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

Benefit assessment according to §35a SGB V[1]

EXTRACT

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

Patient and family involvement

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

IQWiG thanks the respondent and the Leukämie und Lymphom SHG Ruhr-Lippe e. V. self-help group for participating in the written exchange and for their support. The respondent and the Leukämie und Lymphom SHG Ruhr-Lippe e. V. were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the German Medical Association)
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)
BOR	best overall response
BSG	Bundessozialgericht (Federal Social Court)
CAR	chimeric antigen receptor
CD	cluster of differentiation
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
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
FDA	Food and Drug Administration
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)
IRC	independent review committee
mEFS	modified event-free survival
MINE	mesna, ifosfamide, mitoxantrone and etoposide
PBMC	peripheral blood mononuclear cell
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	Preferred Term

Abbreviation	Meaning
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
THRBCL	T-cell/histiocyte-rich large B-cell lymphoma
VAS	visual analogue scale
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug lisocabtagene maraleucel. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 May 2023. Irrespective of the research question of the aforementioned commission, the G-BA commissioned IQWiG with the analysis and presentation (methodological review and presentation of the results) of the TRANSFORM study.

Research question

The aim of the present report is the assessment of the added benefit of lisocabtagene maraleucel in comparison with the appropriate comparator therapy (ACT) in adult patients 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.

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

Table 2: Research questions of the benefit assessment of lisocabtagene maraleucel

Research question	Therapeutic indication	ACT[a]
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[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic[c] stem cell transplantation if there is a response to induction therapy
2	with DLBCL or HGBL who are not eligible for high-dose therapy[d]	Treatment of physician's choice, taking into account ▪ pola-BR[e] ▪ tafasitamab + lenalidomide[e]
3	with PMBCL or FL3B who are not eligible for high-dose therapy[d]	Treatment of physician's choice, taking into account ▪ CEOP ▪ dose-adjusted EPOCH ▪ rituximab monotherapy (only for patients with FL3B)

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research questions 2 and 3) for 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 Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
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. Patients are assumed to generally continue antineoplastic treatment after first-line immunotherapy.
e. 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.

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; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; pola-BR: polatuzumab vedotin, bendamustine, rituximab; SGB: Social Code Book; WHO: World Health Organization

Regarding the determination of the ACT for research question 1, the G-BA pointed out that the present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy 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. For research

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

The company deviated from the G-BA's specification for differentiating between the different research questions and the respective ACTs. In its dossier, it addressed only one research question, covering all patient groups in the present therapeutic indication, and cited axicabtagene ciloleucel as comparator therapy. In addition to a conclusion on the comparison with axicabtagene ciloleucel, the company nevertheless also drew a conclusion on the comparison of lisocabtagene maraleucel versus salvage chemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (SCT) in its derivation of the added benefit. The conclusion relates to all patients in the present therapeutic indication, irrespective of tumour entity or eligibility for high-dose therapy.

The approach of the company is not followed. The present assessment is conducted for the research questions listed in Table 2. Irrespective of the company's deviation from the ACT defined by the G-BA, the company's decision not to classify the research questions according to eligibility for high-dose therapy or according to tumour entity is not appropriate, as different treatment options are possible, depending on these factors.

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

Study pool and study design

The company conducted its information retrieval based on the comparator therapy it specified for the comparison of lisocabtagene maraleucel with axicabtagene ciloleucel. As this did not identify any RCTs on the direct comparison of the 2 drugs, the company also searched for RCTs of the 2 drugs without restricting the comparator therapy used. In this search, the company identified the RCT TRANSFORM (JCAR017-BCM-003) on lisocabtagene maraleucel and the RCT ZUMA-7 (KTE-C19-107) on axicabtagene ciloleucel, each in comparison with induction therapy followed by HDCT with autologous SCT in case of response to induction therapy (hereinafter referred to as induction + HDCT + autologous SCT). Based on these studies, the company conducted an adjusted indirect comparison of lisocabtagene maraleucel and axicabtagene ciloleucel using induction + HDCT + autologous SCT as common comparator, and derived an added benefit of lisocabtagene maraleucel in comparison with axicabtagene ciloleucel on this

basis. In addition, the company also presented the results of the TRANSFORM study and, on this basis, derived an added benefit for the comparison of lisocabtagene maraleucel versus induction + HDCT + autologous SCT.

In addition to the evidence on the comparison of lisocabtagene maraleucel versus axicabtagene ciloleucel or versus induction + HDCT + autologous SCT, the company also presented supplementary results from 2 single-arm studies on treatment with lisocabtagene maraleucel. The company neither conducted an information retrieval on further investigations nor included the results of the studies in its derivation of the added benefit.

The adjusted indirect comparison presented by the company and the single-arm studies on treatment with lisocabtagene maraleucel are not relevant for the present assessment, as they do not investigate a comparison with the G-BA's ACT.

Although the comparator therapy in the TRANSFORM study also does not represent a complete implementation of the G-BA's ACT, it can be interpreted for research question 1 of the present benefit assessment (for explanation, see text section on the implementation of the ACT below). Besides the TRANSFORM study identified by the company, the check of completeness of the study pool identified no further RCT for the comparison of lisocabtagene maraleucel versus induction + HDCT + autologous SCT.

Research questions 2 and 3 of the present benefit assessment refer to patients who are not eligible for high-dose therapy. However, only patients who were eligible for high-dose therapy were included in the TRANSFORM study. Hence, the TRANSFORM study includes no patient population relevant to research questions 2 and 3. In addition, the comparator therapy in the study differs from the G-BA's ACT for the patient groups of research questions 2 and 3.

No data are available to assess the added benefit of lisocabtagene maraleucel compared with the ACT 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 not eligible for high-dose therapy. For this reason, the sections on information retrieval and study pool as well as results on added benefit are not divided according to research questions 1 to 3 in the present assessment.

For research question 1 of the benefit assessment, the TRANSFORM study comparing lisocabtagene maraleucel with induction + HDCT + autologous SCT is included below (for explanation, see text section on the implementation of the ACT below).

Study design

The TRANSFORM study is an ongoing, open-label, multicentre RCT comparing lisocabtagene maraleucel with induction + HDCT + autologous SCT. It included adult patients with DLBCL,

HGBL, PMBCL, FL3B or T-cell/histiocyte-rich large B-cell lymphoma (THRBCL). Patients had to have refractory or relapsed disease within 12 months after completion of first-line chemoimmunotherapy including a cluster of differentiation 20 (CD20) antibody and an anthracycline. The included patients had to be eligible for high-dose therapy. A total of 184 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with lisocabtagene maraleucel or to induction + HDCT + autologous SCT.

Lisocabtagene maraleucel treatment was in compliance with the Summary of Product Characteristics (SPC). In the time between randomization and lymphocyte depletion, patients could receive anticancer therapy for disease control (bridging therapy), if needed. In the comparator arm, patients initially received induction therapy with 3 cycles, choosing from R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), R-ICE (rituximab, ifosfamide, etoposide, carboplatin) or R-GDP (rituximab, dexamethasone, gemcitabine, cisplatin) at the investigator's discretion. Patients who achieved partial or complete response to therapy by Week 9 after randomization subsequently received HDCT and autologous SCT. Patients who did not achieve at least a partial response to induction therapy by Week 9 could receive lisocabtagene maraleucel as subsequent therapy. Analogous to the intervention arm, bridging therapy was also permitted in the comparator arm. The treatment in the comparator arm of the study and the procedure for subsequent therapy in the event of non-response largely corresponds to the specifications for the treatment regimen according to the S3 guideline of the Association of the Scientific Medical Societies (AWMF) for the diagnosis, therapy and follow-up of adult patients with DLBCL and related entities.

Implementation of the appropriate comparator therapy

The G-BA defined induction therapy with mesna, ifosfamide, mitoxantrone and etoposide (MINE), followed by high-dose therapy with autologous or allogeneic SCT in case of response to induction therapy, as ACT for lisocabtagene maraleucel for the treatment of 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 ACT therefore consists of several components: induction therapy, high-dose therapy, and SCT. The regimen used in the comparator arm of the TRANSFORM study differs from the G-BA's ACT with regard to the induction therapy (R-DHAP, R-ICE or R-GDP instead of MINE), but not with regard to the high-dose chemotherapy and the SCT.

Rituximab and platinum-based induction regimens, such as the R-DHAP, R-ICE and R-GDP regimens used in the TRANSFORM study, have long been established in clinical care practice in the present therapeutic indication. There is nothing to suggest that an induction therapy with the regimens used in the TRANSFORM study is less effective than an induction therapy with MINE. In this specific data constellation, the TRANSFORM study can therefore be interpreted for research question 1 of the present assessment, although the induction

regimens used in the study do not correspond to the MINE scheme. The uncertainty resulting from the fact that the ACT was not fully implemented in the comparator arm of the study is taken into account when assessing the certainty of the results (see following text section). In addition, no conclusions on the extent of the added benefit can be derived from the results of the study for this reason.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes is rated as low for the TRANSFORM study. The outcome-specific risk of bias for the results of all patient-relevant outcomes except overall survival, failure of the curative treatment approach and severe adverse events (AEs) is rated as high. Despite a high risk of bias, there is a high certainty of results for the results of the outcome of cytokine release syndrome.

As described above, there is an uncertainty for the TRANSFORM study resulting from the fact that the ACT was not fully implemented in the comparator arm of the study. Nevertheless, in the present specific data constellation, the study can be interpreted for research question 1 of the present assessment. The certainty of conclusions of the study results for research question 1 of the present assessment is reduced, however. On the basis of the TRANSFORM study, no more than hints, e.g. of an added benefit, can therefore be derived for research question 1 of the present assessment. In addition, no conclusions on the extent of the added benefit can be derived from the results of the study for this reason. At outcome level, therefore, only advantages and disadvantages are described below, which are summarized in an overall conclusion on the added benefit.

Results

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 age. For patients < 65 years of age, a statistically significant difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. However, no statistically significant difference between treatment groups was shown for patients ≥ 65 years.

Morbidity

Failure of the curative treatment approach

For the outcome of failure of the curative treatment approach, a statistically significant difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. For the subgroup of patients < 65 years of age, an advantage of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown. For patients ≥ 65 years of age, no conclusion on advantages or disadvantages of lisocabtagene maraleucel compared

with induction + HDCT + autologous SCT for the outcome of failure of the curative treatment approach is possible in the present data situation.

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]).

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

No suitable data are available for health-related quality of life (recorded using EORTC QLQ-C30).

Side effects

SAEs, severe AEs

No statistically significant difference between treatment groups was shown for the outcomes of serious AEs (SAEs) or severe AEs.

Discontinuation due to AEs

The effect estimate cannot be calculated for the outcome of discontinuation due to AEs. Treatment could only be discontinued for a short period at the beginning of the study. Only isolated events occurred for the outcome. Therefore, no consequences arise for the assessment in the present data situation.

Specific AEs

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

The effect estimate cannot be calculated for the outcome of cytokine release syndrome and for serious cytokine release syndrome included therein. A statistically significant difference to the disadvantage of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT was shown for the AEs and SAEs of the superordinate System Organ Class (SOC) immune system disorders, which predominantly comprise the Preferred Term (PT) cytokine release syndrome as AE or SAE. A disadvantage of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT is therefore assumed in each case.

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

There was no statistically significant difference between treatment groups for the outcome of neurological toxicity and for severe neurological toxicity contained therein, as well as for the outcome of severe infections.

Diarrhoea, mucosal inflammation (AEs), general disorders and administration site conditions (severe AEs), gastrointestinal disorders (SAEs)

A statistically significant difference in favour of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT was shown for the specific AEs of diarrhoea and mucosal inflammation, the specific severe AE of general disorders and administration site conditions, and the specific SAE of gastrointestinal disorders.

Acute kidney injury (SAEs)

The effect estimate for the specific SAE of acute kidney injury cannot be calculated. A statistically significant difference in favour of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT was shown for the SAEs of the superordinate SOC renal and urinary disorders, the events of which predominantly comprise the PT acute kidney injury. An advantage of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT is therefore assumed.

Neutrophil count decreased (severe AEs)

The effect estimate for the specific severe AE of neutrophil count decreased cannot be calculated. An approximate consideration of the superordinate SOC is not possible for this outcome, as its events do not predominantly include the PT neutrophil count decreased. In the present data situation, in which there is already a disadvantage for severe neutropenia, this has no consequences for the assessment.

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 neutropenia and lymphopenia.

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, a statistically significant difference was shown in favour 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.

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, a statistically significant

difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. For men, however, no statistically significant difference was shown between treatment groups.

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

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

Research question 1: patients who are eligible for high-dose therapy

As described above, there is an uncertainty for the TRANSFORM study resulting from the fact that the ACT was not fully implemented in the comparator arm of the study. Nevertheless, in the present specific data constellation, the study can be interpreted for research question 1 of the present assessment.

Based on the TRANSFORM study, there are the following advantages and disadvantages at outcome level for research question 1 (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):

- advantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT for the outcome of overall survival in patients < 65 years of age
- advantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT for the outcome of failure of the curative treatment approach in patients < 65 years of age
- advantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT in side effects for the outcomes of gastrointestinal disorders (SAEs), acute kidney injury (SAEs), general disorders and administration site conditions (severe AEs), febrile neutropenia (severe AEs; only in patients with sAAIPI 0 or 1), thrombocytopenia (severe AEs; only in women), diarrhoea (AEs), and mucosal inflammation (AEs)
- disadvantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT in side effects for the outcomes of cytokine release syndrome (including

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

serious cytokine release syndrome), neutropenia (severe AEs), and lymphopenia (severe AEs)

For the outcome of failure of the curative treatment approach, no conclusion on the advantages or disadvantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT is possible in the present data situation for patients ≥ 65 years of age. Likewise, no conclusion on advantages and disadvantages is possible for patient-reported outcomes of symptoms, health status and health-related quality of life, as no suitable data are available.

Only for overall survival are the observed effects based on the entire observation period. For the outcome of failure of the curative treatment approach, the observed effects relate to the period of approximately up to 36 months after randomization, which is of no consequence for the assessment due to the used data cut-off, at which no patient was observed for a longer period of time. For the outcomes in the side effects category, however, the observed effects relate exclusively to a shortened observation period.

Overall, there are both advantages and disadvantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT in adult patients with DLBCL, HGBL, PMBCL or FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

- For patients < 65 years of age, the positive effects of lisocabtagene maraleucel versus induction + HDCT + autologous SCT predominate overall.
- For patients ≥ 65 years of age, neither the positive nor the negative effects of lisocabtagene maraleucel versus induction + HDCT + autologous SCT predominate overall.

In summary, 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, there is a hint of a non-quantifiable added benefit of lisocabtagene maraleucel compared with the ACT.

For patients ≥ 65 years 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, there is no hint of an added benefit of lisocabtagene maraleucel compared with the ACT; an added benefit is therefore not proven.

Research questions 2 and 3: patients who are not eligible for high-dose therapy

Since no data are available for the assessment of the added benefit of lisocabtagene maraleucel in comparison with the ACT in 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 not eligible for high-dose therapy, there is no hint of an added benefit of lisocabtagene maraleucel compared with the ACT for these patients; an added benefit is therefore not proven.

Overall conclusion on added benefit

Table 3 shows a summary of the probability and extent of added benefit of lisocabtagene maraleucel.

Table 3: Lisocabtagene maraleucel – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	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[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic[c] stem cell transplantation if there is a response to induction therapy	Patients ▪ < 65 years: hint of a non-quantifiable added benefit[d] ▪ ≥ 65 years: added benefit not proven
2	with DLBCL or HGBL who are not eligible for high-dose therapy[e]	Treatment of physician's choice, taking into account ▪ pola-BR[f] ▪ tafasitamab + lenalidomide[f]	Added benefit not proven
3	with PMBCL or FL3B who are not eligible for high-dose therapy[e]	Treatment of physician's choice, taking into account ▪ CEOP ▪ dose-adjusted EPOCH ▪ rituximab monotherapy (only for patients with FL3B)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research questions 2 and 3) for 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 Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
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. 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.

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; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; pola-BR: polatuzumab vedotin, bendamustine, rituximab; SGB: Social Code Book; WHO: World Health Organization

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

I 2 Research question

The aim of the present report is the assessment of the added benefit of lisocabtagene maraleucel in comparison with the ACT in adult patients with DLBCL, HGBL, PMBCL or FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

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

Table 4: Research questions of the benefit assessment of lisocabtagene maraleucel

Research question	Therapeutic indication	ACT[a]
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[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic[c] stem cell transplantation if there is a response to induction therapy
2	with DLBCL or HGBL who are not eligible for high-dose therapy[d]	Treatment of physician's choice, taking into account ▪ pola-BR[e] ▪ tafasitamab + lenalidomide[e]
3	with PMBCL or FL3B who are not eligible for high-dose therapy[d]	Treatment of physician's choice, taking into account ▪ CEOP ▪ dose-adjusted EPOCH ▪ rituximab monotherapy (only for patients with FL3B)

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research questions 2 and 3) for 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 Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
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. Patients are assumed to generally continue antineoplastic treatment after first-line immunotherapy.
e. 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.

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; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; pola-BR: polatuzumab vedotin, bendamustine, rituximab; SGB: Social Code Book; WHO: World Health Organization

Regarding the determination of the ACT for research question 1, the G-BA pointed out that the present guidelines and scientific-medical societies and/or the AkdÄ in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy 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. For research questions 2 and 3, the G-BA similarly pointed out that both approved and unapproved drug therapies are listed for the treatment of the corresponding patient groups. In addition, the G-BA pointed out for all research questions that drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company deviated from the G-BA's specification for differentiating between the different research questions and the respective ACTs. In its dossier, it addressed only one research question, covering all patient groups in the present therapeutic indication, and cited axicabtagene ciloleucel as comparator therapy. However, the company's approach in the dossier is not consistent. In addition to a conclusion on the comparison with axicabtagene ciloleucel, the company also drew a conclusion on the comparison of lisocabtagene maraleucel versus salvage chemotherapy followed by HDCT and autologous SCT in its derivation of the added benefit in Section 4.4.3 in Module 4 B of the dossier. The conclusion relates to all patients in the present therapeutic indication, irrespective of tumour entity or eligibility for high-dose therapy. Elsewhere in the dossier, however, it described that the results for the comparison of lisocabtagene maraleucel versus salvage chemotherapy followed by HDCT and autologous SCT were only presented as supplementary information (e.g. Section 4.4.1 in Module 4 B of the dossier).

The approach of the company is not followed. The present assessment is conducted for the research questions listed in Table 4. Irrespective of the company's deviation from the ACT defined by the G-BA, the company's decision not to classify the research questions according to eligibility for high-dose therapy or according to tumour entity is not appropriate, as different treatment options are possible, depending on these factors. For example, SCT is only an option for patients who are eligible for high-dose therapy. In addition, the drug chosen by the company as comparator therapy, axicabtagene ciloleucel, is not approved for the treatment of PMBCL in the present therapeutic indication [3].

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on lisocabtagene maraleucel (status: 27 April 2023)
- bibliographical literature search on lisocabtagene maraleucel (last search on 27 April 2023)
- search in trial registries/trial results databases for studies on lisocabtagene maraleucel (last search on 27 April 2023)
- search on the G-BA website for lisocabtagene maraleucel (last search on 27 April 2023)
- bibliographical literature search on axicabtagene ciloleucel (last search on 27 April 2023)
- search in trial registries/trial results databases for studies on axicabtagene ciloleucel (last search on 27 April 2023)
- search on the G-BA website for axicabtagene ciloleucel (last search on 27 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on lisocabtagene maraleucel (last search on 14 June 2023); for search strategies, see I Appendix A of the full dossier assessment

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

The company conducted its information retrieval based on the comparator therapy it specified for the comparison of lisocabtagene maraleucel with axicabtagene ciloleucel. As this did not identify any RCTs on the direct comparison of the 2 drugs, the company also searched for RCTs of the 2 drugs without restricting the comparator therapy used. In this search, the company identified the RCT TRANSFORM (JCAR017-BCM-003) [4-10] on lisocabtagene maraleucel and the RCT ZUMA-7 (KTE-C19-107) [11,12] on axicabtagene ciloleucel, each in comparison with induction therapy followed by HDCT with autologous SCT in case of response to induction therapy (hereinafter referred to as induction + HDCT + autologous SCT). Based on these studies, the company conducted an adjusted indirect comparison of lisocabtagene maraleucel and axicabtagene ciloleucel using induction + HDCT + autologous SCT as common comparator, and derived an added benefit of lisocabtagene maraleucel in comparison with axicabtagene ciloleucel on this basis. In addition, the company also presented the results of the TRANSFORM study and, on this basis, derived an added benefit for the comparison of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. The procedure for the comparison based on the TRANSFORM study is not consistent in Module 4 B of the dossier (for explanation see Chapter I 2).

In addition to the evidence on the comparison of lisocabtagene maraleucel versus axicabtagene ciloleucel or versus induction + HDCT + autologous SCT, the company also presented supplementary results from 2 single-arm studies on treatment with lisocabtagene maraleucel. The company neither conducted an information retrieval on further investigations nor included the results of the studies in its derivation of the added benefit.

The adjusted indirect comparison presented by the company and the single-arm studies on treatment with lisocabtagene maraleucel are not relevant for the present assessment, as they do not investigate a comparison with the G-BA's ACT. This is explained below.

Evidence presented by the company on the comparison with axicabtagene ciloleucel and on further investigations

Adjusted indirect comparison with axicabtagene ciloleucel

The analyses presented by the company on the adjusted indirect comparison of lisocabtagene maraleucel versus axicabtagene ciloleucel based on the RCTs TRANSFORM and ZUMA-7 are not relevant for the present benefit assessment, as axicabtagene ciloleucel does not correspond to the ACT specified by the G-BA (for an explanation, see Chapter I 2).

Further investigations

As further investigations, the company presented results of the 2 single-arm studies TRANSCEND-WORLD (JCAR017-BCM-001) [13] and PILOT (TRANSCEND-NHL-017006) [14,15] on treatment with lisocabtagene maraleucel as supplementary information in Module 4 B of the dossier. The company neither conducted an information retrieval on further investigations nor included the results of the studies in its derivation of the added benefit. In agreement with the company, the studies TRANSCEND-WORLD and PILOT are not used for the benefit assessment because, as single-arm studies, they do not allow a comparison with the ACT.

Evidence presented by the company on the comparison with induction + HDCT + autologous SCT

Although the comparator therapy in the TRANSFORM study also does not represent a complete implementation of the G-BA's ACT, it can be interpreted for research question 1 of the present benefit assessment (for explanation, see Section I 3.2). Besides the TRANSFORM study identified by the company, the check of completeness of the study pool identified no further RCT for the comparison of lisocabtagene maraleucel versus induction + HDCT + autologous SCT.

Research questions 2 and 3 of the present benefit assessment refer to patients who are not eligible for high-dose therapy. However, only patients who were eligible for high-dose therapy were included in the TRANSFORM study. Hence, the TRANSFORM study includes no patient

population relevant to research questions 2 and 3. In addition, the comparator therapy in the study differs from the G-BA's ACT for the patient groups of research questions 2 and 3.

No data are available to assess the added benefit of lisocabtagene maraleucel compared with the ACT 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 not eligible for high-dose therapy (research questions 2 and 3). For this reason, the following Sections I 3.1 to I 4.4 are not divided according to research questions 1 to 3 in the present assessment.

I 3.1 Studies included

For research question 1 of the benefit assessment, the study comparing lisocabtagene maraleucel with induction + HDCT + autologous SCT presented in the following table is included (for explanation, Section I 3.2).

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
JCAR017-BCM-003 (TRANSFORM[c])	Yes	Yes	No	Yes [4,5]	Yes [6,7]	Yes [8-10]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; HDCT: high-dose chemotherapy; RCT: randomized controlled trial; SCT: stem cell transplantation

I 3.2 Study characteristics

Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TRANSFORM	RCT, open-label, parallel[b]	Patients ≥ 18 and ≤ 75 years with DLBCL NOS (de novo or tiNHL), HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, THRBCL or FL3B according to the 2016 WHO classification: ▪ who are eligible for HDCT ▪ with refractory or relapsed disease[c] < 12 months after completion of first-line therapy that included a CD20 antibody and an anthracycline ▪ ECOG PS ≤ 1	Lisocabtagene maraleucel (N = 92) Induction + HDCT + autologous SCT (N = 92)	Screening: ≤ 28 days Treatment: ▪ Lisocabtagene maraleucel: single infusion, planned approx. 3–5 weeks after randomization ▪ Comparator therapy: 3 cycles of induction therapy of 21 days each followed by HDCT and autologous SCT, planned approx. 9–11 weeks after randomization Observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	53 centres in: Belgium, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, Switzerland, United Kingdom, USA 10/2018 – ongoing Data cut-offs: 26 Nov 2019[e] 10 Nov 2020[f] 8 Mar 2021[g] 13 May 2022[h] (primary analysis)	Primary: event-free survival (EFS) Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. In the comparator arm of the study, subsequent therapy with lisocabtagene maraleucel was possible if any of the following events occurred: failure to achieve complete or partial response by week 9 after randomization, disease progression at any time or need for new antineoplastic therapy due to efficacy concerns from week 18 after randomization.
c. Refractory disease was defined as progressive disease or relapse within 3 months after first-line therapy; relapsed disease was defined as complete response in first-line therapy followed by relapse within 3 to 12 months after first-line therapy.
d. Outcome-specific information is provided in Table 8.
e. Futility analysis, prespecified 9 weeks after randomization.
f. Interim analysis in the presence of 63% of the total events (75 EFS events), prespecified after 60% of the total events (approx. 71 EFS events).
g. Interim analysis in the presence of 82% of total events (98 EFS events), requested by the FDA after 80% of total events.
h. Primary analysis in the presence of 97% of total events (115 EFS events), prespecified after 119 EFS events (100% of total events).

Table 6: Characteristics of the included study – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AE: adverse event; DLBCL: diffuse large B-cell lymphoma; EFS: event-free survival; FL3B: follicular lymphoma grade 3B; HDCT: high-dose chemotherapy; HGBL: high-grade B-cell lymphoma; N: number of randomized patients; NOS: not otherwise specified; PMBCL: primary mediastinal large B-cell lymphoma; RCT: randomized controlled trial; SCT: stem cell transplantation; tiNHL: transformed indolent non-Hodgkin lymphoma; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma; WHO: World Health Organization						

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

Study	Intervention	Comparison
TRANS-FORM	At screening before randomization ▪ unstimulated leukapheresis to obtain peripheral blood mononuclear cells for the production of lisocabtagene maraleucel	
	Lisocabtagene maraleucel single IV administration of 100 × 10^6 CAR-positive viable T-cells on day 29 ± 7 after randomization premedication of lisocabtagene maraleucel <u>Optional bridging therapy for disease control between leukapheresis and < 7 days before lymphocyte depletion:</u> ▪ R-DHAP, R-ICE or R-GDP (1 cycle, see right table column) at the discretion of the investigator ▪ local radiation to a single lesion or subset of lesions if other non-irradiated PET-positive lesions are present <u>Lymphodepleting chemotherapy up to > 2 days before administration of lisocabtagene maraleucel:</u> ▪ fludarabine IV 30 mg/m^2 BSA and cyclophosphamide IV 300 mg/m^2 BSA daily for 3 days (starting 5-7 days before administration of lisocabtagene maraleucel) <u>30 to 60 minutes before administration of lisocabtagene maraleucel:</u> ▪ paracetamol 500 to 650 mg orally and diphenhydramine 25 to 50 mg orally or IV, or, if not available, another H1 antihistamine	Induction + HDCT + autologous SCT <u>Induction regimen (3 cycles of 3 weeks each) of physician's choice:</u> ▪ R-DHAP ▫ rituximab 375 mg/m^2 BSA on day 1 ▫ dexamethasone 40 mg on days 1 to 4 ▫ cytarabine 2 × 2000 mg/m^2 BSA IV on day 2 ▫ cisplatin 100 mg/m^2 BSA IV on day 1 ▪ R-ICE ▫ rituximab 375 mg/m^2 BSA on day 1 ▫ ifosfamide 5000 mg/m^2 BSA on day 2 ▫ etoposide 100 mg/m^2 BSA IV on days 1 to 3 ▫ carboplatin AUC 5 (maximum dose 800 mg) on day 2 ▪ R-GDP ▫ rituximab 375 mg/m^2 BSA on day 1 ▫ dexamethasone 40 mg on days 1 to 4 ▫ gemcitabine 1000 mg/m^2 BSA IV on days 1 and 8 ▫ cisplatin 75 mg/m^2 BSA IV on day 1 <u>If a partial or complete response is achieved at week 9</u>[a]: ▪ HDCT (BEAM scheme[b]) followed by autologous SCT
	Dose adjustment ▪ in case of side effects of chemotherapy at the investigator's discretion	
	Disallowed pretreatment ▪ CD19-targeted CAR T-cell therapy or gene therapy <u>< 1 week before leukapheresis:</u> ▪ Prednisone equivalent > 20 mg daily[c] and cytotoxic chemotherapeutic agents that are not lymphotoxic, as well as intrathecal chemotherapeutic agents <u>< 2 weeks before leukapheresis:</u> ▪ lymphotoxic chemotherapeutic agents, e.g. cyclophosphamide, ifosfamide, bendamustine ▪ radiation to a single lesion if other non-irradiated PET-positive lesions are present <u>< 4 weeks before leukapheresis:</u> ▪ immunosuppressive therapies	

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

Study	Intervention	Comparison
TRANS-FORM	**Disallowed pretreatment (continued)** < 4 weeks before signing the informed consent form: ▪ experimental drugs [d] and radiation in case of progressive disease in irradiated lesions or presence of additional non-irradiated, PET-positive lesions < 6 weeks before study treatment[e] ▪ systemic immunostimulatory agents, e.g. interferon and IL-2 **Disallowed concomitant treatment** ▪ other antineoplastic therapies and immunosuppressants[f, g]	

a. Patients in the comparator arm could be switched to treatment with lisocabtagene maraleucel under the following conditions: failure to achieve partial or complete response by Week 9, disease progression at any time of the study, need to start a new antineoplastic therapy due to efficacy concerns after Week 18 after randomization.
b. Consisting of carmustine (or ranimustine in Japan) 300 mg/m² BSA on day 1, etoposide 200 mg/m² BSA on days 2 to 5, cytarabine 200 mg/m² BSA on days 2 to 5, melphalan 140 mg/m² BSA on day 6.
c. Physiologic replacement, topical and inhaled steroids were permitted.
d. Unless no response or progressive disease was documented on this drug and at least 3 half-lives of this drug had elapsed prior to leukapheresis.
e. Or not allowed within 5 half-lives of the drug, whichever is shorter.
f. Except for life-threatening situations, for other therapeutic indications, or for the management of intervention-related side effects.
g. For patients who received lisocabtagene maraleucel: until lack of response, subsequent therapy, or 1 year following study treatment, whichever came first.

BEAM: carmustine (BCNU), etoposide, cytarabine and melphalan; BSA: body surface area; CAR: chimeric antigen receptor; CD19: cluster of differentiation 19; HDCT: high-dose chemotherapy; IL-2: interleukin 2; IL-6R: interleukin 6 receptor; IV: intravenous; PET: positron emission tomography; RCT: randomized controlled trial; SCT: stem cell transplantation

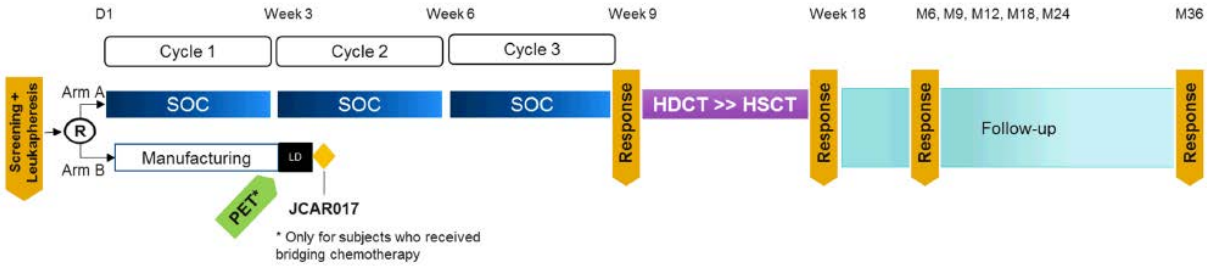
Study design

The TRANSFORM study is an ongoing, open-label, multicentre RCT comparing lisocabtagene maraleucel with induction + HDCT + autologous SCT. It included adult patients with DLBCL, HGBL, PMBCL, FL3B or THRBCL according to the 2016 World Health Organization (WHO) classification.

Patients had to have refractory or relapsed disease within 12 months after completion of first-line chemoimmunotherapy including a CD20 antibody and an anthracycline. The included patients had to be eligible for high-dose therapy. At study enrolment, patients had to be 75 years or younger, be in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and exhibit adequate organ function. Patients with significant cardiovascular conditions within the past 6 months and patients planned to undergo allogeneic SCT were excluded from the study.

A total of 184 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with lisocabtagene maraleucel (N = 92) or to induction + HDCT + autologous SCT (N = 92). Randomization was stratified by response to first-line therapy (relapsed [complete response to first-line therapy followed by relapse within ≥ 3 and < 12 months after first-line therapy] versus refractory [disease progression or relapse within < 3 months after first-line therapy]) and sAAIPI (0 or 1 versus 2 or 3).

Before treatment, the TRANSFORM study required arrangements for the individualized preparation of lisocabtagene maraleucel. Details on the course of the study are presented in Figure 1.



Abbreviations: D = day; HDCT = high dose chemotherapy; HSCT = hematopoietic stem cell transplant; LD = lymphodepleting chemotherapy; M = month; PET = positron emission tomography; R = randomization; SOC = standard of care.

Figure 1: Study scheme of the TRANSFORM study [8]

As part of the assessments for study inclusion, all patients included underwent leukapheresis to obtain peripheral blood mononuclear cells (PBMCs) for the production of lisocabtagene maraleucel. Patients in the comparator arm who could be switched to treatment with lisocabtagene maraleucel under certain conditions as part of the study were therefore able to receive this treatment within a short period of time. For these patients , the median time from confirmation that lisocabtagene maraleucel should be administered as subsequent therapy to infusion was about 15 days in the study. In the TRANSFORM study, subsequent therapy with lisocabtagene maraleucel was thus administered more quickly than would be possible in clinical care, where, after the decision for subsequent therapy with chimeric antigen receptor (CAR)-T cells, these must first be produced.

Treatment with lisocabtagene maraleucel was in compliance with the recommendations of the SPC [16]. According to the SPC, patients with THRBCL are not comprised by the present therapeutic indication of lisocabtagene maraleucel, but only a few patients with THRBCL were included in the study (see Table 9). In the time between randomization and lymphocyte depletion, patients could receive anticancer therapy for disease control (bridging therapy) in the form of chemoimmunotherapy corresponding to one cycle of induction therapy in the comparator arm (i.e. R-DHAP, R-ICE or R-GDP) or in the form of local radiation, if needed.

In the comparator arm, patients initially received induction therapy with 3 cycles, choosing from of R-DHAP, R-ICE or R-GDP at the investigator's discretion. Patients who achieved partial or complete response to therapy by Week 9 after randomization subsequently received HDCT and autologous SCT. Response was assessed in a central assessment by an independent review committee (IRC) on the basis of predefined criteria of a guideline of the sponsor based on the Lugano classification [17]. Patients who, based on these criteria, did not achieve at least a partial response to induction therapy by Week 9 could receive lisocabtagene maraleucel as subsequent therapy. Analogous to the intervention arm, bridging therapy was also permitted in the comparator arm. The treatment in the comparator arm of the study and the procedure for subsequent therapy in the event of non-response largely corresponds to the specifications for the treatment regimen according to the S3 guideline of the AWMF for the diagnosis, therapy and follow-up of adult patients with DLBCL and related entities [18].

Subsequent antineoplastic therapies were at the discretion of the investigator in both study arms and were possible without restriction. For patients in the comparator arm, subsequent therapy with lisocabtagene maraleucel was possible under certain conditions, as described above (for explanation, see also the text section on information on subsequent therapies).

According to the company's information in Module 4 B of the dossier, all patients who were treated with lisocabtagene maraleucel in the TRANSFORM study were asked to enrol into the long-term follow-up study GC-LTFU-001 [19] after completing the study. This long-term follow-up study is to record possible long-term side effects in connection with lisocabtagene maraleucel. Follow-up observation in this study is planned for up to 15 years from the time point of the last infusion of lisocabtagene maraleucel.

The primary outcome of the TRANSFORM study was event-free survival (EFS), operationalized as the time from randomization to death, disease progression, failure to achieve complete response (CR) or partial response (PR) by Week 9 post-randomization, or start of a new antineoplastic therapy due to efficacy concerns. Patient-relevant secondary outcomes were mortality, morbidity, health-related quality of life, and side effects outcomes.

Implementation of the appropriate comparator therapy

The G-BA defined induction therapy with MINE, followed by high-dose therapy with autologous or allogeneic SCT in case of response to induction therapy, as ACT for lisocabtagene maraleucel for the treatment of 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 ACT therefore consists of several components: induction therapy, high-dose therapy, and SCT. The regimen used in the comparator arm of the TRANSFORM study differs from the G-BA's ACT with regard to the

induction therapy (R-DHAP, R-ICE or R-GDP instead of MINE), but not with regard to the high-dose chemotherapy and the SCT.

Rituximab and platinum-based induction regimens, such as the R-DHAP, R-ICE and R-GDP regimens used in the TRANSFORM study, have long been established in clinical care practice in the present therapeutic indication [18,20]. There is nothing to suggest that an induction therapy with these regimens is less effective than an induction therapy with MINE. In this specific data constellation, the TRANSFORM study can therefore be interpreted for research question 1 of the present assessment, although the induction regimens used in the study do not correspond to the MINE scheme. The uncertainty resulting from the fact that the ACT was not fully implemented in the comparator arm of the study is taken into account when assessing the certainty of the results (see Section I 4.2). In addition, no conclusions on the extent of the added benefit can be derived from the results of the study for this reason.

Data cut-offs

To date, 4 data cut-offs have been implemented for the ongoing TRANSFORM study:

- First data cut-off from 26 November 2019: prespecified futility analysis, planned 9 weeks after randomization
- Second data cut-off from 10 November 2020: prespecified interim analysis, planned after the occurrence of 60% of the expected EFS events (about 71 events), performed after 75 events
- Third data cut-off from 8 March 2021: interim analysis requested by the Food and Drug Administration (FDA) after 80% of the total events, performed after 98 events
- Fourth data cut-off from 13 May 2022: prespecified primary analysis, planned after 119 EFS events (100% of expected events), performed after 115 events

Further interim analyses are not planned until the final analysis. According to the planning of the study, the study is scheduled to end when the last patient has reached the planned observation after the end of treatment of about 37 months or has entered the long-term follow-up study. In Module 4 B of the dossier, the company gave 8 December 2023 as the estimated end of the study.

The company used the results of the fourth data cut-off from 13 May 2022 (primary analysis) for its assessment. This approach is appropriate, and, in analogy to the company's approach, this data cut-off is used below for the assessment of all outcomes.

Planned duration of follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
TRANSFORM	
Mortality	
Overall survival	Until death, end of study, or withdrawal of consent
Morbidity	
Failure of curative approach or event-free survival (EFS)	Up to 36 months (± 14 days) after randomization or until death, end of study, or withdrawal of consent, whichever comes first
Symptoms (EORTC QLQ-C30, FACT-LymS) Health status (EQ-5D VAS)	Up to 36 months (± 14 days) after randomization, or until start of subsequent antineoplastic therapy, death, end of study, or withdrawal of consent, whichever comes first
Health-related quality of life (EORTC QLQ-C30)	Up to 36 months (± 14 days) after randomization, or until start of subsequent antineoplastic therapy, death, end of study, or withdrawal of consent, whichever comes first
Side effects	
All outcomes in the side effects category	Intervention arm: up to 90 days after lisocabtagene maraleucel infusion or until start of subsequent antineoplastic therapy, whichever comes first[a, b, c] Comparator arm: up to 90 days after the last dose of chemotherapy or until start of subsequent antineoplastic therapy, whichever comes first[a, b, d]

a. Module 4 B contains discrepant information on follow-up observation after start of subsequent antineoplastic therapy including treatment switching from the comparator arm to lisocabtagene maraleucel; however, it can be inferred from the study documents that events after the start of subsequent therapy, including subsequent therapy with lisocabtagene maraleucel, are not included in the present analyses.
b. AEs reported to the investigators that they consider to be a consequence of the study treatment are additionally recorded up to 36 months after randomization, regardless of the time of occurrence.
c. In the intervention arm, follow-up observation of patients who only received lymphodepletion and no subsequent administration of lisocabtagene maraleucel was only planned for 30 days.
d. In patients in the comparator arm who received subsequent therapy with lisocabtagene maraleucel, outcomes in the side effects category were observed until 90 days after the infusion. These observations are not included in the analyses of this assessment.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial

In the TRANSFORM study, follow-up observation until the end of the study is only planned for the outcome of overall survival.

For EFS and the patient-reported outcomes on symptoms, health status and health-related quality of life, follow-up observation was planned for up to 36 months after randomization. Further systematic shortening of the observation periods for the patient-reported outcomes

resulted from the fact that the follow-up observation ended with the start of subsequent antineoplastic therapy.

The observation periods for outcomes in the side effects category are also systematically shortened, as they were only recorded for the period until lisocabtagene maraleucel infusion in the intervention arm, and only until the last dose of chemotherapy (plus up to 90 days) in the comparator arm, or in each case until the start of subsequent antineoplastic therapy. Only AEs reported to the investigators that they considered to be caused by the study treatment were additionally recorded for up to 36 months after randomization, regardless of the time of occurrence.

In order to draw a reliable conclusion on the total study period or the time to patient death, however, it would be necessary to survey all outcomes over the total period, as was done for survival.

Patient characteristics

Table 9 shows the characteristics of the patients in the study presented by the company in Module 4 B of the dossier.

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

Study Characteristic Category	Lisocabtagene maraleucel N[a] = 92	Induction + HDCT + autologous SCT N[a] = 92
Study TRANSFORM		
Age [years], mean (SD)	58 (13)	54 (14)
Age group, n (%)		
< 65 years	56 (61)	67 (73)
≥ 65 to < 75 years	36 (39)	23 (25)
≥ 75 years	0 (0)	2 (2)
Sex [F/M], %	52/48	34/66
Family origin, n (%)		
White	54 (59)	55 (60)
Asian	10 (11)	8 (9)
Black or African American	4 (4)	3 (3)
Other	2 (2)	1 (1)
No data	22 (24)	25 (27)
Region, n (%)		
United States	58 (63)	57 (62)
Europe	29 (32)	31 (34)
Japan	5 (5)	4 (4)

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

Study Characteristic **Category**	**Lisocabtagene maraleucel** **N[a] = 92**	**Induction + HDCT + autologous SCT** **N[a] = 92**
ECOG PS at baseline, n (%)		
0	46 (50)	49 (53)
1	45 (49)	41 (45)
2	1 (1)	2 (2)
NHL type[b], n (%)		
DLBCL NOS	60 (65)	58 (63)
De novo	53 (58)	50 (54)
tiNHL	7 (8)	8 (9)
HGBL[c]	22 (24)	21 (23)
Double-hit lymphoma	9 (10)	14 (15)
Triple-hit lymphoma	13 (14)	6 (7)
PMBCL	8 (9)	9 (10)
Primary refractory PMBCL	5 (5[d])	7 (8[d])
THRBCL	1 (1)	4 (4)
FL3B	1 (1)	0 (0)
Disease duration		
Time between first diagnosis and randomization [months], median [Q1; Q3]	7.6 [6.0; 11.2]	7.7 [5.7; 10.4]
Time from confirmation of complete response in first-line therapy to relapse [months], median [Q1; Q3][e]	5.9 [4.9; 8.8]	5.1 [3.0; 8.2]
Time between last relapse and randomization [months], median [Q1; Q3][f]	1.2 [0.8; 1.6]	1.1 [0.9; 1.6]
Prior response status, n (%)		
Refractory[g]	67 (73)	70 (76)
Relapsed[h]	25 (27)	22 (24)
sAAIPI at baseline, n (%)		
0 or 1	56 (61)	55 (60)
2 or 3	36 (39)	37 (40)
Ann Arbor stage, n (%)		
I	8 (9)	14 (15)
II	16 (17)	15 (16)
III	18 (20)	13 (14)
IV	50 (54)	50 (54)
CNS involvement, n (%)	1 (1)	3 (3)
Treatment discontinuation, n (%)[i]	11 (12)	55 (60)
Study discontinuation, n (%)	ND	ND

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

Study Characteristic Category	Lisocabtagene maraleucel N[a] = 92	Induction + HDCT + autologous SCT N[a] = 92
a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. According to 2016 WHO criteria. c. According to the inclusion criteria of the study: HGBL with MYC and BCL2 and/or BCL6 rearrangement with DLBCL histology (double/triple-hit lymphoma [DHL/THL]). d. Institute's calculation. e. Data are based on the results of those patients who achieved complete response on first-line therapy (30 vs. 28). f. Data are based on results of 51 patients per study arm. g. Refractory disease was defined as disease progression or relapse within less than 3 months from first-line therapy. h. Relapsed disease was defined as complete response on first-line therapy followed by relapse within 3 to 12 months from first-line therapy. i. The data refer to the discontinuation of the treatment period, which lasted until Week 18 after randomization and also includes treatment discontinuations. Common reasons for discontinuation in the intervention vs. comparator arm were: lack of efficacy (0 vs. 28 patients), relapse (6 vs. 15 patients), other reasons (0 vs. 5 patients). CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FL3B: follicular lymphoma grade 3B; HGBL: high-grade B-cell lymphoma; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; PMBCL: primary mediastinal large B-cell lymphoma; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; sAAIPI: second-line age-adjusted International Prognostic Index; SD: standard deviation; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma; tiNHL: transformed indolent non-Hodgkin lymphoma		

The demographic and clinical patient characteristics are largely balanced between the 2 treatment arms of the TRANSFORM study. The mean age was about 56 years, with more older patients (≥ 65 years) included in the intervention arm (39%) than in the comparator arm (27%). In addition, more women were included in the intervention arm (52%) than in the comparator arm (34%). The majority of patients were of white family origin and were recruited exclusively in Europe, the USA or Japan. The majority of patients had DLBCL (about 64%) or HGBL (about 24%); patients with PMBCL, THRBCL or FL3B were only included in notably smaller proportions, including only one patient with FL3B in total. At randomization, a median time of about 8 months had passed since the initial diagnosis. Most patients had refractory disease (about 75%). Patients who had achieved CR as the best response in first-line therapy (about 32%) had relapsed after a median period of about 6 or 5 months. At about 60%, the majority of patients had a low to low-intermediate risk according to the prognostic index (sAAIPI of 0 or 1).

The most common reasons for discontinuation of the treatment period were lack of efficacy (0% versus 30%) and relapse (7% versus 16%). The company's dossier contains no information on the proportion of study discontinuations at any time point. For the assessment, it is assumed that there were only few study discontinuations until the present data cut-off (see Figure 2 in I Appendix B.1 of the full dossier assessment). The lack of information on study discontinuation has no consequences for the present assessment.

Course of treatment and administered therapies

Table 10 shows the course of treatment and the administered therapies in the study presented by the company in Module 4 B of the dossier.

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

Study Therapy administered Category	Lisocabtagene maraleucel N = 92	Induction + HDCT + autologous SCT N = 91
Study TRANSFORM		
Bridging therapy, n (%)	58 (63)	–[a]
Reasons for bridging therapy, n (%)		
High tumour burden	28 (30)	–
Rapid progression	23 (25)	–
Other	7 (8)	–
Therapy regimen for bridging therapy, n (%)		
R-DHAP	13 (14)	
R-ICE	29 (32)	
R-GDP	16 (17)	
Lymphodepletion, n (%)	90 (98)	–[a]
Lisocabtagene maraleucel infusion, n (%)	90 (98)	–[a]
Induction therapy		91 (100)
Initial treatment regimen for induction therapy, n (%)		
R-DHAP	–	15 (17)
R-ICE	–	58 (64)
R-GDP	–	18 (20)
Switch of treatment regimen, n (%)	–	12 (13)
Reasons for switching treatment regimen, n (%)		
Adverse event	–	4 (4)
Unsatisfactory response	–	5 (6)
Other	–	3 (3)
HDCT, n (%)	–	43 (47)
Autologous SCT, n (%)	–	43 (47)

a. In the comparator arm, 60 patients received lisocabtagene maraleucel as subsequent therapy. Of these, 11 (18%) had previously received bridging therapy.

HDCT: high-dose chemotherapy; N: number of randomized patients; RCT: randomized controlled trial; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; SCT: stem cell transplantation

In the intervention arm, 63% of patients received bridging therapy, mostly due to high tumour burden (30%) or rapid progression (25%). The most common treatment regimen used was R-ICE (32%). Almost all patients in the intervention arm received lymphodepletion followed by lisocabtagene maraleucel infusion during the course of treatment (98%).

In the comparator arm, almost all patients received induction therapy. The most common treatment regimen used was R-ICE (64%). The treatment regimen was switched in 13% of

patients, mainly due to an adverse event (4%) or unsatisfactory response (6%). HDCT followed by autologous SCT was performed in 47% of patients in the comparator arm.

Information on the course of the study

Table 11 shows the mean and median treatment duration of the patients and (if available) the mean and median observation period for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Lisocabtagene maraleucel** **N = 92[a]**	**Induction + HDCT + autologous SCT** **N = 92[a]**
TRANSFORM		
Treatment duration [days][b]		
Median [Q1; Q3]	34.0 [31.0; 36.0]	R-DHAP: 46.0 [42.0; 64.0][c] R-ICE: 62.0 [42.0; 66.0][c] R-GDP: 61.5 [21.0; 66.5][c]
Mean (SD)	36.6 (12.4)	R-DHAP: 49.4 (17.9)[c] R-ICE: 55.0 (15.7)[c] R-GDP: 47.9 (22.4)[c]
Observation period [months]		
Overall survival[d]		
Median [Q1; Q3]	17.5 [13.3; 22.3]	17.5 [9.6; 21.6]
Mean (SD)	18.1 (7.6)	16.4 (8.5)
Failure of curative approach or event-free survival	ND	
Symptoms (EORTC QLQ-C30, FACT-LymS)	ND	
Health status (EQ-5D VAS)	ND	
Health-related quality of life (EORTC QLQ-C30)	ND	
Side effects	ND	

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b. The time from randomization to the infusion of lisocabtagene maraleucel (in the intervention arm) or to the last dose of induction therapy (in the comparator arm) is indicated. The time from randomization to autologous SCT in the comparator arm is not provided in the company's dossier.
c. Data are based on those patients who received at least one treatment cycle of the respective regimen (R-DHAP: n = 15; R-ICE: n = 63; R-GDP: n = 24). Switching the induction regimen was possible in case of toxicity or unsatisfactory response in the opinion of the investigator.
d. The observation period is calculated on the basis of the observed time until end of study of all patients.

EORTC: European Organisation for Research and Treatment of Cancer; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; HDCT: high-dose chemotherapy; N: number of patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; SCT: stem cell transplantation; SD: standard deviation; VAS: visual analogue scale

In the intervention arm, the median time between randomization and completion of treatment with lisocabtagene maraleucel infusion was 34 days. This corresponds to the duration of 29 ± 7 days provided for in the study protocol. For the comparator arm, the company's dossier does not provide any information on the time to completion of treatment with autologous SCT; the median time between randomization and the last dose of induction therapy was between 46 and 62 days, depending on the regimen. Information on the duration of treatment in the comparator arm until the completion of treatment with autologous SCT is not available, but HDCT and autologous SCT were planned at a fixed time point approximately 4 weeks after the start of the last dose of induction chemotherapy. It is therefore assumed that the therapeutic strategy in patients in the comparator arm was completed about 3 to 4 weeks after the last dose of induction chemotherapy.

At the present data cut-off, the median duration of follow-up observation for overall survival was about 18 months in both study arms. For all other outcomes, the company's dossier contains no information on the observation period.

According to the planning of the study, the follow-up observation for failure of the curative approach or EFS was to take place for a period of up to 36 months from randomization. At the time of the fourth data cut-off on 13 May 2022, however, this shortened observation period according to the study planning does not have any effect, as no patient had been observed for more than 36 months at this time (see I Appendix B.2 Figure 5 of the full dossier assessment).

Although the follow-up observation of the outcomes on symptoms, health status and health-related quality of life was also planned for about 36 months according to the study planning, it was discontinued when subsequent antineoplastic therapy was started, resulting in systematically shortened observation periods compared with overall survival.

Follow-up observation of the side effects outcomes was also discontinued at the start of subsequent antineoplastic therapy and was additionally linked to the time from randomization to the infusion of lisocabtagene maraleucel (in the intervention arm) or to the last dose of chemotherapy (in the comparator arm) plus up to 90 days (see Table 8). Data for the entire observation period are therefore not available for these outcomes. Although the company presented neither outcome-specific observation periods nor sufficient information on treatment duration up to and including autologous SCT in the comparator arm, it can be inferred with sufficient certainty on the basis of the available information that the observation periods are shortened and differ between the study arms.

Information on subsequent therapies

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

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT

Study Type of therapy	Patients with subsequent therapy n (%)	
	Lisocabtagene maraleucel N = 92	Induction + HDCT + autologous SCT N = 92
TRANSFORM		
Total	30 (32.6)	65 (70.7)
Systemic antineoplastic therapy	30 (32.6)	23 (25.0)
Stem cell transplantation	10 (10.9)	2 (2.2)
Autologous	3 (3.3)	0 (0)
Allogeneic	7 (7.6)	2 (2.2)
External radiotherapy	4 (4.3)	0 (0)
Surgical cancer treatment	0 (0)	0 (0)
Lisocabtagene maraleucel	–	60 (65.2)[a]

a. The median time [Q1; Q3] from confirmation that lisocabtagene maraleucel should be administered as subsequent therapy to infusion was about 15 [13; 23] days. Of the 60 patients who received lisocabtagene maraleucel as subsequent therapy, 11 (18%) had previously received a bridging therapy.

n: number of patients with subsequent therapy; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial

In the TRANSFORM study, subsequent therapies were permitted without restrictions in both study arms. Overall, 30 (33%) patients in the intervention arm and 65 (71%) patients in the comparator arm received at least one subsequent antineoplastic therapy. In relation to the patients in whom an EFS event other than death occurred (40 patients in the intervention arm versus 69 patients in the comparator arm, see Table 16), this means that 75% of these patients in the intervention arm and 94% in the comparator arm received at least one subsequent antineoplastic therapy.

In the intervention arm, all patients with subsequent therapy received systemic antineoplastic therapy. In 10 (33%) of these patients, subsequent was associated with SCT. The dossier contained no detailed information on which systemic antineoplastic therapies were administered. External radiotherapy was used in 4 (13%) of the patients with subsequent therapy.

During the study, patients in the comparator arm could receive subsequent therapy with lisocabtagene maraleucel at the investigator's discretion if the IRC confirmed that at least one of the following events had occurred:

- failure to achieve CR or PR by Week 9 after randomization (after 3 cycles of induction therapy)
- disease progression at any time
- need to start a new antineoplastic therapy due to efficacy concerns after Week 18 after randomization

Treatment with lisocabtagene maraleucel was administered to 60 (92%) of the patients in the comparator arm who received subsequent therapy. In 2 thirds of these patients, lisocabtagene maraleucel was confirmed to be administered as a subsequent therapy even before HDCT and autologous SCT.

The guideline recommends CD19-targeted CAR T-cell therapy for the treatment of ≥ 2nd relapse if this has not already been carried out in second-line therapy [18]. In addition to lisocabtagene maraleucel, other CAR-T cell therapies are approved for the treatment of ≥ 2nd relapse, but not for all tumour entities included in the TRANSFORM study. Besides, all patients already underwent leukapheresis for the production of lisocabtagene maraleucel as part of the assessments for study inclusion, making this CAR T-cell therapy available within a short period of time. As already described, it can therefore be assumed that in the TRANSFORM study the subsequent therapy with lisocabtagene maraleucel was administered more quickly than would be possible in clinical care.

Overall, it is assumed that subsequent therapies were adequately implemented in the TRANSFORM study.

Risk of bias across outcomes (study level)

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

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: lisocabtagene maraleucel vs. induction + HDCT + autologous SCT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
TRANSFORM	Yes	Yes	No	No	Yes	Yes	Low
HDC: high-dose chemotherapy; RCT: randomized controlled trial; SCT: stem cell transplantation							

The risk of bias across outcomes is rated as low for the TRANSFORM study.

Limitations resulting from the open-label study design are described in Section I 3.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that, based on the characteristics of the population groups included in the TRANSFORM study and the participating study centres, it can be assumed that the results of the study are fully transferable to the German health care context. According to the company, the study was conducted in Germany (about 6.5% of randomized patients) and other Western industrialized countries (Europe and North America), with the majority of patients being of Caucasian family origin (about 60%).

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

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

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

Table 14 shows the outcomes for which data are available from the TRANSFORM study.

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

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

a. Operationalized as event rate and event-free survival; includes the events of death from any cause, disease progression, failure to respond (CR or PR not achieved) by Week 9 after randomization, start of new antineoplastic therapy due to efficacy concerns, whichever occurs first; see text below for explanation.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as AEs of the PT cytokine release syndrome.
d. 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 text below for explanation.
e. Operationalized as AEs of the SOC nervous system disorders.
f. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC nervous system disorders.
g. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC infections and infestations.
h. The following events are considered: diarrhoea (PT, AEs), mucosal inflammation (PT, AEs), gastrointestinal disorders (SOC, SAEs), acute kidney injury (PT, SAEs), general disorders and administration site conditions (SOC, severe AEs), neutrophil count decreased (PT, severe AEs), neutropenia (PT, severe AES), febrile neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), and lymphopenia (PT, severe AEs).
i. No usable data available; see text below for explanation.

AE: adverse event; 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; MedDRA: Medical Dictionary for Regulatory Activities; PR: partial response; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Failure of the curative treatment approach: consideration of event rate and time-to-event analysis

In the present therapeutic indication, curative therapy is possible in principle. Failure to achieve remission or occurrence of relapse after achieving remission means that the curative treatment approach in this line of therapy has failed. In the present treatment situation,

failure of the curative treatment approach in the current line of therapy is a patient-relevant event because, albeit possible in principle, cure is less likely to be achieved in a subsequent line of therapy. Failure of the curative treatment approach is therefore considered a patient-relevant outcome in this assessment.

In the TRANSFORM study, failure of the curative treatment approach was not directly recorded as an outcome. As an approximation, the present assessment considers 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. The proportion of patients with event (referred to below as "event rate") and also the time to the occurrence of an event (EFS) is used for the assessment. The operationalization of the outcome is explained below.

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 PR by Week 9 after randomization
- start of new antineoplastic therapy due to efficacy concerns

As described in Section I 3.2, the therapeutic strategy in the comparator arm of the TRANSFORM study included a response assessment after induction therapy, which was decisive for the further course of treatment. Patients who achieved partial or complete response to induction therapy by Week 9 after randomization could then receive HDCT and autologous SCT, thereby completing the treatment regimen in the comparator arm. Patients who did not achieve at least partial response to the induction therapy by Week 9 did not receive HDCT with subsequent autologous SCT, however. Response was assessed in a central assessment by an IRC on the basis of predefined criteria of a guideline of the sponsor based on the Lugano classification [17]. This procedure for non-response largely corresponds to the specifications for the treatment regimen in the comparator arm of the study according to the S3 guideline of the AWMF [18]. Recording the component of failure to achieve CR or PR by Week 9 after randomization as an event in the composite outcome is considered to be adequate for representing failure of the curative treatment approach overall.

Regarding start of new antineoplastic therapy due to efficacy concerns as a component of the composite outcome, it remains unclear whether this event per se constitutes a failure of the curative treatment approach without disease progression having been previously identified as a qualifying event. However, the start of new antineoplastic therapy due to efficacy concerns was only occasionally recorded as an event in the EFS, as disease progression was the main qualifying event for the outcome (see Table 16). In addition, according to the

information in the study documents, for the majority of patients the reasons for starting new antineoplastic therapy due to efficacy concerns were predominantly progression (79 of 95 patients who started new antineoplastic therapy in both study arms [83%]) or, in the comparator arm, existing residual disease that did not allow HDCT to be performed (8 of 65 patients [12%]). These events already represent independent qualifying events for the composite outcome and are therefore directly included in this outcome.

Operationalization may not include all progression events

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 the curative treatment approach (i.e. in this case at time points of recording from Week 18 after randomization). However, failure to achieve CR after completion of treatment was not recorded in the EFS outcome in the TRANSFORM study. In the present operationalization, the failure to achieve CR or PR by Week 9 and the occurrence of progression at any time were recorded in the EFS, but not the failure to achieve CR after completion of treatment.

For a comprehensive representation of failure of the curative treatment approach, failure to achieve CR by Week 18 would also have to be recorded in the EFS as an independent qualifying event, in addition to the other events already included (death from any cause, failure to achieve CR or PR by Week 9 after randomization, or start of new antineoplastic therapy due to efficacy concerns). This would include patients with PR by Week 9, who had no progression and thus no qualifying event for the EFS outcome in the subsequent course of the study. For the time-to-event analysis, it would also mean that for patients who did not achieve CR by Week 18 but experienced progression in the further course of the study, the qualifying event was already reached by Week 18. It is not clear from the company's dossier how many of the patients in the TRANSFORM study this applies to.

Despite this uncertainty, EFS is used as an approximate outcome to represent failure of the curative treatment approach. This appears justified in the present data situation, because Module 4 B of the dossier shows that after completion of treatment in both arms by Week 18, only a few patients had PR as best overall response (BOR) (6 patients in the intervention arm and 15 in the comparator arm). It cannot be inferred from the data whether these patients experienced disease progression in the further course after PR and thus whether a qualifying event occurred or not.

In order to address the existing uncertainty regarding the failure to achieve CR by Week 18, a sensitivity analysis which additionally rated the presence of PR as best response by Week 18 as event for the outcome of failure of the curative treatment approach was performed for the event rate. The result of this sensitivity analysis is presented in Table 16 in addition to the results of the operationalization presented by the company and is considered in the

assessment for the outcome of failure of the curative treatment approach. It should be noted that this analysis was based on the assumption that none of the additionally included patients subsequently experienced progression within the observation period of the study. However, 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 events for the outcome in the sensitivity analysis.

Other presented operationalizations are not suitable

In addition to the EFS, the company presented analyses on an outcome it referred to as "modified event-free survival (mEFS)" in Module 4 B of its dossier. The operationalization of mEFS largely corresponds to that of EFS, but takes into account failure to achieve CR (instead of CR or PR) by Week 9 after randomization as qualifying event. This operationalization is unsuitable for representing failure of the curative treatment approach. In accordance with the S3 guideline of the AWMF [18], it is not yet assumed that the curative treatment approach has already failed if PR is present after completion of induction therapy. At Week 9 after randomization, treatment in the comparator arm of the TRANSFORM study was not yet completed, as HDCT and autologous SCT were not yet performed at this time. Failure to achieve PR by Week 9 was therefore categorized as event in the mEFS, although at this time point this did not necessarily mean failure of the curative treatment approach. In addition, failure to achieve CR after completion of the treatment regimen by Week 18 was not rated as an event in the mEFS either. The analyses on the mEFS presented by the company in Module 4 B of the dossier are therefore not suitable for the present assessment.

In Module 4 B of the dossier, the company additionally presented analyses on the proportion of patients with relapses (referred to by the company as "relapse rate"). For these analyses, however, it remains unclear on the basis of the information in Module 4 B which events were recorded. In addition, there is discrepant information on the operationalization (relapse rates after a response [PR or CR] or proportion of patients with disease progression or death at any time) in Section 4.3.1.3.1.2.1 in Module 4 B of the dossier. The company did not provide any data on the individual events taken into account. Since analyses of the relapse rate were not planned according to the planning of the study, it is not possible to assess to what extent the results presented by the company are suitable for the assessment.

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

In Module 4 B of the dossier, the company presented analyses on symptoms recorded using the EORTC QLQ-C30 and FACT-LymS, on health status recorded using the EQ-5D VAS, and on health-related quality of life recorded using the EORTC QLQ-C30. However, it did not use the analyses for its assessment on the grounds that no sufficiently reliable results were available. According to the company in Module 4 B of the dossier, there was a high proportion of missing values already at study start, resulting from restrictions due to the COVID-19 pandemic.

Recordings for patient-reported outcomes were available only for a small proportion of the randomized patients (about 54%) already at study start. The company only included patients in its analysis for whom a subsequent value was available in addition to a value at study start. As a result, only 50% of patients in total were included in the analyses. In addition, the proportion of missing values increased markedly and differentially between the study arms over the course of the study. Due to discrepant information within the dossier, it remains unclear why there was a high proportion of missing values already at the start of the study. In contrast to the information provided by the company in Module 4 B of the dossier, the study documents stated that the high proportion of missing values was due not only to operational obstacles in connection with the COVID-19 pandemic but also to technical and logistical obstacles in connection with the implementation of an electronic data collection system for recording the patient-reported outcomes. According to the study documents, it could therefore be assumed that the majority of the missing data was probably purely coincidental. However, it is not clear from the information in the study documents what proportion of the missing values was missing purely by chance and what proportion was missing for potentially informative reasons. The reasons for not completing questionnaires were recorded according to the electronic case report form (eCRF) of the TRANSFORM study, but were not provided in the company's dossier. Without knowing the proportion of values that were missing purely by chance, it is not possible to assess whether the results are fundamentally interpretable. Therefore, the analyses on the patient-reported outcomes presented by the company in Module 4 B of the dossier are not suitable for assessment.

In Module 4 B, the company additionally presented analyses of time to first deterioration or improvement by ≥ 15 points for the majority of the outcomes on symptoms and health-related quality of life (recorded using the EORTC QLQ-C30). However, the early benefit assessment procedure requires analyses for a response threshold of 10 points for the EORTC QLQ-C30 [21]. The company presented these analyses exclusively for the subscale of fatigue without explaining this in Module 4 B of the dossier.

Side effects

Overall rates of AEs including progression events

The analyses on the overall rates of AEs presented by the company in Module 4 B of the dossier do not explicitly exclude progression events. However, based on the results, it is not assumed that progression events were included in the analyses to a relevant extent. Therefore, the analyses of the overall rates of AEs presented by the company are disregarded.

Consideration of AEs after starting subsequent therapy with lisocabtagene maraleucel

In Module 4 B of the dossier, the company stated that AEs in the comparator arm were also recorded after the start of subsequent therapy with lisocabtagene maraleucel. In contrast, events after the start of other subsequent antineoplastic therapies were not recorded in

either arm. Such a recording would result in an imbalance in the analyses between the arms, as AEs under any subsequent therapy would not be recorded in the intervention arm, whereas AEs after the start of subsequent therapy with lisocabtagene maraleucel would be recorded in the comparator arm. However, it is clear from the study documents that although AEs were recorded after the start of subsequent therapy with lisocabtagene maraleucel, like AEs after other subsequent therapies, they were not included in the analyses on outcomes in the side effects category presented by the company in Module 4 B of the dossier (see Table 8). Therefore, the analyses of AEs presented in Module 4 B that occurred in both study arms before the start of any subsequent antineoplastic therapies are used.

Follow-up observation of AEs classified as treatment-related

As described in Section I 3.2, most AEs were observed only for a shortened period of time in the TRANSFORM study. AEs rated by the investigators as being caused by the study treatment, were observed beyond the shortened observation period. In the present data situation, the analyses of AEs are nevertheless suitable for the assessment, as it is assumed on the basis of the Kaplan-Meier curves (see I Appendix B.3 of the full dossier assessment) that at most only very few such events were included in the present analyses.

Discontinuation due to AEs

In Module 4 B of the dossier, the company did not present any analyses on the outcome of discontinuation due to AEs without explanation. The study documents show that there were only a few discontinuations due to AEs (see Table 16). As these were treatment discontinuations, only events could be recorded that occurred until the infusion of lisocabtagene maraleucel in the intervention arm or until the autologous SCT in the comparator arm. AEs that would lead to treatment discontinuation could still have occurred after the infusion of lisocabtagene maraleucel or after autologous SCT, but were no longer recorded (from approx. Week 5 in the intervention arm and from approx. Week 10 in the comparator arm). In the present data constellation, the missing analyses therefore have no consequences for the assessment.

Cytokine release syndrome

For the outcome of cytokine release syndrome, the operationalization via the PT of the same name is considered for the assessment. A severe event is represented via the operationalization as SAE of the PT cytokine release syndrome. This is due to the fact that the operationalization of severe AEs for this PT in the TRANSFORM study differs from the CTCAE criteria and that, in addition, there were discrepant results in the SAEs recorded for the PT.

In contrast to the CTCAE classification in version 4.03 [22] used in the study, the operationalization of severe events in the TRANSFORM study was adjusted according to the information in the study protocol, in order to better reflect the events associated with the

administration of CAR-T cells according to the information in the study protocol. However, it should be noted that the definition according to the study protocol appears less strict compared with the CTCAE classification in version 5.0 [23], in which the criteria for the classification of cytokine release syndrome were also adapted. In the TRANSFORM study, events for this PT occurred exclusively in the intervention arm. Based on the modified criteria according to the study protocol, only one patient with event out of a total of 45 patients was categorized as grade ≥ 3. In contrast, the study documents show that 11 patients with event were hospitalized. In accordance with this information, 12 patients out of a total of 45 patients with event received a categorization as serious. Against this background, the analyses of severe events of the PT cytokine release syndrome according to the classification modified according to the study protocol are not considered suitable for the assessment. Instead, serious events of the PT are used for the assessment.

Approximate consideration of superordinate SOCs for the assessment of specific AEs

For some specific AEs for which events only occurred in one study arm, the company presented only proportions of patients with event in Module 4 B of the dossier. The company provided no information on statistical significance for these AEs, although it could have calculated p-values using the log-rank test. In addition, only few Kaplan-Meier curves are available for these AEs. If the superordinate SOC of the specific AE mainly comprised events of the relevant PT, the available results of the SOC were considered approximately for the assessment. This was possible for (serious) cytokine release syndrome (PT, AE/SAE) and acute kidney injury (PT, SAE).

I 4.2 Risk of bias

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

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

Study		Outcomes													
	Study level	Overall survival	Failure of the curative treatment approach[a]	Symptoms (EORTC QLQ-C30, FACT-LymS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Cytokine release syndrome[c]	Serious cytokine release syndrome[d]	Neurological toxicity[e]	Severe neurological toxicity[f]	Severe infections[g]	Further specific AEs[h]
TRANSFORM	L	L	L	–[i]	–[i]	–[i]	H[j]	L	H[k]	H[j]	H[j]	H[j, l]	H[j]	H[j]	H[j, l]

a. Operationalized as event rate and event-free survival; includes the events of death from any cause, disease progression, failure to respond (CR or PR not achieved) by Week 9 after randomization, start of new antineoplastic therapy due to efficacy concerns, whichever occurs first; see Section I 4.1 for explanation.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as AEs of the PT cytokine release syndrome.
d. 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 for explanation.
e. Operationalized as AEs of the SOC nervous system disorders.
f. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC nervous system disorders.
g. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC infections and infestations.
h. The following events are considered: diarrhoea (PT, AEs), mucosal inflammation (PT, AEs), gastrointestinal disorders (SOC, SAEs), acute kidney injury (PT, SAEs), general disorders and administration site conditions (SOC, severe AEs), neutrophil count decreased (PT, severe AEs), neutropenia (PT, severe AES), febrile neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), and lymphopenia (PT, severe AEs).
i. No usable data available; see Section I 4.1 for the reasoning.
j. Incomplete observations for potentially informative reasons.
k. Lack of blinding in the presence of subjective decision on treatment discontinuation.
l. Lack of blinding in the presence of subjective recording of outcomes; for other specific AEs, this applies to non-severe, non-serious AEs.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low;
MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial;
SAE: serious adverse event; SOC: System Organ Class

The outcome-specific risk of bias for the results of all patient-relevant outcomes except overall survival, failure of the curative treatment approach and severe AEs is rated as high.

No suitable data are available for the outcomes of symptoms (recorded via EORTC QLQ-C30 and FACT-LymS), health status (recorded via EQ-5D VAS), and health-related quality of life (recorded via EORTC QLQ-C30) (see Section I 4.1 for explanation).

The risk of bias of results on SAEs, (severe) cytokine release syndrome, (severe) neurological toxicity, severe infections, and other specific AEs is rated as high due to incomplete observations for potentially informative reasons. Results on non-serious and non-severe specific AEs have an additional high risk of bias due to the lack of blinding. The results of the outcome of discontinuation due to AEs also have a high risk of bias due to the lack of blinding in the presence of subjective decision on treatment discontinuation.

As described in Section I 4.1, the superordinate SOC immune system disorders (AEs) is considered as an approximation to assess the data situation, as no effect estimate and no Kaplan-Meier curves are available for the outcome of cytokine release syndrome. In this SOC, events for the PT cytokine release syndrome were predominantly recorded as AEs. The approximate consideration of the SOC shows that, 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.

Summary assessment of the certainty of conclusions

As described in Section I 3.2, there is an uncertainty for the TRANSFORM study resulting from the fact that the ACT was not fully implemented in the comparator arm of the study. Nevertheless, in the present specific data constellation, the study can be interpreted for research question 1 of the present assessment. The certainty of conclusions of the study results for research question 1 of the present assessment is reduced, however. On the basis of the TRANSFORM study, no more than hints, e.g. of an added benefit, can therefore be derived for research question 1 of the present assessment. In addition, no conclusions on the extent of the added benefit can be derived from the results of the study for this reason. At outcome level, therefore, only advantages and disadvantages are described below, which are summarized in an overall conclusion on the added benefit.

I 4.3 Results

Table 16 summarizes the results for the comparison of lisocabtagene maraleucel versus induction + HDCT + autologous SCT in adult patients 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 the time-to-event analyses (if available) are presented in I Appendix B, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs in I Appendix C of the full dossier assessment. No Kaplan-Meier curves are available in the company's dossier for the outcomes of discontinuation due to AEs, cytokine release syndrome, (severe) neurological toxicity, acute kidney injury (PT, SAEs), and neutrophil count decreased (PT, severe AEs). For the outcomes of (serious) cytokine release syndrome and acute kidney injury (PT, SAEs), the Kaplan-Meier curves for the respective superordinate outcomes of immune system disorders (SOC, AEs/SAEs) and renal and urinary disorders (SOC, SAEs) are shown instead.

Table 16: 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 the curative treatment approach					
Event rate[b]	92	– 44 (47.8)	92	– 71 (77.2)	RR 0.62 [0.49; 0.79]; 0.001[c]
Death	92	– 4 (4.3)	92	– 2 (2.2)	–
PD after achieving CR or PR	92	– 33 (35.9)	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)	–
Event rate: Sensitivity analysis plus PR as BOR by Week 18	92	– 59 (64.1)	92	– 77 (83.7)	RR 0.77 [0.64; 0.92]; 0.003[c]
PR as BOR by Week 18	92	– 15 (16.3)	92	– 6 (6.5)	–
Event-free survival (EFS)	92	NA [9.5; NC] 44 (47.8)	92	2.4 [2.2; 4.9] 71 (77.2)	0.36 [0.24; 0.52]; < 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 16: 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
Cytokine release syndrome[f]	92	NA [1.48; NC] 45 (48.9)	91	NA 0 (0)	NC[f]
Including: serious cytokine release syndrome[g, h]	92	NA 12 (13.0)	91	NA 0 (0)	NC[h]
Neurological toxicity[i]	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[j]	92	NA 10 (10.9)	91	NA 5 (5.5)	2.61 [0.71; 9.58]; 0.148
Severe infections[k]	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 16: 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)[l]	92	NA 0 (0)	91	NA 5 (5.5)	NC[l]
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
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 16: 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. 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. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [24]).
d. See Section I 4.1 for reasons.
e. Operationalized as CTCAE grade ≥ 3.
f. Operationalized as AEs of the PT cytokine release syndrome. Module 4 B provides only data on the proportion of patients with event for this outcome. 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 the full dossier assessment.
g. 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 for explanation.
h. Module 4 B provides only data on the proportion of patients with event for this outcome. 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 the full dossier assessment.
i. Operationalized as AEs of the SOC nervous system disorders.
j. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC nervous system disorders.
k. Operationalized as severe AEs (CTCAE grade ≥ 3) of the SOC infections and infestations.
l. Module 4 B provides only data on the proportion of patients with event for this outcome. 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 the full dossier assessment.

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; 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; SD: stable disease; SOC: System Organ Class; VAS: visual analogue scale

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 age. For patients < 65 years of age, a statistically significant difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. However, no statistically significant difference between treatment groups was shown for patients ≥ 65 years.

Morbidity

Failure of the curative treatment approach

For the outcome of failure of the curative treatment approach, a statistically significant difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. The sensitivity analysis, in which the presence of PR as BOR at Week 18 after randomization was rated as event, also showed a statistically significant difference in favour of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT (for an explanation of the sensitivity analysis, see Section I 4.1). However, it remains unclear how the patients with PR as BOR at Week 18 are distributed among the subgroups relevant to the assessment (for a supplementary presentation of the subgroup results for the outcome, see I Appendix D of the full dossier assessment). For the subgroup of patients < 65 years of age, it is nevertheless assumed that even taking into account failure to achieve CR at Week 18 after randomization, there is an advantage of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT. This is due to the fact that the effect for this subgroup is robust in a sensitivity analysis under the assumption that all patients with PR as BOR at Week 18 are < 65 years old, as is the case for the entire study population. In contrast, for patients ≥ 65 years of age, no conclusion on advantages or disadvantages of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT for the outcome of failure of the curative treatment approach is possible in the present data situation due to the uncertainty.

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 EORTC QLQ-C30 and FACT-LymS) and health status (recorded using EQ-5D VAS), for reasons, see Section I 4.1).

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).

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs.

Severe AEs

No statistically significant difference between treatment groups was found for the outcome of severe AEs.

Discontinuation due to AEs

The effect estimate cannot be calculated for the outcome of discontinuation due to AEs. Treatment could only be discontinued for a short period at the beginning of the study. Only isolated events occurred for the outcome. Therefore, no consequences arise for the assessment in the present data situation (see Section I 4.1 for details).

Specific AEs

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

The effect estimate cannot be calculated for the outcome of cytokine release syndrome and for serious cytokine release syndrome included therein. A statistically significant difference to the disadvantage of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT was shown for the AEs and SAEs of the superordinate SOC immune system disorders, which predominantly comprise the PT cytokine release syndrome as AE or SAE. A disadvantage of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT is therefore assumed in each case.

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.

Severe infections (severe AEs)

No statistically significant difference between treatment groups was shown for the outcome of severe infections.

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.

Gastrointestinal disorders (SAEs)

A statistically significant difference in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT was shown for the specific SAE of gastrointestinal disorders.

Acute kidney injury (SAEs)

The effect estimate for the specific SAE of acute kidney injury cannot be calculated. A statistically significant difference in favour of lisocabtagene maraleucel compared with induction + HDCT + autologous SCT was shown for the SAEs of the superordinate SOC renal and urinary disorders, the events of which predominantly comprise the PT acute kidney injury. An advantage of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT is therefore assumed.

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.

Neutrophil count decreased (severe AEs)

The effect estimate for the specific severe AE of neutrophil count decreased cannot be calculated. An approximate consideration of the superordinate SOC is not possible for this outcome, as its events do not predominantly include the PT neutrophil count decreased. In the present data situation, in which there is already a disadvantage for severe neutropenia, this has no consequences for the assessment.

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 neutropenia and lymphopenia.

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 sAAIPI. 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 2 or 3, however, no statistically significant difference between treatment groups was shown.

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, a statistically significant difference was shown in favour of lisocabtagene maraleucel versus induction + HDCT + autologous SCT. For men, however, no statistically significant difference was shown between treatment groups.

I 4.4 Subgroups and other effect modifiers

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

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- sAAIPI (0 or 1 versus 2 or 3)

No subgroup analyses are available for the outcomes of (serious) cytokine release syndrome, (severe) neurological toxicity and severe infections in the company's dossier.

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

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

The results are presented in Table 17. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B of the full dossier assessment. For the subgroup results presented in the present assessment, the company's dossier contains Kaplan-Meier curves for the subgroups only for the outcome of overall survival.

Table 17: Subgroups (overall survival, side effects) – 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][a]	 p-value[a]
TRANSFORM						
Overall survival						
Age						
< 65 years	56	NA 9 (16.1)	67	NA [17.9; NC] 27 (40.3)	0.32 [0.15; 0.68]	0.003
≥ 65 years	36	23.0 [12.0; NC] 19 (52.8)	25	29.9 [16.3; NC] 11 (44.0)	1.40 [0.66; 2.96]	0.378
Total					Interaction:	0.007[b]
Febrile neutropenia (PT, severe AEs[b])						
sAAIPI						
0 or 1	56[c]	NA 4 (7.1)	54[c]	NA [3.7; NC] 15 (27.8)	0.19 [0.06; 0.59]	0.004
2 or 3	36[c]	NA 7 (19.4)	37[c]	NA 6 (16.2)	1.10 [0.37; 3.31]	0.865
Total					Interaction:	0.048[b]
Thrombocytopenia (PT, severe AEs[b])						
Sex						
Male	44[c]	1.9 [0.5; NC] 27 (61.4)	60[c]	2.8 [1.8; 3.1] 38 (63.3)	0.92 [0.56; 1.51]	0.739
Female	48[c]	NA [1.9; NC] 19 (39.6)	31[c]	0.6 [0.5; 1.3] 24 (77.4)	0.34 [0.18; 0.62]	0.001
Total					Interaction:	0.003[b]

a. Unstratified Cox proportional hazards model.
b. Based on Cox proportional hazards model with treatment, subgroup characteristic and interaction term (treatment x subgroup characteristic).
c. Different data between the results tables and the Kaplan-Meier curves; the data on the number of analysed patients from the Kaplan-Meier curves were used here.

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

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. However, no statistically significant difference between treatment groups was found for patients ≥ 65 years.

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 2 or 3, however, no statistically significant difference between treatment groups was shown.

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. For men, however, no statistically significant difference was shown between treatment groups.

I 5 Probability and extent of added benefit

The approach for deriving an overall conclusion on the added benefit based on the aggregation of advantages and disadvantages observed at outcome level constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Overall conclusion on added benefit

Research question 1: patients who are eligible for high-dose therapy

As described in Section I 3.2, there is an uncertainty for the TRANSFORM study resulting from the fact that the ACT was not fully implemented in the comparator arm of the study. Nevertheless, in the present specific data constellation, the study can be interpreted for research question 1 of the present assessment.

Based on the TRANSFORM study, there are the following advantages and disadvantages at outcome level for research question 1 (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):

- advantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT for the outcome of overall survival in patients < 65 years of age
- advantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT for the outcome of failure of the curative treatment approach in patients < 65 years of age
- advantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT in side effects for the outcomes of gastrointestinal disorders (SAEs), acute kidney injury (SAEs), general disorders and administration site conditions (severe AEs), febrile neutropenia (severe AEs; only in patients with sAAIPI 0 or 1), thrombocytopenia (severe AEs; only in women), diarrhoea (AEs), and mucosal inflammation (AEs)
- disadvantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT in side effects for the outcomes of cytokine release syndrome (including serious cytokine release syndrome), neutropenia (severe AEs), and lymphopenia (severe AEs)

For the outcome of failure of the curative treatment approach, no conclusion on the advantages or disadvantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT is possible in the present data situation for patients ≥ 65 years of age. Likewise, no conclusion on advantages and disadvantages is possible for patient-reported outcomes of symptoms, health status and health-related quality of life, as no suitable data are available.

Only for overall survival are the observed effects based on the entire observation period. For the outcome of failure of the curative treatment approach, the observed effects relate to the period of approximately up to 36 months after randomization, which is of no consequence for the assessment due to the used data cut-off, at which no patient was observed for a longer period of time. For the outcomes in the side effects category, however, the observed effects relate exclusively to a shortened observation period.

Overall, there are both advantages and disadvantages of lisocabtagene maraleucel in comparison with induction + HDCT + autologous SCT in adult patients with DLBCL, HGBL, PMBCL or FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

- For patients < 65 years of age, the positive effects of lisocabtagene maraleucel versus induction + HDCT + autologous SCT predominate overall.
- For patients ≥ 65 years of age, neither the positive nor the negative effects of lisocabtagene maraleucel versus induction + HDCT + autologous SCT predominate overall.

In summary, 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, there is a hint of a non-quantifiable added benefit of lisocabtagene maraleucel compared with the ACT.

For patients ≥ 65 years 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, there is no hint of an added benefit of lisocabtagene maraleucel compared with the ACT; an added benefit is therefore not proven.

Research questions 2 and 3: patients who are not eligible for high-dose therapy

No data are available to assess the added benefit of lisocabtagene maraleucel compared with the ACT 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 not eligible for high-dose therapy. For these patients, there is no hint of added benefit of lisocabtagene maraleucel in comparison with the ACT; an added benefit is therefore not proven.

I 5.2 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of lisocabtagene maraleucel in comparison with the ACT is summarized in Table 18.

Table 18: Lisocabtagene maraleucel – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	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[b]	Induction therapy with MINE followed by high-dose therapy with autologous or allogeneic[c] stem cell transplantation if there is a response to induction therapy	Patients ▪ < 65 years: hint of a non-quantifiable added benefit[d] ▪ ≥ 65 years: added benefit not proven
2	with DLBCL or HGBL who are not eligible for high-dose therapy[e]	Treatment of physician's choice, taking into account ▪ pola-BR[f] ▪ tafasitamab + lenalidomide[f]	Added benefit not proven
3	with PMBCL or FL3B who are not eligible for high-dose therapy[e]	Treatment of physician's choice, taking into account ▪ CEOP ▪ dose-adjusted EPOCH ▪ rituximab monotherapy (only for patients with FL3B)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the induction therapy (research question 1) and for the treatment (research questions 2 and 3) for 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 Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).
b. It is assumed that patients are eligible for high-dose therapy with curative intent.
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. 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.

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; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PMBCL: primary mediastinal large B-cell lymphoma; pola-BR: polatuzumab vedotin, bendamustine, rituximab; SGB: Social Code Book; WHO: World Health Organization

The assessment described above deviates from that of the company. Based on the results of the TRANSFORM study, the company derived an indication of considerable added benefit compared with salvage chemotherapy followed by HDCT with autologous SCT. At the same time, based on the analyses of the indirect comparison of lisocabtagene maraleucel with axicabtagene ciloleucel, the company derived an indication of a non-quantifiable added benefit of lisocabtagene maraleucel versus axicabtagene ciloleucel. The company related each of both comparisons to all patients in the present therapeutic indication, irrespective of tumour entity or eligibility for high-dose therapy.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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