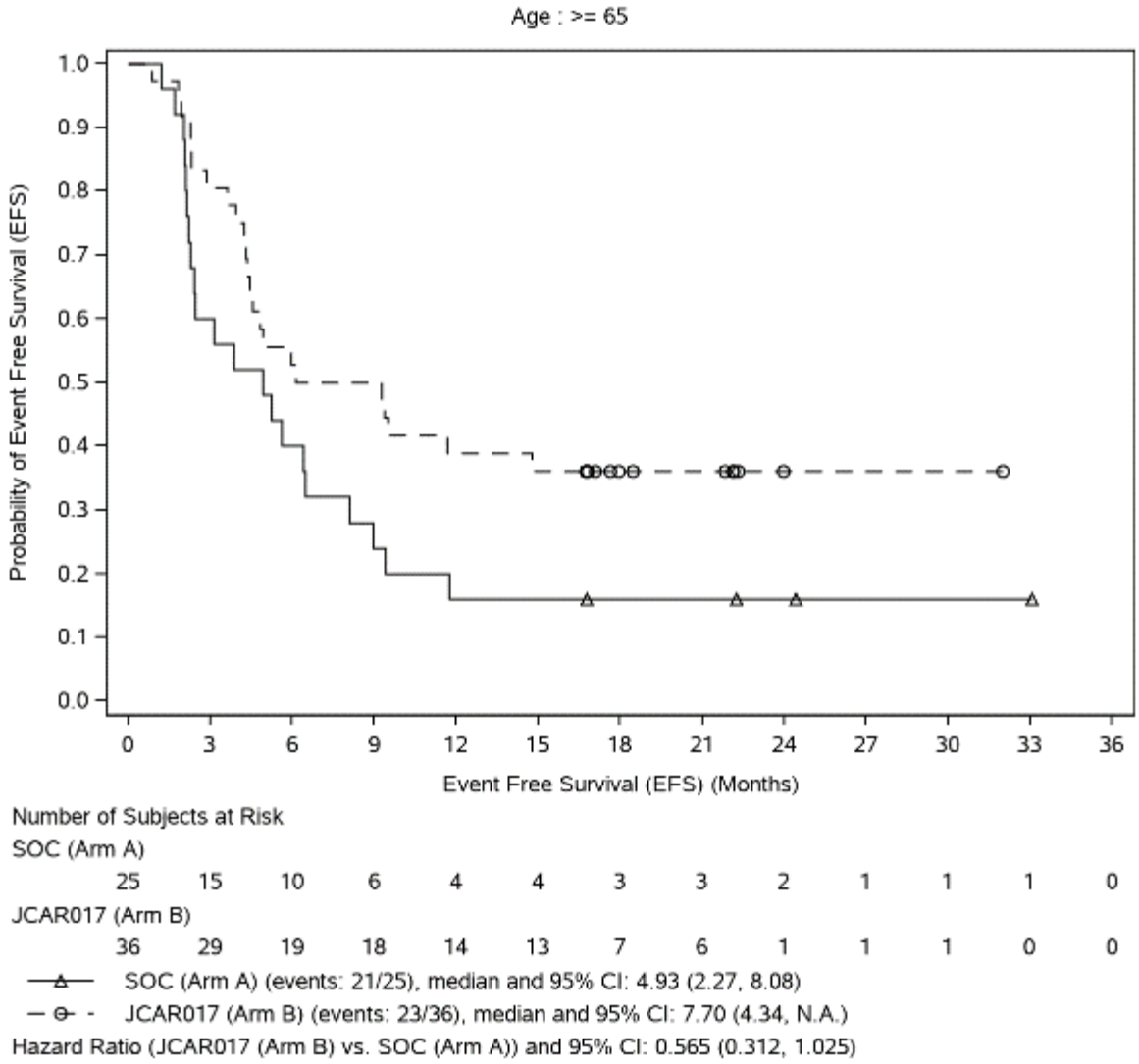

Figure 7: Kaplan-Meier curves for the outcome of failure of curative treatment (EFS including failure to achieve CR by 18 weeks after randomization) of the TRANSFORM study, 4th data cut-off (13 May 2022), subgroup ≥ 65 years