Lisocabtagene maraleucel (DLBCL, PMBCL, FL3B)

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 for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
aQCC cohort	adjusted qualifying comparator cohort
BCL	B-cell lymphoma
BSA	body surface area
CAR	Chimeric Antigen Receptor
CD	cluster of differentiation
DLBCL	diffuse large B-cell lymphoma
EMA	European Medicines Agency
FL	follicular lymphoma
FL3B	follicular lymphoma grade 3B
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HGBL	highly malignant B-cell lymphoma
iNHL	indolent NHL
IPI	International Prognostic Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
IV	intravenous
LDC	lymphocyte depletion chemotherapy
MAIC	matching-adjusted indirect comparison
MYC	myelocytomatosis oncogene
NHL	non-Hodgkin's lymphoma
NOS	not otherwise specified
ORR	objective response rate
PFS	intention to treat
PMBCL	primary mediastinal B-cell lymphoma
PMBCLs	peripheral blood mononuclear cells
RCT	randomized controlled trial
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
tFL	transformed follicular lymphoma

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 August 2022. With the decision of 01 December 2022, new information on the appropriate comparator therapy (ACT) was submitted by the G-BA and the date of publication was postponed to 16 January 2023.

Research question

The aim of this report is to assess the added benefit of lisocabtagene maraleucel compared with individualized therapy, taking into account lymphoma subentity, disease biology, prior therapy, course of the disease and general condition as ACT in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after 2 or more lines of systemic therapy.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

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

Therapeutic indication	**ACT[a]**
Adults with relapsed or refractory DLBCL, PMBCL and FL3B after 2 or more lines of systemic therapy	Individual therapy[b, c] taking into account the lymphoma subentity, disease biology, prior therapy, course of disease and general condition

a. Presented is the ACT specified by the G-BA.
b. Within the framework of a clinical trial, the following therapies are considered suitable comparators for the individualized therapy:

- ASHAP, bendamustine, CEPP, CEOP, DHAP, DHAX, DICEP, dose-adjusted EPOCH, ESHAP, GemOx, GDP, gemcitabine + vinorelbine, ICE, lenalidomide (only for patients with non-GCB DLBCL), MEP, MINE, PEPC, each of the therapies mentioned ± rituximab

as well as

- polatuzumab vedotin + bendamustine + rituximab, tafasitamab + lenalidomide, monotherapy brentuximab vedotin (only for patients with CD30+ DLBCL), monotherapy chlorambucil, monotherapy etoposide, monotherapy pixantrone, gemcitabine + rituximab, monotherapy rituximab, monotherapy ibrutinib (only for patients with non-GCB DLBCL), axicabtagen ciloleucel, tisagenlecleucel, radiation or BSC.
- Moreover, stem cell transplantation (autologous or allogeneic) is considered a component of the individualized therapy.

c. It is assumed that for suitable patients, rituximab will be used as part of salvage chemotherapy (e.g. no receipt of rituximab in prior therapy, no refractivity to rituximab, existing CD20 expression in lymphoma).

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BSC: best supportive care; CD: cluster of differentiation; CEPP: cyclophosphamide, etoposide, prednisone, procarbazine; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DHAP: dexamethasone, cisplatin, cytarabine; DHAX: dexamethasone, cytarabine, oxaliplatin; DICEP: dose-intensified cyclophosphamide, etoposide, cisplatin; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; FL3B: follicular lymphoma grade 3B; G-BA: Federal Joint Committee; GCB: germinal centre B-cell type; GemOx: gemcitabine, oxaliplatin; GDP: gemcitabine, dexamethasone, cisplatin or carboplatin; ICE: ifosfamide, carboplatin, etoposide; MEP: methotrexate, etoposide, cisplatin; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PEPC: prednisolone, etoposide, procarbazine, cyclophosphamide; PMBCL: primary mediastinal large B-cell lymphoma

In principle, the company follows the ACT of an individualized therapy as defined by the G-BA, taking into account the aspects listed in Table 2 and additionally, if possible, including allogeneic stem cell transplantation (based on a consultation with the G-BA on 19 March 2020). However, the therapies named by the company in its inclusion criteria as suitable comparators in the context of individualized therapy differ from those considered suitable according to the G-BA. For example, the company did not include tafasitamab in combination with lenalidomide as a suitable comparator in its assessment. Furthermore, it did not take into account radiation or autologous stem cell transplantation.

The present benefit assessment takes into account the comparators deemed suitable by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Concurring with the company, the check of the completeness of the study pool identified no randomized controlled trials (RCTs) on the direct comparison of lisocabtagene maraleucel versus the ACT.

The company did not include any studies for a direct comparison. It therefore carried out an information retrieval for further investigations and identified, in addition to two uncontrolled studies on the intervention side (TRANSCEND-NHL-001 and TRANSCEND WORLD), 3 studies on the comparator side (NDS-NHL-001, ZUMA-1 and JULIET), from which it used individual arms in each case.

For the company's study pool on further investigations, there are indications in the dossier that it is potentially incomplete on the comparator side. In its bibliographic search, the company additionally identified studies on the comparator site that are potentially relevant for the analyses it submitted, but did not consider them for its assessment without further explanation. As the company did not provide any justification for this in the dossier, nor any references to the studies, it is not possible to check whether the study pool is incomplete.

Regardless of the potential incompleteness of the study pool on the part of the ACT, the data presented by the company are not suitable for deriving conclusions on the added benefit of lisocabtagene maraleucel compared to the ACT. This is justified below.

Evidence provided by the company

For lisocabtagene maraleucel, the company included the single-arm TRANSCEND-NHL-001 study, originally designed for phase 1, and the single-arm phase 2 TRANSCEND WORLD study. From each of these studies, it used a subpopulation of adult patients with refractory or relapsed B-cell non-Hodgkin's lymphoma (NHL) who, depending on the study, met certain criteria regarding histology, pretreatment and the administered dose of lisocabtagene maraleucel.

Moreover, the company used comparisons of individual arms from different studies. For these comparisons, the company identified the studies NDS-NHL-001, ZUMA-1 and JULIET on the side of the ACT on the comparators deemed suitable by the G-BA.

Evidence on lisocabtagene maraleucel

Study TRANSCEND-NHL-001

The TRANSCEND-NHL-001 study is an ongoing, single-arm study comprising 2 cohorts, 1 cohort enrolling adult patients with DLBCL and 1 cohort on patients with mantle cell lymphoma, who are not the subject of the present research question. Enrolment of patients in the study started in January 2016.

The DLBCL cohort included adult patients with not otherwise specified (NOS) DLBCL including transformed indolent NHL (iNHL), highly malignant B-cell lymphoma (HGBL) with myelocytomatosis oncogene (MYC) and B-cell lymphoma (BCL) 2 and/or BCL6 rearrangements with DLBCL histology, PMBCL or FL3B. Patients had to have refractory or relapsed disease either after at least 2 prior therapies, including an anthracycline and rituximab (or another anti-cluster of differentiation [CD]20 agent) or after autologous stem cell transplantation.

Before the treatment, the study required preparations for the individualized production of the Chimeric Antigen Receptor (CAR) T-cell preparation. According to the study design, leukapheresis was performed as soon as possible after the screening investigations, but at the latest within 2 weeks after study inclusion, to collect peripheral blood mononuclear cells (PBMCs) for the preparation of lisocabtagene maraleucel. According to the study design, leukapheresis was to take place within 4 weeks before the infusion with lisocabtagene maraleucel. In fact, according to information provided by the company in Module 4 A of the dossier, the median time between leukapheresis and infusion for the subpopulation of the study used by it was 37 days at the most recent data cut-off. Within this period, patients could receive anti-cancer treatment for disease control (bridging) if needed.

In the dossier, the company presents analyses of patients in the DLBCL cohort who were scheduled for a single infusion of 50 x 10^6 or 100 x 10^6 viable CAR-T cells.

Study TRANSCEND WORLD

TRANSCEND WORLD is an ongoing, single-arm, phase 2 study on adult patients with aggressive B-cell NHL comprising a total of 7 cohorts with indications that partially deviate from the therapeutic indication. In the dossier, the company takes into account results on patients from cohorts 1 and 3. These cohorts included patients with refractory or relapsed DLBCL NOS (de novo or transformed follicular lymphoma [FL]), HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology or FL3B. Cohort 1 included patients after at least 2 prior therapies, including an anthracycline and rituximab (or another anti-CD20 agent). Cohort 3 included patients from Japan who met the criteria for cohort 1 or were in the second-line. However, the latter only applied to individual patients included in cohort 3; the majority fulfilled the criteria for cohort 1. Patients were enrolled in the study from June 2018.

All patients were treated once (IV) with a target dose of 100 x 10^6 viable CAR-T cells. The procedure in the study corresponds to that in the TRANSCEND-NHL-001 study, with slight deviations. These deviations relate in particular to leukapheresis, which according to the study design was to take place about 5 weeks before the infusion with lisocabtagene maraleucel. In fact, according to information provided by the company in Module 4 A of the dossier, the median time between leukapheresis and infusion for the subpopulation of the study used by it was 42 days at the most recent data cut-off.

Evidence on the ACT

Study NDS-NHL-001

The NDS-NHL-001 study is a non-interventional, retrospective study conducted by the company on the treatment of patients with aggressive B-cell NHL with relapsed or refractory disease after at least one previous line of therapy, which includes patients from clinical centres and research databases. According to the statistical analysis plan (SAP) for the study, patients with histologically confirmed DLBCL NOS, HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL or FL3B were included. In addition, patients had to have relapsed or refractory disease after at least 2 previous therapies, including treatment with an anthracycline and rituximab (or another anti-CD20 agent). The initial diagnosis of aggressive B-cell NHL had to have occurred from 2003 onwards. According to the study protocol, the aim of the NDS-NHL-001 study was to evaluate clinical outcomes in the above-described patient group in clinical, oncological care. In addition, the possibility of using the collected data for a comparison with data collected in single-arm intervention studies is described. The company submitted such an analysis based on the study to the European Medicines Agency (EMA) in the context of the approval of lisocabtagene maraleucel.

Clinical centres and research databases from external partners (COTA, Flatiron and Guardian Research Network) served as data sources for the NDS-NHL-001 study. A total of 1451 patients were included in the baseline cohort of the NDS-NHL-001 study. From these, a cohort was selected for the analyses within the framework of the approval according to the criteria described in the SAP. For the analyses based on the NDS-NHL-001 study in the dossier, the company selected a group of patients from the same baseline cohort using a separate protocol CA082-023 with a different selection process, which it referred to as the adjusted qualifying comparator cohort (aQCC cohort). According to the company, this cohort included only patients who received a therapy considered a suitable comparator by the G-BA within the scope of the ACT. Moreover, according to protocol CA082-023, the most recent line of therapy that represents a suitable comparator was considered for each patient.

Study ZUMA-1

ZUMA-1 is a single-arm phase 1/2 study on the treatment with axicabtagen ciloleucel that enrolled adult patients with refractory DLBCL, PMBCL or tFL after ≥ 1 line of chemotherapy, including an anti-CD20 antibody and an anthracycline. Patients or their disease had to be either

- refractory to the last chemotherapy, or
- have relapsed within 12 months of an autologous stem cell transplantation, or
- be refractory to or have not responded to the last salvage therapy after an autologous stem cell transplantation.

Refractory disease to last chemotherapy was defined as progressive disease or no better response than stable disease with a duration of response ≤ 6 months.

In phase 1 of the ZUMA-1 study, different regimens of lymphocyte depletion chemotherapy (LDC) with different CAR-T cell doses were tested to determine dose-limiting toxicity. Phase 2 of the study comprises a total of 6 cohorts, with cohorts 1 and 2 representing the pivotal cohorts of the study and being potentially relevant for the present research question. Cohorts 3 to 6 belong to the safety management part of the study and are irrelevant as the treatment was not in line with the specifications of the SPC for axicabtagen ciloleucel.

In cohorts 1 and 2 of the study, patients were treated once (IV) with a target dose of 2 x 10^6 viable CAR-T cells/kg body weight or a maximum dose of 2 x 10^8 viable CAR-T cells from a body weight of 100 kg. In phase 2 of the ZUMA-1 study, a total of 111 patients were included in cohort 1 (DLBCL) or cohort 2 (PMBCL or tFL) depending on their disease subentity. Of these, 101 patients actually received axicabtagen ciloleucel treatment.

Before treatment with axicabtagen ciloleucel, arrangements for the individual production of the CAR T-cell preparation had been necessary in the ZUMA-1 study, similar to the studies on lisocabtagene maraleucel. According to the study design, the planned duration between leukapheresis and the infusion of axicabtagen ciloleucel was not specified. However, the information in the benefit assessment procedure for axicabtagen ciloleucel (G-BA process number 2022-05-15-D-820) shows that the median time between leukapheresis and infusion was 23 days. In contrast to the studies on lisocabtagene maraleucel, however, during this time bridging was not allowed in cohorts 1 and 2 of the ZUMA-1 study. Moreover, also in contrast to the studies on lisocabtagene maraleucel, the study design did not intend premedication with paracetamol and diphenhydramine prior to the infusion of axicabtagen ciloleucel for every patient in cohorts 1 and 2, although this is recommended according to the SPC. Just like the possibility of a bridge therapy, a corresponding specification was only added for the safety management part of the study for cohorts 3 to 6.

Study JULIET

JULIET is a single-arm phase 2 study on the treatment with tisagenlecleucel including adult patients with relapsed or refractory DLBCL after ≥ 2 chemotherapy lines including rituximab and anthracycline, who, in addition, did not respond to, were not suitable or did not consent to autologous stem cell transplantation.

Patients were treated once (IV) with a target dose of 5 x 10^8 viable CAR-T cells, with a dose between 1 x 10^8 to 5 x 10^8 cells being allowed. In the JULIET study, bridging between leukapheresis and infusion of tisagenlecleucel was allowed. Depending on the tisagenlecleucel production site, patients were included in either the main cohort (USA) or in cohort A (EU).

As in the studies on lisocabtagene maraleucel, preparations for the patient-specific production of the CAR T-cell preparation were also necessary in the JULIET study prior to treatment. However, there were clear differences in the process. On the one hand, the screening was to take place within 4 to 8 weeks before the planned infusion with tisagenlecleucel. The leukapheresis was either to be carried out within this period as part of the screening or a so-called historical leukapheresis product, i.e. a leukapheresis product already collected before the screening examinations, could be used. Patient inclusion in the JULIET study did not occur with leukapheresis, but only with the acceptance and confirmation of the suitability of the leukapheresis product by the production site. The information in the benefit assessment procedure for tisagenlecleucel (G-BA process number 2020-03-15-D-530) shows that the median time of 112 days between screening and infusion or study exit was conspicuously long. In addition, there was also a long period between screening and study inclusion (median time: 54 days). Other aspects of the treatment process are largely comparable for the JULIET study and the studies on lisocabtagene maraleucel.

Comparisons of individual arms from different studies

In Module 4 A, the company presents separate analyses for the comparison of the studies TRANSCEND-NHL-001 and TRANSCEND WORLD with a subpopulation of the NDS-NHL-001 study on some of the comparators named as suitable by the G-BA. The company conducted these comparisons of individual arms exclusively for the outcome of overall survival and uses, among other things, confounder-adjusted comparisons and naive comparisons with the individual arms of its studies and the aQCC cohort of the NDS-NHL-001 study. Secondly, the company presented separate analyses comparing the single-arm studies TRANSCEND-NHL-001 and TRANSCEND WORLD with the ZUMA-1 study on axicabtagen ciloleucel and the JULIET study on tisagenlecleucel. For overall survival, objective response rate (ORR) and AEs, the company conducted matching-adjusted indirect comparison (MAIC)-based comparisons of individual arms without a common comparator and naive comparisons based on these studies.

Assessment of the evidence presented by the company

Comparison of individual arms based on individual patient data compared to the NDS-NHL-001 study

Implementation of the ACT in the aQCC cohort of the NDS-NHL-001 study as well as similarity of the populations questionable

The G-BA specified individualized therapy as ACT taking into account the lymphoma subentity, disease biology, prior therapy, course of disease and general condition.

However, in Module 4 A of the dossier, it only presented insufficient information on these features. For example, for a large proportion of patients from the aQCC cohort of the NDS-NHL-001 study, no information is available on important patient characteristics that could be

used to assess the general condition and the treatment situations in which the patients are. Due to the lack of information on the general condition of the patients, neither the suitability of the patients of the aQCC cohort of the NDS-NHL-001 study for CAR-T cell therapy nor their suitability for other treatment options such as high-dose chemotherapy with autologous stem cell transplantation can be assessed. Thus, it remains unclear whether the patients on the intervention and the comparator side are sufficiently comparable with regard to their suitability for CAR-T cell therapy or other treatment options. However, it cannot be derived from the available information that the best possible individualized therapy was implemented for the patients in the aQCC cohort, taking into account their general condition.

Moreover, apart from results on the outcome of overall survival from the NDS-NHL-001 study, no results on other patient-relevant outcomes are available. Therefore, balancing of the benefits and harms is not possible for the comparison presented by the company on the basis of this study, irrespective of the aspects already described.

Comparison of individual arms versus axicabtagen ciloleucel or tisagenlecleucel

On the basis of the comparisons versus axicabtagen ciloleucel or tisagenlecleucel presented by the company, it is only possible to make statements about patients for whom the use of axicabtagen ciloleucel or tisagenlecleucel represents suitable individualized therapy. Irrespective of this, however, the data presented by the company on the comparison of lisocabtagene maraleucel versus axicabtagen ciloleucel or tisagenlecleucel are not suitable for the benefit assessment. This is justified below.

Comparability of the studies on lisocabtagene maraleucel and axicabtagen ciloleucel

In the studies on lisocabtagene maraleucel, there are clear differences with regard to the study design, in particular the inclusion criteria (e.g. on the response of the disease to the most recent pretreatment) and the study procedure (possibility of bridging) compared to the study on axicabtagen ciloleucel, which call into question the comparability of the patients on the intervention and comparator side for the analyses presented by the company.

The available data on patient characteristics for the studies show that, as a consequence of the different inclusion criteria, the ZUMA-1 study only included patients who either had no better response than stable disease to their last chemotherapy or a relapse within 12 months of the previous autologous stem cell transplant. In contrast, approximately 30% and 16% of the patients in the studies on lisocabtagene maraleucel had chemotherapy-sensitive disease and thus a better response than stable disease to their last chemotherapy or relapse after ≥ 12 months following autologous stem cell transplantation. The patients in the ZUMA-1 study were also more often in the more advanced disease stages III and IV according to Ann Arbor (about 85%) than the patients in the TRANSCEND-NHL-001 study (about 69%) or in the

TRANSCEND WORLD study (about 55%). In addition, the patients in the ZUMA-1 study also tended to be in a later line of therapy than in the studies on the intervention side.

Before treatment, preparations for the patient-specific production of the CAR T-cell preparation are necessary for both the treatment with lisocabtagene maraleucel and the treatment with axicabtagen ciloleucel, which can take several weeks. According to the S3 guideline on diagnosis, treatment and follow-up for adult patients with DLBCL and related entities, patients in the present therapeutic indication should be offered systemic treatment to bridge the waiting period until CAR-T cells are used with curative intent. In contrast to the studies on lisocabtagene maraleucel, however, such a bridge therapy between leukapheresis and infusion was not allowed in cohorts 1 and 2 of the ZUMA-1 study, and was accordingly not used in any of the included patients.

Overall, the comparability of the patients on the intervention and comparator side for the analyses submitted by the company were considered as not given against this background.

Comparability of the studies on lisocabtagene maraleucel and tisagenlecleucel

In the studies on lisocabtagene maraleucel, there are clear differences with regard to the study design, in particular the inclusion criteria (e.g. on the response of the disease to the most recent pretreatment) and the study procedure (possibility of bridging) compared to the study on axicabtagen ciloleucel, which call into question the comparability of the patients on the intervention and comparator side for the analyses presented by the company.

On the one hand, there are differences with regard to the time of study inclusion and thus the start of observation. In the lisocabtagene maraleucel studies, inclusion started with the leukapheresis within 14 days of the start of screening and all patients were observed from the date of leukapheresis. In contrast, in the JULIET study, leukapheresis was either performed during the screening, which took place within 4 to 8 weeks before the planned infusion of tisagenlecleucel, or a so-called historical leukapheresis product was used. Patients were only included in the study after the leukapheresis product had been adopted and accepted by the production sites. These differences regarding the course of the JULIET study are also reflected in the median times between screening or study inclusion and infusion or study exit for the JULIET study.

Moreover, there is a much longer waiting time until the start of treatment on the comparator side. In the JULIET study, the time between screening tests, which also included leukapheresis, and infusion with tisagenlecleucel or study withdrawal was significantly longer than in the studies on lisocabtagene maraleucel (median time: 112 days in the JULIET study compared to 37 days in TRANSCEND-NHL-001 and 42 days in TRANSCEND WORLD). The time between leukapheresis and infusion in the JULIET study was thus clearly longer than the time for

production and release of the CAR-T cells according to the SPCs of tisagenlecleucel, which is usually 3 to 4 weeks.

Moreover, observation in the JULIET study also started with a clear delay in relation to leukapheresis due to the delayed study inclusion. In contrast, observation of the patients in the studies on lisocabtagene maraleucel started immediately after leukapheresis and thus much earlier.

The differences described are also reflected in the further course of the study. Thus, it can be assumed that due to the longer waiting time, more patients from the JULIET study dropped out before the infusion of the cells than from the studies on lisocabtagene maraleucel, and as a result the number of patients with a bridge therapy was also clearly higher. This indicates a higher proportion of patients with worsening of the disease on the comparator side. Moreover, due to the more frequent use of bridging, side effects following infusion may also occur more frequently on the comparator side than on the intervention side. Due to the different time point of study inclusion on the intervention and the comparator side, there could also be differences in the recording of the outcomes due to a shortened observation period for the comparator therapy.

Overall, the comparability of the patients on the intervention and comparator side for the analyses submitted by the company were considered as not given against this background.

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of lisocabtagene maraleucel in comparison with the ACT. For the comparisons of individual arms from different studies on lisocabtagene maraleucel presented by the company with treatment options it described as conventional, this is due in particular to the fact that the implementation of individualized therapy taking into account the lymphoma subentity, the biology of the disease, the previous therapy, the course of the disease and the general condition as ACT cannot be assessed on the basis of the insufficient information, for example on patient characteristics. Apart from results on the outcome of overall survival, there are also no results on other patient-relevant outcomes for the comparator side, so that a balancing of the benefits and harms is not possible. The comparisons of individual arms from different studies on lisocabtagene maraleucel with axicabtagen ciloleucel or tisagenlecleucel presented by the company are not suitable for conclusions on the added benefit, as the comparability of the patients on the intervention and the comparator side for the analyses presented by the company is not considered to be given due to differences in the design and procedure of the studies.

Results on added benefit

As no suitable data are available for the benefit assessment, there is no hint of an added benefit of lisocabtagene maraleucel compared with the ACT; an added benefit is therefore not proven.

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

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

[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].

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with relapsed or refractory DLBCL, PMBCL and FL3B after 2 or more lines of systemic therapy	Individual therapy[b, c] taking into account the lymphoma subentity, disease biology, prior therapy, course of disease and general condition	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Within the framework of a clinical trial, the following therapies are considered suitable comparators for the individual therapy:

- ASHAP, bendamustine, CEPP, CEOP, DHAP, DHAX, DICEP, dose-adjusted EPOCH, ESHAP, GemOx, GDP, gemcitabine + vinorelbine, ICE, lenalidomide (only for patients with non-GCB DLBCL), MEP, MINE, PEPC, each of the therapies mentioned ± rituximab

as well as

- polatuzumab vedotin + bendamustine + rituximab, tafasitamab + lenalidomide, monotherapy brentuximab vedotin (only for patients with CD30+ DLBCL), monotherapy chlorambucil, monotherapy etoposide, monotherapy pixantrone, gemcitabine + rituximab, monotherapy rituximab, monotherapy ibrutinib (only for patients with non-GCB DLBCL), axicabtagene ciloleucel, tisagenlecleucel, radiation or BSC.
- Moreover, stem cell transplantation (autologous or allogeneic) is considered a component of the individualized therapy.

c. It is assumed that for suitable patients, rituximab will be used as part of salvage chemotherapy (e.g. no receipt of rituximab in prior therapy, no refractivity to rituximab, existing CD20 expression in lymphoma).

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BSC: best supportive care; CD: cluster of differentiation; CEPP: cyclophosphamide, etoposide, prednisone, procarbazine; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DHAP: dexamethasone, cisplatin, cytarabine; DHAX: dexamethasone, cytarabine, oxaliplatin; DICEP: dose-intensified cyclophosphamide, etoposide, cisplatin; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; FL3B: follicular lymphoma grade 3B; G-BA: Federal Joint Committee; GCB: germinal centre B-cell type; GemOx: gemcitabine, oxaliplatin; GDP: gemcitabine, dexamethasone, cisplatin or carboplatin; ICE: ifosfamide, carboplatin, etoposide; MEP: methotrexate, etoposide, cisplatin; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PEPC: prednisolone, etoposide, procarbazine, cyclophosphamide; PMBCL: primary mediastinal large B-cell lymphoma

The GBA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of lisocabtagene maraleucel compared with individualized therapy, taking into account lymphoma subentity, disease biology, prior therapy, course of the disease and general condition as ACT in adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after 2 or more lines of systemic therapy.

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

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

Therapeutic indication	**ACT[a]**
Adults with relapsed or refractory DLBCL, PMBCL and FL3B after 2 or more lines of systemic therapy	Individual therapy[b, c] taking into account the lymphoma subentity, disease biology, prior therapy, course of disease and general condition

a. Presented is the ACT specified by the G-BA.
b. Within the framework of a clinical trial, the following therapies are considered suitable comparators for the individualized therapy:
- ASHAP, bendamustine, CEPP, CEOP, DHAP, DHAX, DICEP, dose-adjusted EPOCH, ESHAP, GemOx, GDP, gemcitabine + vinorelbine, ICE, lenalidomide (only for patients with non-GCB DLBCL), MEP, MINE, PEPC, each of the therapies mentioned ± rituximab

as well as

- polatuzumab vedotin + bendamustine + rituximab, tafasitamab + lenalidomide, monotherapy brentuximab vedotin (only for patients with CD30+ DLBCL), monotherapy chlorambucil, monotherapy etoposide, monotherapy pixantrone, gemcitabine + rituximab, monotherapy rituximab, monotherapy ibrutinib (only for patients with non-GCB DLBCL), axicabtagene ciloleucel, tisagenlecleucel, radiation or BSC.
- Moreover, stem cell transplantation (autologous or allogeneic) is considered a component of the individualized therapy.

c. It is assumed that for suitable patients, rituximab will be used as part of salvage chemotherapy (e.g. no receipt of rituximab in prior therapy, no refractivity to rituximab, existing CD20 expression in lymphoma).

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BSC: best supportive care; CD: cluster of differentiation; CEPP: cyclophosphamide, etoposide, prednisone, procarbazine; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DHAP: dexamethasone, cisplatin, cytarabine; DHAX: dexamethasone, cytarabine, oxaliplatin; DICEP: dose-intensified cyclophosphamide, etoposide, cisplatin; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; FL3B: follicular lymphoma grade 3B; G-BA: Federal Joint Committee; GCB: germinal centre B-cell type; GemOx: gemcitabine, oxaliplatin; GDP: gemcitabine, dexamethasone, cisplatin or carboplatin; ICE: ifosfamide, carboplatin, etoposide; MEP: methotrexate, etoposide, cisplatin; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PEPC: prednisolone, etoposide, procarbazine, cyclophosphamide; PMBCL: primary mediastinal large B-cell lymphoma

In principle, the company follows the ACT of an individualized therapy as defined by the G-BA, taking into account the aspects listed in Table 4 and additionally, if possible, including allogeneic stem cell transplantation (based on a consultation with the G-BA on 19 March 2020). However, the therapies named by the company in its inclusion criteria as suitable comparators in the context of individualized therapy differ from those considered suitable

according to the G-BA. For example, the company did not include tafasitamab in combination with lenalidomide as a suitable comparator in its assessment. Furthermore, it did not take into account radiation or autologous stem cell transplantation.

The present benefit assessment takes into account the comparators deemed suitable by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

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 lists on lisocabtagene maraleucel (status: 01 June 2022)
- bibliographical literature search on lisocabtagene maraleucel (last search on 1 June 2022)
- search in trial registries/trial results databases for studies on lisocabtagene maraleucel (last search on 1 June 2022)
- search on the G-BA website for lisocabtagene maraleucel (last search on 15 July 2022)
- bibliographical literature search on the ACT (last search on 01 June 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 01 June 2022)
- search on the G-BA website for the ACT (last search on 15 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on lisocabtagene maraleucel (last search on 8 September 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCTs on the direct comparison of lisocabtagene maraleucel versus the ACT.

The company did not include any studies for a direct comparison. It therefore carried out an information retrieval for further investigations and identified, in addition to two uncontrolled studies on the intervention side, 3 studies on the comparator side, from which it used individual arms in each case.

The check of the completeness of the company's study pool identified no additional potentially relevant studies on lisocabtagene maraleucel. The completeness of the study pool on the ACT was not checked. However, the dossier already suggests that the company's study pool for further studies is potentially incomplete on the comparator side.

In Section 4.3.2.4.1.2 in Module 4 A of the full dossier assessment, the company states that it identified 29 publications on 20 potentially relevant studies in its bibliographic search for further studies for indirect comparisons. These were, among others, publications on the studies ZUMA-1 [3] and JULIET [4], which the company included for the comparisons of individual arms from different studies (see Section I 3.1). In addition, according to the company, 16 studies on different interventions described by it as "real-world" studies had

been identified, including 5 on axicabtagen ciloleucel, 2 on tisagenlecleucel, 3 on axicabtagen ciloleucel + tisagenlecleucel, 2 on allogeneic stem cell transplantation, 2 on polatuzumab vedotin, 1 on polatuzumab vedotin + axicabtagen ciloleucel/tisagenlecleucel and 1 on pixantrone. Irrespective of the question of whether these studies are suitable for the implementation of the ATC in the sense of an individualized therapy, the company does not provide any information as to why it does not consider these studies further. For example, it included the ZUMA-1 study for the comparison against axicabtagen ciloleucel and the JULIET study for the comparison against tisagenlecleucel, but did not provide any information on the other studies it identified on axicabtagen ciloleucel and/or tisagenlecleucel. In the dossier, the company neither provides a reason why it did not further consider the additionally identified studies that are potentially relevant for its comparisons, nor references to the studies. Therefore, the available data do not permit to check whether the study pool is incomplete. Hence, the company's study pool for further investigations on the ACT is potentially incomplete.

Regardless of the potential incompleteness of the study pool on the part of the ACT, the data presented by the company are not suitable for deriving conclusions on the added benefit of lisocabtagene maraleucel compared to the ACT. This is justified below.

I 3.1 Evidence provided by the company

For lisocabtagene maraleucel, the company included the single-arm TRANSCEND-NHL-001 study [5,6], originally designed for phase 1, and the single-arm phase 2 study TRANSCEND WORLD [7,8]. From each of these studies, it used a subpopulation of adult patients with refractory or relapsed B-cell NHL who, depending on the study, met certain criteria regarding histology, pretreatment and the administered dose of lisocabtagene maraleucel (for details see Section I 3.1.1).

Moreover, the company used comparisons of individual arms from different studies. For these comparisons, it identified the studies NDS-NHL-001 [9], ZUMA-1 [3] and JULIET [4] on the side of the ACT.

An overview of the studies included by the company can be found in Table 8 in Appendix B of the full dossier assessment.

I 3.1.1 Evidence on lisocabtagene maraleucel

I 3.1.1.1 Study TRANSCEND-NHL-001

The TRANSCEND-NHL-001 study is an ongoing, single-arm study comprising 2 cohorts: 1 cohort enrolling adult patients with DLBCL and 1 cohort on patients with mantle cell lymphoma, who are not the subject of the present research question. The study was originally planned as a

phase 1 study, but was modified for the approval so that there was a seamless transition to phase 2. Enrolment of patients in the study started in January 2016.

The DLBCL cohort included adult patients with NOS DLBCL including transformed iNHL, HGBL with MYC and BCL 2 and/or BCL6 rearrangements with DLBCL histology, PMBCL or FL3B. Patients had to have refractory or relapsed disease either after at least 2 prior therapies, including an anthracycline and rituximab (or another anti-CD20 agent) or after autologous stem cell transplantation.

The study originally consisted of a dose-finding and a dose-expansion phase, which was modified by the addition of a dose-confirmation group for the evaluation of efficacy and safety with the aim of obtaining regulatory approval. Patients were allocated to different groups for dose finding, dose expansion and dose confirmation, in which they received intravenous treatment with 50 x 10^6 (once), 50 x 10^6 (twice), 100 x 10^6 (once) or 150 x 10^6 (once) viable CAR-T cells, depending on their allocation.

Before the treatment, the study required arrangements for the individualized production of the CAR T-cell preparation. Figure 1 in I Appendix C shows a schematic presentation of the details on the course of the TRANSCEND-NHL-001 study. According to the study design, leukapheresis was performed as soon as possible after the screening investigations, but at the latest within 2 weeks after study inclusion, to collect peripheral blood mononuclear cells (PBMCs) for the preparation of lisocabtagene maraleucel. According to the study design, leukapheresis was to take place within 4 weeks before the infusion with lisocabtagene maraleucel. In fact, according to information provided by the company in Module 4 A of the dossier, the median time between leukapheresis and infusion for the subpopulation of the study used by it was 37 days at the data cut-off of 4 January 2023. Within this period, patients could receive anti-cancer therapy for disease control (bridge therapy) in the form of low-dose chemotherapy or local radiotherapy if needed, which had to be completed ≥ 7 days before LDC. LDC was to be given 2 to 7 days before the planned infusion with lisocabtagene maraleucel and consisted of cyclophosphamide 300 mg/m² body surface area (BSA)/day and fludarabine 30 mg/m² BSA/day, each administered IV for 3 days. Patients should not be treated with lisocabtagene maraleucel if they showed a worsening of their clinical condition compared to that observed at study inclusion which the treating physician deemed to be associated with an increased risk of AEs. A total of 345 patients were included in the DLBCL cohort of the study. Of these, 270 received one of the doses of lisocabtagene maraleucel investigated in the study.

After the last infusion of lisocabtagene maraleucel, patients were followed up for a period of 24 months. Following follow-up or in case of early study withdrawal, all patients treated with lisocabtagene maraleucel had the opportunity to participate in the GC-LTFU-001 study [10] for long-term follow-up for up to 15 years after the last infusion.

Primary outcomes of the study were the overall response rate (ORR), the probability of dose-limiting toxicity and adverse events (AEs). Secondary outcomes included overall survival, morbidity and health-related quality of life.

Data cut-offs and analysis populations

According to the company, 4 data cut-offs are available for the TRANSCEND-NHL-001 study:

- Data cut-off 1: 12 April 2019 (primary data cut-off)
- Data cut-off 2: 12 August 2019 (data cut-off for the European approval)
- Data cut-off 3: 19 June 2020 (data cut-off subsequently presented in the course of the approval procedure)
- Data cut-off 4: 04 January 2021 (data cut-off subsequently presented in the course of the approval procedure)

In the dossier, the company presents analyses of patients in the DLBCL cohort who were scheduled for a single infusion of 50 x 10^6 or 100 x 10^6 viable CAR-T cells. This corresponds to the range of the target dose according to the SPC of 44 to 120 x 10^6 viable CAR-T cells [11]. For the TRANSCEND-NHL-001 study, the company took into account both analyses of the second data cut-off of 12 August 2019 and analyses of the most recent data cut-off of 4 January 2021 for its assessment. At the time point of the most recent data cut-off, 291 patients in the DLBCL cohort had undergone leukapheresis and were scheduled for treatment with lisocabtagene maraleucel in the range of the target dose specified in the SPC. In the dossier, the company refers to this group as intention to treat (ITT) population. In fact, 223 patients in this group received lisocabtagene maraleucel according to the SPC [11]. In Module 4A of the dossier, the company refers to this group as treated population.

Presented results

In Module 4 A of the dossier, the company presents analyses on overall survival, tumour response, progression-free survival (PFS) and AEs for the ITT population for the most recent data cut-off of 4 January 2021. For further outcomes of the categories of morbidity and health-related quality of life, the company only presented analyses on the treated population at the most recent data cut-off. For the comparisons of individual arms, the company partly considered analyses based on the ITT population at the most recent data cut-off, and partly used analyses on the treated population or on previous data cut-offs (for details see Section I 3.1.3).

I 3.1.1.2 Study TRANSCEND WORLD

TRANSCEND WORLD is an ongoing, single-arm, phase 2 study on adult patients with aggressive B-cell NHL comprising a total of 7 cohorts with indications that partially deviate from the

therapeutic indication. In the dossier, the company takes into account results on patients from cohorts 1 and 3. These cohorts included patients with refractory or relapsed DLBCL NOS (de novo or [tFL]), HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology or FL3B. Cohort 1 included patients after at least 2 prior therapies, including an anthracycline and rituximab (or another anti-CD20 agent). Cohort 3 included patients from Japan who met the criteria for cohort 1 or were in the second-line. However, the latter only applied to individual patients included in cohort 3; the majority fulfilled the criteria for cohort 1. The other cohorts of the TRANSCEND WORLD study included patients who were in a different treatment situation or had other tumour entities and were therefore not included the present research question. Patients were enrolled in the study from June 2018.

All patients were treated once (IV) with a target dose of 100 x 10^6 viable CAR-T cells. Preparations for the patient-specific production of the CAR T-cell preparation were also necessary in the TRANSCEND WORLD study prior to treatment. The procedure in the study corresponds to that in the TRANSCEND-NHL-001 study, with slight deviations (for details see Figure 2 in I Appendix C). The deviation compared to the TRANSCEND-NHL-001 study relates in particular to leukapheresis, which according to the study design was to take place about 5 weeks before the infusion with lisocabtagene maraleucel. In fact, according to information provided by the company in Module 4 A of the dossier, the median time between leukapheresis and infusion for the subpopulation of the study used by it was 42 days at the data cut-off of 4 January 2021. As in the TRANSCEND-NHL-001 study, patients in the TRANSCEND WORLD study could also receive a bridge therapy within this period, and the LDC specifications were also consistent between the 2 studies. In addition, as in the TRANSCEND-NHL-001 study, treatment with lisocabtagene maraleucel should not take place if patients showed a worsening of their clinical condition compared to the condition observed at study inclusion. In total, 58 patients in cohorts 1 and 3 who met the inclusion and exclusion criteria of the study received leukapheresis (referred to by the company as the ITT population). 46 of these patients received treatment with lisocabtagene maraleucel according to the SPC (referred to as “treated population” by the company).

Following the infusion and the subsequent 2-year follow-up, or in the case of early study withdrawal, patients in the TRANSCEND WORLD study also had the opportunity to participate in the GC-LTFU-001 study for long-term follow-up for up to 15 years after the infusion.

Primary outcome of the study was ORR; secondary outcomes included overall survival, morbidity, health-related quality of life and AEs.

Data cut-offs and analysis populations

According to the company, 4 data cut-offs are available for the TRANSCEND WORLD study:

- Data cut-off 1: 22 February 2019 (interim analysis)

- Data cut-off 2: 13 September 2019 (data cut-off for the European approval)
- Data cut-off 3: 19 June 2020 (primary analysis)
- Data cut-off 4: 04 January 2021 (data cut-off subsequently presented in the course of the approval procedure)

In the dossier, the company presented analyses on patients from cohorts 1 and 3. For its assessment of the TRANSCEND WORLD study, the company took into account both analyses of the 3rd data cut-off of 19 June 2020 and analyses of the 4th data cut-off of 4 January 2021. As described above, 58 patients were part of the ITT population (44 in cohort 1 and 14 in cohort 3) at the time point of the most recent data cut-off. 46 patients (36 in cohort 1 and 10 in cohort 3) from this group received lisocabtagene maraleucel according to the SPC [11].

Presented results

In Module 4 A of the dossier, the company presents analyses on overall survival, tumour response, PFS and AEs for the ITT population of the TRANSCEND WORLD study, analogous to the TRANSCEND-NHL-001 study, for the most recent data cut-off of 4 October 2021. For further outcomes of the categories of morbidity and health-related quality of life, the company only presented analyses on the treated population at the most recent data cut-off. For the comparisons of individual arms, the company partly considered analyses based on the ITT population at the most recent data cut-off, and partly used analyses on the treated population or on previous data cut-offs. Moreover, it partially only considered patients from cohort 1 (for details, see Section I 3.1.3).

I 3.1.2 Evidence on the ACT

I 3.1.2.1 Study NDS-NHL-001

The NDS-NHL-001 study is a non-interventional, retrospective study conducted by the company on the treatment of patients with aggressive B-cell NHL with relapsed or refractory disease after at least one previous line of therapy, which includes patients from clinical centres and research databases. According to the statistical analysis plan (SAP) for the study [12], patients with histologically confirmed DLBCL NOS, HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL or FL3B were considered. In addition, patients had to have relapsed or refractory disease after at least 2 previous therapies, including treatment with an anthracycline and rituximab (or another anti-CD20 agent). In addition, the disease had to be diagnosed for the first time in 2003 or later. According to the study protocol [13], the aim of the study was to evaluate clinical outcomes in the above-described patient group in clinical, oncological care. In addition, the possibility of using the collected data for a comparison with data collected in single-arm intervention studies is described. The definition of the population according to the study protocol deviated slightly and was adjusted and specified in more detail in the SAP.

The SAP also specifies in more detail an analysis that the company submitted to the EMA in the context of the approval of lisocabtagene maraleucel [14]. This analysis refers to the comparison of patients from the NDS-NHL-001 study with patients from TRANSCEND-NHL-001. For this analysis, the SAP describes a selection process that further specifies the patient group from the NDS-NHL-001 study for the comparison. In the dossier, the company presented the evidence report for the comparison [9]. The report shows that clinical centres (2 centres with N = 250 in North America and 9 centres with N = 399 in Europe) and research databases from external partners served as data sources for the NDS-NHL-001 study. In addition, data from electronic patient records collected from the COTA (N = 392) and Flatiron (N = 277) databases and the Guardian Research Network (N = 133) on patients whose treatment took place in the US health care context were considered. A total of 1451 patients were included in the baseline cohort of the NDS-NHL-001 study. The report then describes further selection steps that were applied for the selection of the patient group designated by the company as the qualifying comparator cohort (QCC cohort), which served as the basis for the comparison with the TRANSCEND-NHL-001 study in the context of the approval procedure.

For the analyses in the dossier that are based on the NDS-NHL-001 study, the company applied a different selection process based on the same baseline cohort (N = 1451), which it describes in a separate protocol, CA082-023 [15]. The deviating selection criteria result in a patient group for the analyses in the dossier, which the company refers to as the aQCC cohort. In the selection, differences exist particularly with regard to treatment, as according to the company, this cohort only included patients who received a therapy that is considered a suitable comparator by the G-BA within the scope of the ACT. Moreover, according to protocol CA082-023, the most recent line of therapy that represents a suitable comparator was considered for each patient. In the NDS-NHL-001 study, in contrast, the 3rd line of treatment was considered for each patient, regardless of which therapy was used.

For the recorded outcomes (overall survival, PFS as well as various outcomes on treatment response), the patients in the study were observed for up to 24 months from the start of the corresponding line of treatment (index date).

Presented results

In Module 4 A, the company presents results for the aQCC cohort (N = 182) selected according to CA082-023 for the outcome of overall survival at the data cut-off of 20 December 2019 and considers these for its comparison of individual arms (for details see Section I 3.1.3).

I 3.1.2.2 Study ZUMA-1

ZUMA-1 is a single-arm phase 1/2 study on the treatment with axicabtagen ciloleucel that enrolled adult patients with refractory DLBCL, PMBCL or tFL after ≥ 1 line of chemotherapy,

including an anti-CD20 antibody and an anthracycline. Patients or their disease had to be either:

- refractory to the last chemotherapy, or
- have relapsed within 12 months of an autologous stem cell transplantation, or
- be refractory to or have not responded to the last salvage therapy after an autologous stem cell transplantation.

Refractory disease to last chemotherapy was defined as progressive disease or no better response than stable disease with a duration of response ≤ 6 months.

In phase 1 of the ZUMA-1 study, different LDC regimens with different CAR-T cell doses were tested to determine dose-limiting toxicity. Phase 2 of the study comprises a total of 6 cohorts, with cohorts 1 and 2 representing the pivotal cohorts of the study, and cohorts 3 to 6 being added in several protocol amendments in the safety management part of the study, which is still ongoing. The safety management part of the study aimed to investigate the effects of prophylactic therapies such as tocilizumab, levetiracetam or corticosteroids on the toxicity of axicabtagen ciloleucel. However, in cohorts 3 to 6, treatment was not in line with the specifications of the SPC for axicabtagen ciloleucel [16]. Thus, only the pivotal cohorts 1 and 2 of the study are potentially relevant for the present research question.

In cohorts 1 and 2 of the study, patients were treated once (IV) with a target dose of 2×10^6 viable CAR-T cells/kg body weight or a maximum dose of 2×10^8 viable CAR-T cells from a body weight of 100 kg. In phase 2 of the ZUMA-1 study, a total of 111 patients were included in cohort 1 (DLBCL; n = 81) or cohort 2 (PMBCL or tFL; n = 30) depending on their disease subentity. Of these, 101 patients actually received treatment with axicabtagen ciloleucel (cohort 1: n = 77, cohort 2: n = 24).

Before treatment with axicabtagen ciloleucel, preparations for the patient-specific production of the CAR T-cell preparation had been necessary in the ZUMA-1 study, similar to the studies on lisocabtagene maraleucel (for details see Figure 3 in I Appendix C). According to the study design, the screening examinations should be performed within 28 days prior to study inclusion and leukapheresis should be performed within 5 days after determination of the suitability, simultaneously with inclusion in the study. 5 days before the administration of axicabtagen ciloleucel, patients received LDC consisting of cyclophosphamide 500 mg/m² BSA/day and fludarabine 30 mg/m² BSA/day, each administered IV, for 3 days. Following the infusion of axicabtagen ciloleucel, patients were hospitalized for at least 7 days.

According to the study design, the planned duration between leukapheresis and the infusion of axicabtagen ciloleucel was not specified. However, the information in the benefit assessment procedure for axicabtagen ciloleucel (G-BA process number 2022-05-15-D-820)

shows that the median time between leukapheresis and infusion was 23 days [17]. As the option of bridge therapy was only added in the safety management part of the study for cohorts 3 to 6, bridge therapy was not allowed in the period between leukapheresis and infusion of CAR-T cells in pivotal cohorts 1 and 2 of the ZUMA-1 study, which is in contrast to the studies on lisocabtagene maraleucel.

Moreover, also in contrast to the studies on lisocabtagene maraleucel, the study design did not intend premedication with paracetamol and diphenhydramine prior to the infusion of axicabtagen ciloleucel for every patient in cohorts 1 and 2, although this is recommended according to the SPC [16]. Just like the possibility of a bridge therapy, a corresponding specification was only added for the safety management part of the study for cohorts 3 to 6.

After the axicabtagen ciloleucel infusion, patients were followed up for periods of up to 15 years.

Primary outcome of the study was ORR; secondary outcomes included overall survival, PFS and AEs.

Presented results

In Module 4 A, the company uses results of cohorts 1 and 2 of phase 2 at the data cut-off of 11 August 2018 for the ZUMA-1 study, which were submitted as part of the benefit assessment procedure of axicabtagen ciloleucel [17-19] and takes these into account for its comparison of individual arms (for details see Section I 3.1.3). For the outcomes of overall survival and ORR, the company considered all patients included in cohorts 1 and 2 (N = 111), and for the comparison of AEs all patients from these cohorts who were treated with axicabtagen-ciloleucel (N = 101).

I 3.1.2.3 Study JULIET

JULIET is a single-arm phase 2 study on the treatment with tisagenlecleucel including adult patients with relapsed or refractory DLBCL after ≥ 2 chemotherapy lines including rituximab and anthracycline, who, in addition, did not respond to, were not suitable or did not consent to autologous stem cell transplantation.

Patients were treated once (IV) with a target dose of 5×10^8 viable CAR-T cells, with a dose between 1×10^8 to 5×10^8 cells being allowed. Depending on the tisagenlecleucel production site, a total of 167 patients were included in either the main cohort (USA; n = 147) or in cohort A (EU; n = 20). Of these, 115 patients actually received treatment with tisagenlecleucel (main cohort: n = 99, cohort A: n = 16).

As in the studies on lisocabtagene maraleucel, preparations for the patient-specific production of the CAR T-cell preparation were also necessary in the JULIET study prior to treatment (for

details see Figure 4 in I Appendix C). However, there are clear differences in the procedure compared to the studies TRANSCEND-NHL-001 and TRANSCEND WORLD.

On the one hand, the screening was to take place within 4 to 8 weeks before the planned infusion with tisagenlecleucel. The leukapheresis was either to be carried out within this period as part of the screening or a so-called historical leukapheresis product, i.e. a leukapheresis product already collected before the screening examinations, could be used. Patient inclusion in the JULIET study did not occur with leukapheresis, but only with the acceptance and confirmation of the suitability of the leukapheresis product by the production site. For the JULIET study, the company does not provide any information on the time period between screening (incl. leukapheresis) or study inclusion and the infusion of CAR-T cells in the dossier. However, the information in the benefit assessment procedure for tisagenlecleucel (G-BA process number 2020-03-15-D-530) shows that the median time of 112 days between screening and infusion or study exit was conspicuously long [20]. In addition, according to the information from this procedure, there was also a long period of time between screening and study inclusion (median time: 54 days).

Other aspects of the treatment process are largely comparable for the JULIET study and the studies on lisocabtagene maraleucel. Thus, bridge therapy for disease control was allowed at the discretion of the attending physician. LDC was to be given up to 2 days before the infusion of tisagenlecleucel and consisted of cyclophosphamide 250 mg/m² BSA/day and fludarabine 25 mg/m² BSA/day, each administered IV for 3 days. In patients with resistance to cyclophosphamide, a 2-day LDC with bendamustine (90 mg/m² BSA, IV) could also be performed. This affected 14% of the patients in the JULIET study.

After the infusion of tisagenlecleucel, patients were followed up for periods of up to 5 years. After 5 years or in case of early study withdrawal, all patients treated with tisagenlecleucel could be followed up within a long-term observation for up to 15 years according to protocol CCTL019A2205B [21].

Primary outcome of the study was ORR; secondary outcomes included overall survival, health-related quality of life and AEs.

Presented results

In Module 4 A, the company uses results for the data cut-off of 1 July 2019 for the JULIET study, which were submitted as part of the benefit assessment procedure of tisagenlecleucel [20] and takes these into account for its comparison of individual arms (for details see Section I 3.1.3). For the outcomes of overall survival and ORR, the company considered all patients included (N = 167), and for the comparison of AEs all patients who were treated with tisagenlecleucel (N = 115).

I 3.1.3 Comparisons of individual arms from different studies

Under "Further studies" in Module 4 A, the company presents various analyses on comparisons of individual arms from different studies for the comparison of lisocabtagene maraleucel with the ACT. The following Table 5 provides an overview of the comparisons conducted by the company and the statistical models used.

Table 5: Comparisons conducted by the company (multipage table)

Comparison studies	Models used by the company for the comparison[a]	Data type	Outcomes
Lisocabtagene maraleucel vs. conventional treatment options[b]			
TRANSCEND-NHL-001[c] vs. NDS-NHL-001 (aQCC cohort)[d, e]	▪ **Weighted (IPTW, with PS weighting)** ▪ univariate (naive comparison) ▪ multivariate (with adjustment for confounders)	IPD vs. IPD	▪ Overall survival
TRANSCEND WORLD[f] vs. NDS-NHL-001 (aQCC cohort)[d, e]	▪ Univariate (naive comparison)[g]	IPD vs. IPD	▪ Overall survival
Lisocabtagene maraleucel vs. axicabtagene ciloleucel			
TRANSCEND-NHL-001[h] vs. ZUMA-1[i]	▪ **Weighted (MAIC, ESS model[j], limited analysis population)[k]** ▪ univariate (naive comparison, limited analysis population)[k, l] ▪ univariate (naive comparison)	IPD vs. aggregate data	▪ Overall survival ▪ ORR ▪ AEs[m]
TRANSCEND WORLD[h] vs. ZUMA-1[i]	▪ Univariate (naive comparison, limited analysis population)[k, l] ▪ univariate (naive comparison)	IPD vs. aggregate data	▪ Overall survival ▪ ORR ▪ AEs[m]
Lisocabtagene maraleucel vs. tisagenlecleucel			
TRANSCEND-NHL-001[h] vs. JULIET[n]	▪ **Weighted (MAIC, ESS model[j], limited analysis population)[o]** ▪ univariate (naive comparison, limited analysis population)[l, o] ▪ univariate (naive comparison)	IPD vs. aggregate data	▪ Overall survival ▪ ORR ▪ AEs[m]
TRANSCEND WORLD[h] vs. JULIET[n]	▪ Univariate (naive comparison, limited analysis population)[l, o] ▪ univariate (naive comparison)	IPD vs. aggregate data	▪ Overall survival ▪ ORR ▪ AEs[m]

Table 5: Comparisons conducted by the company (multipage table)

Comparison studies	Models used by the company for the comparison[a]	Data type	Outcomes
a. The main statistical model used by the company for the respective comparison is highlighted in bold. The models are Cox proportional hazards models (overall survival) or generalized models with suitable link functions (ORR, AEs). Only main analyses and supplementary analyses are presented. Further sensitivity analyses of the company are not presented. b. The company describes the therapies administered in the aQCC cohort of the NDS-NHL-001 study as conventional therapy options. Except for 3 patients who received allogeneic stem cell transplantation including induction therapy, only (immune) chemotherapies were used. c. Data cut-off: 12 August 2019. d. Data cut-off: 20 December 2019. e. Subpopulation of an baseline cohort of 1451 patients from different databases compiled within the framework of the NDS-NHL-001 study according to protocol CA082-023. f. Data cut-off: 19 June 2020; the company only used cohort 1. g. According to the information provided by the company in Module 4 A of the dossier, no adjustment could be made for the comparison with the aQCC cohort of the NDS-NHL-001 study in order to obtain meaningful results due to the small number of cases and the underlying methodological complexity (upstream multiple imputation in combination with the calculation of propensity scores). The company explained that it only discussed the naive comparison for this reason. h. Data cut-off: 4 January 2021. i. Data cut-off: 11 August 2018. j. Gradual inclusion of confounders until the ESS is ≥ 20% for the last time. k. The company restricted the analysis populations of the studies TRANSCEND-NHL-001 and TRANSCEND WORLD on the basis of confounders. Patients with ECOG PS ≥ 2, bridge therapy, secondary CNS involvement, previous allogeneic SCT, disease subentity FL3B, creatinine clearance ≤ 60 ml/min, LVEF < 50%, ALC < 0.1 x 10^9/l were excluded. Patients with missing values in all confounders considered were excluded. l. In Module 4 A of the dossier, the company refers to these analyses as "MAIC without adjustment", however, these are unweighted models. m. The company used the population treated with CAR-T cells as initial population for analyses of AEs from the studies TRANSCEND-NHL-001, TRANSCEND WORLD, ZUMA-1 and JULIET. n. Primary data cut-off: 1 July 2019. o. The company restricted the analysis populations of the studies TRANSCEND-NHL-001 and TRANSCEND WORLD on the basis of confounders. Patients with ECOG PS ≥ 2, secondary CNS involvement, previous allogeneic SCT, disease subentity PMBCL and FL3B, creatinine clearance ≤ 60 ml/min, LVEF < 45%, ALC < 0.3 x 10^9/l were excluded. Patients with missing values in all confounders considered were excluded. AE: adverse event; ALC: absolute lymphocyte count; aQCC: adjusted qualifying comparator cohort; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESS: effective sample size; FL3B: follicular lymphoma grade 3B; IPD: individual patient data; IPTW: inverse probability of treatment weighting; LVEF: left ventricular ejection fraction; MAIC: matching-adjusted indirect comparison; ORR: overall response rate; PMBCL: primary mediastinal B-cell lymphoma; PS: propensity score; SCT: stem cell transplantation			

The company presents separate analyses for the comparison of the studies TRANSCEND-NHL-001 and TRANSCEND WORLD with a subpopulation of the NDS-NHL-001 study on some of the comparators named as suitable by the G-BA. The company described these comparisons of individual arms without a common comparator as well as the selection of the corresponding subpopulation from the NDS-NHL-001 study in a separate protocol (CA082-023, for

explanation see also Section I 3.1.2). The company conducted these comparisons of individual arms exclusively for the outcome of overall survival and uses, among other things, confounder-adjusted comparisons and naive comparisons with the individual arms of its studies and the aQCC cohort.

Secondly, the company presented separate analyses comparing the single-arm studies TRANSCEND-NHL-001 and TRANSCEND WORLD with the ZUMA-1 study on axicabtagen ciloleucel and the JULIET study on tisagenlecleucel. For overall survival, ORR and AEs, the company conducted MAIC-based comparisons of individual arms without a common comparator and naive comparisons based on these studies.

Details on the statistical models, data cut-offs and patient populations used by the company for the various comparisons can be found in Table 5.

I 3.2 Assessment of the evidence presented by the company

As described in Section I 3.1, the company compared results on the outcomes of overall survival, ORR and AEs from different studies for the comparison of lisocabtagene maraleucel with the options of the ACT for adult patients with relapsed or refractory DLBCL, PMCBL and FL3B after 2 or more lines of systemic treatment. Because of several aspects, the data presented by the company are unsuitable for the benefit assessment of lisocabtagene maraleucel in comparison with the ACT. This is justified below.

Comparison of individual arms based on individual patient data compared to the NDS-NHL-001 study.

Implementation of the ACT in the aQCC cohort of the NDS-NHL-001 study as well as similarity of the populations questionable

The G-BA specified individualized therapy as ACT taking into account the lymphoma subentity, disease biology, prior therapy, course of disease and general condition.

However, in Module 4 A of the dossier, it only presented insufficient information on these features. For example, for a large proportion of patients from the aQCC cohort of the NDS-NHL-001 study, no information is available on important patient characteristics that could be used to assess the general condition and the treatment situations in which the patients are. For example, information on the ECOG PS is missing for 41% of patients, information on the International Prognostic Index (IPI) score is missing for 96% and information on the Ann Arbor stage of disease is missing for 29%. Due to the lack of information on the general condition of the patients, neither the suitability of the patients of the aQCC cohort of the NDS-NHL-001 study for CAR-T cell therapy nor their suitability for other treatment options such as high-dose chemotherapy with autologous stem cell transplantation can be assessed. Thus, it remains unclear whether the patients on the intervention and the comparator side are sufficiently

comparable with regard to their suitability for CAR-T cell therapy or other treatment options. However, it cannot be derived from the available information that the best possible individualized therapy was implemented for the patients in the aQCC cohort, taking into account their general condition.

Moreover, the proportion of patients in the aQCC cohort of the NDS-NHL-001 study who had received autologous stem cell transplantation in the previous therapy amounted to 10% and was thus low. In comparison, the proportion in the studies on lisocabtagene maraleucel was notably higher at approx. 30%. This could also suggest a different health care situation in which the patients found themselves at the beginning of the observation. This is also supported by the different time point from which the follow-up could start for the patients. In the studies on the intervention side, patients were included from 2016 or 2018, while on the comparator side, retrospective observation could begin much earlier due to the inclusion criterion of first diagnosis since 2003. In the dossier, the company provides no information on the index date and thus on the period in which the patients in the aQCC cohort of the NDS-NHL-001 study were actually observed. It is therefore not possible to assess the extent to which there may be differences in the health care situation for the two sides of the comparison and whether autologous stem cell transplantation would not have been preferable as individualized therapy for a larger proportion of patients in the aQCC cohort.

From the available information on the drugs/drug combinations used in the aQCC cohort, it is clear that the therapies used, which the company described as conventional, are mainly (immuno)chemotherapy regimens. However, treatment options to be expected within the framework of the current German health care context, such as antibody-drug conjugates or CAR-T cell therapies were hardly used or not used at all (see Table 4-110 in Section 4.3.2.4.2.1 of Module 4 A of the full dossier assessment). In addition, it must be taken into account that the company considered suitable comparators for individualized therapy that deviated in part from the G-BA's determination (see Chapter I 2). In addition, the information available on the specific use of the treatment regimens for the patients in the aQCC cohort of the NDS-NHL-001 study is insufficient. In the dossier, the company provides neither information on the dosage nor on the duration of treatment. Thus, it cannot be assessed whether the recommendations according to the German Society of Haematology and Medical Oncology (DGHO) [22], which are available for some of the regimens used, have been implemented.

Overall, against this background, it cannot be assessed whether individualized therapy has been implemented for the aQCC cohort of the NDS-NHL-001 study.

Further aspects on the comparison of individual arms based on individual patient data compared to the NDS-NHL-001 study

In addition, the missing information on the general condition as well as on further patient characteristics such as the molecular subtype (47% missing values) or the secondary involvement of the central nervous system (44% missing values) described above mean that confounders identified as relevant by the company itself are not taken into account in the analyses comparing lisocabtagene maraleucel with therapies in the aQCC cohort of the NDS-NHL-001 study. Although the company describes that its systematic search identified 38 potential confounders it considers relevant, it does not consider confounders for its comparisons for which the studies it used provide no information or for which ≥ 30% of the patients have missing values. For example, for the aQCC cohort of the NDS-NHL-001 study, the company does not consider 12 of 29 confounders it describes as relevant and available due to a high percentage of missing values. The company does not discuss the non-consideration of the confounders it has identified as relevant, such as the ECOG PS, the IPI score or the molecular subtype, and does not draw any conclusions from this.

Moreover, apart from results on the outcome of overall survival from the NDS-NHL-001 study, no results on other patient-relevant outcomes are available. Therefore, balancing of the benefits and harms is not possible for the comparison presented by the company on the basis of this study, irrespective of the aspects already described.

Comparison of individual arms versus axicabtagen ciloleucel or tisagenlecleucel

On the basis of the comparisons versus axicabtagen ciloleucel or tisagenlecleucel presented by the company, it is only possible to make statements about patients for whom the use of axicabtagen ciloleucel or tisagenlecleucel represents suitable individualized therapy. Irrespective of this, however, the data presented by the company on the comparison of lisocabtagene maraleucel versus axicabtagen ciloleucel or tisagenlecleucel are not suitable for the benefit assessment. This is justified below.

Comparability of the studies on lisocabtagene maraleucel and axicabtagen ciloleucel

In Module 4 A, the company presents, among other things, separate MAIC-based and naive comparisons of results from the studies TRANSCEND-NHL-001 and TRANSCEND WORLD on lisocabtagene maraleucel with the ZUMA-1 study on axicabtagen ciloleucel as a further CAR-T cell therapy for the outcomes of overall survival, ORR and AEs. In the studies on lisocabtagene maraleucel, there are clear differences with regard to the study design, in particular the inclusion criteria, and the study procedure compared to the study on axicabtagen ciloleucel, which call into question the comparability of the patients on the intervention and comparator side for the analyses presented by the company.

Only patients with chemotherapy-refractory disease or with a relapse after autologous stem cell transplantation were included in the ZUMA-1 study. In the ZUMA-1 study, chemotherapy-refractory was defined as progressive disease or no better response than stable disease with a duration of response ≤ 6 months. Disease was considered relapsed if the relapse occurred within 12 months of an autologous stem cell transplantation or the disease was refractory or unresponsive to the last salvage therapy after an autologous stem cell transplant. In contrast, the studies TRANSCEND-NHL-001 and TRANSCEND WORLD each included patients with refractory or relapsed disease after chemotherapy, and the TRANSCEND-NHL-001 study additionally included patients with refractory or relapsed disease after autologous stem cell transplantation. The degree of response to the last therapy as well as the duration of response were not well defined in the studies on lisocabtagene maraleucel. In contrast to the ZUMA-1 study, the studies on lisocabtagene maraleucel also allowed the inclusion of patients with relapse after the last chemotherapy, i.e. patients whose disease had responded to the last chemotherapy.

Table 6 shows some central characteristics on the disease history of the patients who were included in the studies TRANSCEND-NHL-001 and TRANSCEND WORLD as well as in the ZUMA-1 study.

Table 6: Characteristics of the study population – non-RCT, comparison of individual arms: lisocabtagene maraleucel vs. axicabtagen ciloleucel

Study characteristic category	TRANSCEND-NHL-001 lisocabtagene maraleucel	TRANSCEND WORLD lisocabtagene maraleucel	ZUMA-1 axicabtagen ciloleucel
	N[a] = 291	N[a] = 58	N[a] = 111
Refractory, relapsed or chemotherapy-sensitive disease, n (%)			
Relapse after autologous SCT[b]	45 (15.5)	ND	22 (19.8[c])
Refractory to the last chemotherapy[d], n (%)	160 (55.0)	ND	89 (80.2[c])
Chemotherapy-sensitive[e]	86 (29.6)	9 (15.5)	–
Best response to most recent chemotherapy, n (%)			
Stable disease	ND	ND	15 (13.5[c])
Progressive disease	ND	ND	74 (66.7[c])
Disease stage according to Ann Arbor, n (%)			
I or II	81 (27.8)	26 (44.8[c])	17 (15.3)
III or IV	202 (69.4)	32 (55.2[c])	94 (84.7)
Missing	8 (2.7)	0 (0)	0 (0)
Number of prior lines of systemic therapy, n (%)			
< 4	194[c] (66.7[c])	45[c] (77.6[c])	64[c] (57.7[c])
≥ 4	97[c] (33.3[c])	13[c] (22.4[c])	47[c] (42.3[c])

a. Number of patients who underwent leukapheresis and were thus included. Values which are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. In the studies TRANSCEND-NHL-001 and TRANSCEND WORLD, disease was considered relapsed if a relapse occurred < 12 months after autologous SCT. In the ZUMA-1 study, disease was considered relapsed if a relapse occurred ≤ 12 months after an autologous stem cell transplantation or the disease was refractory or unresponsive to the last salvage therapy after an autologous stem cell transplantation.
c. Institute's calculation.
d. In the studies TRANSCEND-NHL-001 and TRANSCEND WORLD, refractory disease was defined as stable disease or progressive disease as best response. In the ZUMA-1 study, refractory disease was defined as progressive disease or no better response than stable disease with a duration of response ≤ 6 months.
e. In the studies TRANSCEND-NHL-001 and TRANSCEND WORLD, chemotherapy-sensitive disease was defined as a better response than stable disease to the last chemotherapy or a relapse ≥ 12 months after autologous SCT.

n: number of patients in the category; N: number of patients included; ND: no data; SCT: stem cell transplantation

The data show that, as a result of the different inclusion criteria, the ZUMA-1 study only included patients who either had no better response than stable disease to their last

chemotherapy or had a relapse within 12 months of their previous autologous stem cell transplantation. In contrast, approximately 30% and 16% of the patients in the studies on lisocabtagene maraleucel had chemotherapy-sensitive disease and thus a better response than stable disease to their last chemotherapy or relapse after ≥ 12 months following autologous stem cell transplantation. Thus, there are clear differences between the populations of the lisocabtagene maraleucel study and ZUMA-1 in terms of response to the last therapy.

The patients in the ZUMA-1 study were also more often in the more advanced disease stages III and IV according to Ann Arbor (about 85%) than the patients in the TRANSCEND-NHL-001 study (about 69%) or in the TRANSCEND WORLD study (about 55%). In addition, the patients in the ZUMA-1 study also were more often in a later line of therapy (≥ 4) than in the studies on the intervention side.

Treatment with CAR-T cell preparations cannot be initiated immediately after the decision for a Car-T cell therapy. Before treatment, preparations for the patient-specific production of the CAR T-cell preparation are necessary for both treatment with lisocabtagene maraleucel and treatment with axicabtagen ciloleucel [11,16]. These can take several weeks. In the present therapeutic indication, there is therefore a relevant risk that the patients' condition will deteriorate before the CAR-T cells are used. According to the S3 guideline on diagnosis, treatment and follow-up for adult patients with DLBCL and related entities, patients in the present therapeutic indication should be offered systemic treatment to bridge the waiting period until CAR-T cells are used with curative intent [23]. In contrast to the studies on lisocabtagene maraleucel, however, such a bridge therapy between leukapheresis and infusion was not allowed in cohorts 1 and 2 of the ZUMA-1 study, and was accordingly not used in any of the included patients. Nevertheless, there was a median relevant time span of 23 days between leukapheresis and the infusion of CAR-T cells in the study. In contrast, bridge therapy was allowed in the studies on lisocabtagene maraleucel and was used in 64% of patients in the TRANSCEND-NHL-001 study and in 83% of patients in TRANSCEND WORLD.

In summary, due to differences in the study design (inclusion criteria, option of a bridge therapy), there are clear differences between the patients considered. Firstly, the patients in the ZUMA-1 study with axicabtagen ciloleucel only had chemotherapy-refractory disease or early relapsed disease after autologous stem cell transplantation. Secondly, they were in a more advanced stage of the disease and in a later line of treatment than the patients in the studies on lisocabtagene maraleucel. Moreover, the ZUMA-1 study offered no possibility of a bridge therapy between leukapheresis and infusion of the CAR-T cells, whereas this was used for a large proportion of patients in the studies on lisocabtagene maraleucel.

Overall, the comparability of the patients on the intervention and comparator side for the analyses submitted by the company were considered as not given against this background.

Comparability of the studies on lisocabtagene maraleucel and tisagenlecleucel

As already described above for the comparison of the studies on lisocabtagene maraleucel with the ZUMA-1 study, treatment with CAR T-cell preparations cannot be started immediately after the decision for CAR T-cell therapy, and the waiting time until the therapy is applied plays a major role in the present therapeutic indication. As for axicabtagen ciloleucel and lisocabtagene maraleucel, preparations for the patient-specific preparation of the CAR T-cell preparation are also required for treatment with tisagenlecleucel [24]. In Module 4 A, the company presents, among other things, separate MAIC-based and naive comparisons of results from the studies TRANSCEND-NHL-001 and TRANSCEND WORLD on lisocabtagene maraleucel with the JULIET study on tisagenlecleucel as a further CAR-T cell therapy for the outcomes of overall survival, ORR and AEs. In the studies on lisocabtagene maraleucel, however, there are clear differences with regard to the procedure in the preparations before the infusion of the CAR-T cell preparation compared to the study on tisagenlecleucel, which call into question the comparability of the patients on the intervention and the comparator side for the analyses presented by the company.

There are, for instance, differences with regard to the time of study inclusion and thus the start of observation. In the lisocabtagene maraleucel studies, inclusion started with the leukapheresis within 14 days of the start of screening and all patients were observed from the date of leukapheresis. In contrast, in the JULIET study, leukapheresis was either performed during the screening, which took place within 4 to 8 weeks before the planned infusion of tisagenlecleucel, or a so-called historical leukapheresis product was used. Patients were only included in the study after the leukapheresis product had been adopted and accepted by the production sites.

These differences regarding the course of the JULIET study are also reflected in the median times between screening or study inclusion and infusion or study exit for the JULIET study. As already described in Section I 3.1, the time between screening examinations, which included leukapheresis, and infusion with tisagenlecleucel or study withdrawal was significantly prolonged for the JULIET study compared to the studies on lisocabtagene maraleucel (in the JULIET study a median of 112 days in contrast to 37 days and 42 days in the TRANSCEND-NHL-001 and TRANSCEND WORLD studies, respectively). The time between leukapheresis and infusion in the JULIET study was thus also significantly longer than the time specified for production and release of the CAR-T cells according to the SPCs of tisagenlecleucel [24], which is usually 3 to 4 weeks. Thus, on the comparator side, the waiting time until therapy is clearly prolonged - in contrast to the specifications of the SPC. According to information in the EMA assessment report for tisagenlecleucel, this was due to problems during the production of the CAR-T cells. [25]. The EMA critically discussed the delay in the assessment report within the framework of the approval, and the company had to demonstrate that the production problems had been rectified for the approval.

In addition, study inclusion in the JULIET study, with a median of 54 days before infusion or study withdrawal, also occurred with a significant delay compared to leukapheresis (median 112 days before infusion or study entry). Thus, observation in the JULIET study also began with a clear delay in relation to leukapheresis. In contrast, observation of the patients in the studies on lisocabtagene maraleucel started immediately after leukapheresis and thus much earlier.

The differences described are also reflected in the further course of the study. Thus, it can be assumed that due to the longer waiting time, more patients from the JULIET study (32%) dropped out before the cells were infused than from TRANSCEND-NHL-001 and TRANSCEND WORLD (22 to 24%). In addition, significantly more patients in the JULIET study needed bridge therapy (88.6%) than in TRANSCEND-NHL-001 and TRANSCEND WORLD (63.6% and 74.1% respectively). This indicates a higher proportion of patients with worsening of the disease on the comparator side. Moreover, due to the more frequent use of bridging, side effects following infusion may also occur more frequently on the comparator side than on the intervention side. Due to the different time point of study inclusion on the intervention and the comparator side, there could also be differences in the recording of the outcomes due to a shortened observation period for the comparator therapy.

Overall, the comparability of the patients on the intervention and comparator side for the analyses submitted by the company were considered as not given against this background.

Further aspects on the comparison of lisocabtagene maraleucel with axicabtagen ciloleucel or tisagenlecleucel

Irrespective of the content-related aspects described above, the MAIC analyses submitted by the company to compare the results of lisocabtagene maraleucel with the results of the ZUMA-1 study or the JULIET study are not suitable for the benefit assessment.

In case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data [26]. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Thus, comparisons based on MAIC analyses without a common comparator are generally not suitable for the assessment of an added benefit.

In the MAIC analyses presented by the company for the comparison of lisocabtagene maraleucel with axicabtagen ciloleucel, a very large proportion of patients from the studies on lisocabtagene maraleucel are also not taken into account. This is mainly due to the fact that the company only considered 36% or 17% of patients who did not receive bridge therapy for these comparisons from the studies on lisocabtagene maraleucel. However, these patients only present a minor proportion of the study populations. In contrast, all patients from the ZUMA-1 study are included in the analyses, thus also those who might have needed a bridge

therapy but did not receive it due to the requirements of the study. In addition to the aspects described above regarding the patients included, this also contributes to the fact that the analyses presented for the comparison of axicabtagen ciloleucel with lisocabtagene maraleucel are not suitable for the present benefit assessment.

In addition, the analyses submitted by the company do not show any effects for the outcomes considered by the company, with the exception of some specific AE outcomes, for which it can be ruled out with sufficient certainty that they do not result solely from systematic bias due to confounders.

For the specific AE outcomes, however, there are additional aspects that call comparability into question. For example, the severity of the AE "severe cytokine release syndrome" was not determined according to the Common Terminology Criteria for Adverse Events (CTCAE) in both the studies on lisocabtagene maraleucel and the study on tisagenlecleucel. According to information in the dossier, a cytokine release syndrome could be classified as grade 3 and thus as severe in the studies TRANSCEND-NHL-001 and TRANSCEND WORLD if multiple or high-dose vasopressors had to be used, whereas in the JULIET study the use of low-dose vasopressors could already lead to a classification as grade 3. Consequently, the severe cytokine release syndrome was recorded on the comparator side using a potentially broader operationalization than on the intervention side, and the comparability of results for intervention and comparator therapy is not given for this specific AE outcome.

In contrast, the operationalization of the severity of the cytokine release syndrome in the studies on lisocabtagene maraleucel and the ZUMA-1 study was largely comparable. However, the measures for managing the events that occurred were much stricter in the studies on lisocabtagene maraleucel. Thus, in these studies, the use of tocilizumab and/or dexamethasone was already possible from grade 1 if the symptoms occurred within 72 hours after the infusion of the CAR-T cells. However, in the ZUMA-1 study, the use of these drugs was only planned for AEs of grade 2 and above and with simultaneous presence of extensive comorbidities or old age. For grade 1 AEs, the ZUMA-1 study only intended treatment of symptoms with antipyretics or analgesics. Another difference between the studies on lisocabtagene maraleucel and axicabtagen ciloleucel is also evident in the use of premedication before the infusion of CAR-T cells. According to the study protocol, regular use of paracetamol and diphenhydramine as premedication was not planned for cohorts 1 and 2 of the ZUMA-1 study. The information in the benefit assessment procedure on axicabtagen ciloleucel (G-BA process number 2022-05-15-D-820) [17] shows that in some cases these drugs were used in only half of the patients (recorded over a period of 3 months from the infusion of axicabtagen ciloleucel). In the studies on lisocabtagene maraleucel, on the other hand, premedication with these drugs was planned for all patients according to the study design. This difference in the use of these antiemetic, antipyretic and analgesic drugs as

premedication could also have an impact on the occurrence of AEs that may occur following CAR-T cell administration. Overall, against the background of the differences in premedication and in the handling of events that occurred, it remains unclear whether the results on specific AEs for intervention and comparator therapy are comparable.

Moreover, as already described in Chapter I 3, the completeness of the study pool for the comparison of lisocabtagene maraleucel versus axicabtagen ciloleucel or tisagenlecleucel is questionable, as the company's bibliographic search identified some studies on axicabtagen ciloleucel and/or tisagenlecleucel, but did not consider these studies without further explanation.

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of lisocabtagene maraleucel in comparison with the ACT. For the comparisons of individual arms from different studies on lisocabtagene maraleucel presented by the company with treatment options it described as conventional, this is due in particular to the fact that the implementation of individualized therapy taking into account the lymphoma subentity, the biology of the disease, the previous therapy, the course of the disease and the general condition as ACT cannot be assessed on the basis of the insufficient information, for example on patient characteristics. Apart from results on the outcome of overall survival, there are also no results on other patient-relevant outcomes for the comparator side, so that a balancing of the benefits and harms is not possible. The comparisons of individual arms from different studies on lisocabtagene maraleucel with axicabtagen ciloleucel or tisagenlecleucel presented by the company are not suitable for conclusions on the added benefit, as the comparability of the patients on the intervention and the comparator side for the analyses presented by the company is not considered to be given due to differences in the design and procedure of the studies.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of lisocabtagene maraleucel compared with the ACT in adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after 2 or more lines of systemic treatment. There was no hint of an added benefit of lisocabtagene maraleucel in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of lisocabtagene maraleucel in comparison with the ACT is summarized in Table 7.

Table 7: Lisocabtagene maraleucel – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with relapsed or refractory DLBCL, PMBCL and FL3B after 2 or more lines of systemic therapy	Individual therapy[b, c] taking into account the lymphoma subentity, disease biology, prior therapy, course of disease and general condition	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Within the framework of a clinical trial, the following therapies are considered suitable comparators for the individualized therapy:

- ASHAP, bendamustine, CEPP, CEOP, DHAP, DHAX, DICEP, dose-adjusted EPOCH, ESHAP, GemOx, GDP, gemcitabine + vinorelbine, ICE, lenalidomide (only for patients with non-GCB DLBCL), MEP, MINE, PEPC, each of the therapies mentioned ± rituximab

as well as

- polatuzumab vedotin + bendamustine + rituximab, tafasitamab + lenalidomide, monotherapy brentuximab vedotin (only for patients with CD30+ DLBCL), monotherapy chlorambucil, monotherapy etoposide, monotherapy pixantrone, gemcitabine + rituximab, monotherapy rituximab, monotherapy ibrutinib (only for patients with non-GCB DLBCL), axicabtagene ciloleucel, tisagenlecleucel, radiation or BSC.
- Moreover, stem cell transplantation (autologous or allogeneic) is considered a component of the individualized therapy.

c. It is assumed that for suitable patients, rituximab will be used as part of salvage chemotherapy (e.g. no receipt of rituximab in prior therapy, no refractivity to rituximab, existing CD20 expression in lymphoma).

ASHAP: doxorubicin, methylprednisolone, cytarabine, cisplatin; BSC: best supportive care; CD: cluster of differentiation; CEPP: cyclophosphamide, etoposide, prednisone, procarbazine; CEOP: cyclophosphamide, etoposide, vincristine, prednisone; DHAP: dexamethasone, cisplatin, cytarabine; DHAX: dexamethasone, cytarabine, oxaliplatin; DICEP: dose-intensified cyclophosphamide, etoposide, cisplatin; DLBCL: diffuse large B-cell lymphoma; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; FL3B: follicular lymphoma grade 3B; G-BA: Federal Joint Committee; GCB: germinal centre B-cell type; GemOx: gemcitabine, oxaliplatin; GDP: gemcitabine, dexamethasone, cisplatin or carboplatin; ICE: ifosfamide, carboplatin, etoposide; MEP: methotrexate, etoposide, cisplatin; MINE: mesna, ifosfamide, mitoxantrone, etoposide; PEPC: prednisolone, etoposide, procarbazine, cyclophosphamide; PMBCL: primary mediastinal large B-cell lymphoma

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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