# Lisocabtagene maraleucel (follicular lymphoma)

## 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**

No feedback of persons concerned was received within the framework of the present dossier assessment.

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# Part I: Benefit assessment

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# I List of tables[2]

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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 |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MAIC | matching-adjusted-indirect-comparison |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SmPC | Summary of Product Characteristics |

## I 1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 11 April 2025.

### Research question

The aim of this report is to assess the added benefit of lisocabtagene maraleucel in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

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

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy | Individualized treatment[d, e] choosing from<br>▪ bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization,<br>▪ lenalidomide + rituximab,<br>▪ rituximab monotherapy,<br>▪ mosunetuzumab,<br>▪ tisagenlecleucel and<br>▪ zanubrutinib in combination with obinutuzumab |

a. Presented is the ACT specified by the G-BA.
b. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the therapeutic indication, when determining the ACT, the G-BA assumes that lisocabtagene maraleucel is not an option for the treatment of diagnosed grade 3b follicular lymphoma in this therapeutic indication. This subentity is not assigned to the indolent non-Hodgkin lymphomas. Accordingly, the new WHO classification 2022 for lymphoid tumours uses the new term "follicular large cell lymphoma" to distinguish the entity formerly known as "follicular lymphoma grade 3b" from the classic follicular lymphomas (grades 1 to 3a).
c. For this therapeutic indication, the G-BA assumes that for patients with follicular lymphoma, due to a correspondingly advanced stage of the disease particularly with regard to a symptomatic course (e.g. according to the GELF criteria), there is an indication for systemic antineoplastic therapy and therefore, among other things, a watchful waiting strategy is not an option. Further, patients are presumed not to be therapeutically indicated for radiotherapy at the time of treatment with lisocabtagene maraleucel. For this therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time point of treatment with lisocabtagene maraleucel.
d. The treatment decision is made in particular taking into account the prior therapy, the course of the disease and the patient's general condition.
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The initial individualized treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; WHO: World Health Organization

The G-BA adjusted the ACT on 25 February 2025. The company deviated from the current ACT specified by the G-BA. It also considers individualized treatment to be an ACT, taking into account the previous therapy, the course of the disease and the patient's general condition, although in some cases it names other or additional therapy options. For example, the company names mosunetuzumab and tisagenlecleucel as treatment options in the context of individualized treatment, in line with the G-BA's specification, but also names axicabtagene-ciloleucel (for patients with at least 3 previous systemic therapies) and epcoritamab as treatment options, which deviates from the G-BA's ACT. The company does not consider the 3 other options named by the G-BA (bendamustine + obinutuzumab, lenalidomide + rituximab

and rituximab as monotherapy) to be part of the ACT. The company did not comment on the treatment option zanubrutinib in combination with obinutuzumab, as this combination was not included in the ACT named by the G-BA at the time of its consultation with the G-BA on 26 September 2024. The company's deviations remain without consequences for the present benefit assessment, as it presents suitable data neither on the treatment options specified by the G-BA nor on those specified by itself.

The present assessment was conducted in comparison with the G-BA's ACT (see Table 2). The assessment was 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 for completeness of the study pool revealed no randomized controlled trial (RCT) for the research question that allowed either a direct comparison or an adjusted indirect comparison via a common comparator of lisocabtagene maraleucel versus the ACT specified by the G-BA for the research question.

It should be noted that the company lists the TRANSFORM FL study in Module 4 C. This is an RCT comparing lisocabtagene maraleucel with rituximab + cyclophosphamide + doxorubicin + vincristine sulphate + prednisone (R-CHOP) or bendamustine + rituximab or lenalidomide + rituximab in adults with relapsed or refractory follicular lymphoma. Thus, the study investigates an option of individualized treatment according to the ACT of the present benefit assessment (lenalidomide + rituximab). The study could thus include a potentially relevant subpopulation for the research question of the present benefit assessment. However, in Module 4 C, the company states that this study was discontinued and therefore no results are available.

For the benefit assessment, the company presented the results of the single-arm pivotal study TRANSCEND FL with lisocabtagene maraleucel as well as the study CA082-092. The CA082-092 study compared data from the TRANSCEND FL study with data from one study each on mosunetuzumab (GO29781 study), tisagenlecleucel (ELARA study) and axicabtagene-ciloleucel (ZUMA-5 study).

The evidence presented by the company is not suitable for the derivation of an added benefit of lisocabtagene maraleucel in comparison with the ACT specified by the G-BA.

***Evidence provided by the company***

*TRANSCEND FL study*

The ongoing study TRANSCEND FL is a single-arm, multicentre phase II study on treatment with lisocabtagene maraleucel. The study included adult patients with histologically confirmed grade 1, 2 or 3a follicular lymphoma or marginal zone lymphoma. To be enrolled in the study,

patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 and at least 1 measurable lesion.

In accordance with the present therapeutic indication (at least 2 previous systemic therapies), the company only considered the patient population of cohorts 1 and 2 (114 of the total of 139 [82%] patients in the TRANSCEND FL study). The previous therapies of these patients had to have contained a monoclonal anti-cluster of differentiation (CD)20 drug in combination with an alkylating agent. Stem cell transplantation was permitted as a previous therapy.

Lisocabtagene maraleucel treatment was in compliance with the Summary of Product Characteristics (SmPC). In the time between leukapheresis and lymphodepleting chemotherapy, all patients could receive systemic anti-cancer therapies or radiotherapies for disease control (bridging therapy).

The study's primary outcome was overall response rate. Further secondary outcomes are outcomes in the categories mortality, morbidity, health-related quality of life, and side effects.

*Study CA082-092*

The CA082-092 study involves comparisons of individual arms from different studies, consisting of patient-specific data from the single-arm study TRANSCEND FL on lisocabtagene maraleucel (intervention side) each in comparison with aggregated data from the single-arm studies GO29781 on mosunetuzumab, ELARA on tisagenlecleucel and ZUMA-5 on axicabtagene-ciloleucel (comparator side) in patients with relapsed or refractory follicular lymphoma after 2 or more lines of therapy.

For the comparisons of lisocabtagene maraleucel (TRANSCEND FL study) with mosunetuzumab, tisagenlecleucel or axicabtagene-ciloleucel, the company presented both a naive comparison and matching-adjusted-indirect-comparison (MAIC) analyses without a common comparator as main and sensitivity analyses for the outcomes response, progression-free survival and individual specific AEs in Module 4 C.

***Studies TRANSCEND FL and CA082-092 unsuitable for the benefit assessment***

The evidence presented by the company is not suitable for the derivation of an added benefit of lisocabtagene maraleucel in comparison with the ACT specified by the G-BA.

For the TRANSCEND FL study, this is due to the fact that it is a single-arm study and a comparison with the ACT is therefore impossible.

For the CA082-092 study, the unsuitability of the comparisons with mosunetuzumab and tisagenlecleucel is mainly due to the fact that MAIC analyses without a common comparator

are generally not an adequate option for confounder adjustment. Irrespective of this, there are further serious shortcomings in the company's approach:

- The study pool on the comparator side is potentially incomplete.
- The company’s approach for the identification of confounders is not appropriate. Systematic confounder identification was not carried out.
- In Module 4 C, the company does not present any patient-relevant outcomes for the outcome categories mortality, morbidity and health-related quality of life. It is therefore not possible to weigh up the positive and negative effects across all outcome categories for the comparison presented.

The comparison of lisocabtagene maraleucel with axicabtagene ciloleucel conducted in the study is not relevant for this benefit assessment, as this option does not correspond to the ACT.

**Results on added benefit**

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of lisocabtagene maraleucel in comparison 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** |
|---|---|---|
| Adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy | Individualized treatment[d, e] choosing from<br>▪ bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization,<br>▪ lenalidomide + rituximab,<br>▪ rituximab monotherapy,<br>▪ mosunetuzumab,<br>▪ tisagenlecleucel and<br>▪ zanubrutinib in combination with obinutuzumab | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the therapeutic indication, when determining the ACT, the G-BA assumes that lisocabtagene maraleucel is not an option for the treatment of diagnosed grade 3b follicular lymphoma in this therapeutic indication. This subentity is not assigned to the indolent non-Hodgkin lymphomas. Accordingly, the new WHO classification 2022 [3] for lymphoid tumours uses the new term "follicular large cell lymphoma" to distinguish the entity formerly known as "follicular lymphoma grade 3b" from the classic follicular lymphomas (grades 1 to 3a).
c. For this therapeutic indication, the G-BA assumes that for patients with follicular lymphoma, due to a correspondingly advanced stage of the disease particularly with regard to a symptomatic course (e.g. according to the GELF criteria), there is an indication for systemic antineoplastic therapy and therefore, among other things, a watchful waiting strategy is not an option. Further, patients are presumed not to be therapeutically indicated for radiotherapy at the time of treatment with lisocabtagene maraleucel. For this therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time point of treatment with lisocabtagene maraleucel.
d. The treatment decision is made in particular taking into account the prior therapy, the course of the disease and the patient's general condition.
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The initial individualized treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; WHO: World Health Organization

The G-BA decides on the added benefit.

## I 2 Research question

The aim of this report is to assess the added benefit of lisocabtagene maraleucel in comparison with the ACT in adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

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

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy | Individualized treatment[d, e] choosing from<br>▪ bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization,<br>▪ lenalidomide + rituximab,<br>▪ rituximab monotherapy,<br>▪ mosunetuzumab,<br>▪ tisagenlecleucel and<br>▪ zanubrutinib in combination with obinutuzumab |

a. Presented is the ACT specified by the G-BA.
b. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the therapeutic indication, when determining the ACT, the G-BA assumes that lisocabtagene maraleucel is not an option for the treatment of diagnosed grade 3b follicular lymphoma in this therapeutic indication. This subentity is not assigned to the indolent non-Hodgkin lymphomas. Accordingly, the new WHO classification 2022 [3] for lymphoid tumours uses the new term "follicular large cell lymphoma" to distinguish the entity formerly known as "follicular lymphoma grade 3b" from the classic follicular lymphomas (grades 1 to 3a).
c. For this therapeutic indication, the G-BA assumes that for patients with follicular lymphoma, due to a correspondingly advanced stage of the disease particularly with regard to a symptomatic course (e.g. according to the GELF criteria), there is an indication for systemic antineoplastic therapy and therefore, among other things, a watchful waiting strategy is not an option. Further, patients are presumed not to be therapeutically indicated for radiotherapy at the time of treatment with lisocabtagene maraleucel. For this therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time point of treatment with lisocabtagene maraleucel.
d. The treatment decision is made in particular taking into account the prior therapy, the course of the disease and the patient's general condition.
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The initial individualized treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; WHO: World Health Organization

The G-BA adjusted the ACT on 25 February 2025. The company deviated from the current ACT specified by the G-BA. It also considers individualized treatment to be an ACT, taking into account the previous therapy, the course of the disease and the patient's general condition, although in some cases it names other or additional therapy options. For example, the company names mosunetuzumab and tisagenlecleucel as treatment options in the context of individualized treatment, in line with the G-BA's specification, but also names axicabtagene-ciloleucel (for patients with at least 3 previous systemic therapies) and epcoritamab as treatment options, which deviates from the G-BA's ACT. The company does not consider the 3 other options named by the G-BA (bendamustine + obinutuzumab, lenalidomide + rituximab and rituximab as monotherapy) to be part of the ACT. The company did not comment on the treatment option zanubrutinib in combination with obinutuzumab, as this combination was not included in the ACT named by the G-BA at the time of its consultation with the G-BA on 26 September 2024. The company's deviations remain without consequences for the present benefit assessment, as it presents suitable data neither on the treatment options specified by the G-BA nor on those specified by itself.

The present assessment was conducted in comparison with the G-BA's ACT (see Table 4Table 4). The assessment was 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

Sources used by the company in the dossier:

- Study list on lisocabtagene maraleucel (status: 03 February 2025)
- Bibliographical literature search on lisocabtagene maraleucel (last search on 3 February 2025)
- Search in trial registries/trial results databases for studies on lisocabtagene maraleucel (last search on 10 February 2025)
- Search on the G-BA website for lisocabtagene maraleucel (last search on 10 February 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on lisocabtagene maraleucel (last search on 5 May 2025); for search strategies, see I Appendix A of the full dossier assessment

**Direct comparison**

Concurring with the company, the check for completeness of the study pool revealed no RCT for the research question that allowed either a direct comparison or an adjusted indirect comparison via a common comparator of lisocabtagene maraleucel versus the ACT specified by the G-BA for the research question.

It should be noted that the company lists the TRANSFORM FL study in Module 4 C [4]. This is an RCT comparing lisocabtagene maraleucel with R-CHOP or bendamustine + rituximab or lenalidomide + rituximab in adults with relapsed or refractory follicular lymphoma. Thus, the study investigates an option of individualized treatment according to the ACT of the present benefit assessment (lenalidomide + rituximab). The study could thus include a potentially relevant subpopulation for the research question of this benefit assessment. However, in Module 4 C, the company states that this study was discontinued and therefore no results are available.

**Further investigations**

The company conducted an information retrieval for further studies with lisocabtagene maraleucel. It identified the pivotal single-arm study TRANSCEND FL [5] and the non-interventional study CA082-092 [6,7], which it used jointly for the benefit assessment. The CA082-092 study compared data from the TRANSCEND FL study with data from one study each on mosunetuzumab (GO29781 study [8]), tisagenlecleucel (ELARA study [9]) and axicabtagene-ciloleucel (ZUMA-5 study [10]). In addition, the pU refers to the results of the retrospective study CA082-013 [11], which it had submitted as supplementary information for

the marketing authorization, but had not comprehensively processed it and did not use it to derive the added benefit.

The company did not conduct an information retrieval for the ACT.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of lisocabtagene maraleucel compared to the ACT for the patients in this therapeutic indication. Section I 3.1 describes the evidence presented by the company, and the reasons for its unsuitability for the benefit assessment are provided.

### I 3.1 Evidence provided by the company

**TRANSCEND FL study**

The ongoing study TRANSCEND FL is a single-arm, multicentre phase II study on treatment with lisocabtagene maraleucel. The study included adult patients with histologically confirmed grade 1, 2 or 3a follicular lymphoma or marginal zone lymphoma. Patients with confirmed or previous combination of diffuse large B-cell lymphoma and follicular lymphoma, with transformed follicular lymphoma or duodenal type follicular lymphoma according to the subclassification of the World Health Organization were excluded from participation in the study. To be enrolled in the study, patients had to have an ECOG PS ≤ 1 and at least 1 measurable lesion.

The study investigates different patient populations: patients with relapsed and refractory follicular lymphoma with at least 3 prior systemic therapies (Cohort 1), with 2 prior systemic therapies (Cohort 2), with 1 prior systemic therapy (Cohort 3 and Cohort 3 Extension) and patients with relapsed or refractory marginal zone lymphoma with at least 2 prior systemic therapies (Cohort 4).

In accordance with the present therapeutic indication (at least 2 previous systemic therapies), the company only considered the patient population of Cohorts 1 and 2 (114 of the total of 139 [82%] patients in the TRANSCEND FL study). The previous therapies of these patients had to have contained a monoclonal anti-CD20 drug in combination with an alkylating agent. Stem cell transplantation was permitted as a previous therapy.

Treatment with lisocabtagene maraleucel was in compliance with the recommendations of the SmPC [12]. According to the study design, leukapheresis for the sampling of peripheral blood mononuclear cells for the production of lisocabtagene maraleucel should be performed approximately 5 weeks prior to infusion with lisocabtagene maraleucel. Lymphodepleting chemotherapy was given over 3 days and was to be initiated between Days 9 to 4 before the infusion of lisocabtagene maraleucel. In the time between leukapheresis and lymphodepleting chemotherapy, all patients could receive systemic anti-cancer therapies or radiotherapies for

disease control (bridging therapy). The study provided for the use of lisocabtagene maraleucel at a dose of 100 x $10^6$ anti-CD19 CAR-T cells per kg body weight.

The study's primary outcome was overall response rate. Further secondary outcomes are outcomes in the categories mortality, morbidity, health-related quality of life, and side effects.

In Module 4 C, results for 2 data cut-offs were available at the time of dossier preparation. The data cut-off for the first interim analysis was 27 January 2023. In addition, the company described that an addendum to the first interim analysis had been prepared, which was submitted to the European regulatory agency for approval and was carried out with a data cut-off date of 10 January 2024. The company used the data cut-off of 10 January 2024 for the presentation of the results of the TRANSCEND FL study (median follow-up: 31.5 months). In the CA082-092 study described below, the data cut-off of 27 January 2023 was considered for the TRANSCEND FL study (median follow-up: 19.3 months).

**Study CA082-092**

The CA082-092 study compares individual arms from different studies, consisting of patient-specific data from the single-arm TRANSCEND FL study on lisocabtagene maraleucel (intervention side, see above for description), with aggregated data from the single-arm GO29781 study on mosunetuzumab, ELARA on tisagenlecleucel, and ZUMA-5 on axicabtagene ciloleucel (comparator side) in patients with relapsed or refractory follicular lymphoma after 2 or more lines of therapy.

The single-arm GO29781 study investigated mosunetuzumab in adult patients with relapsed or refractory follicular lymphoma (grade 1, 2 and 3a). Patients had received at least 2 previous lines of therapy, including anti-CD20 therapy and an alkylating agent. The study included a total of 90 patients. Treatment with mosunetuzumab was in compliance with the SmPC. Primary outcome of the study was complete response. The data cut-off of 27 August 2021 with a median follow-up of approx. 18 months was used for the CA082-092 study.

The single-arm study ELARA investigated tisagenlecleucel in adult patients with histologically confirmed, relapsed or refractory follicular lymphoma (grade 1, 2 and 3a) after 2 or more prior lines of therapy or after an autologous stem cell transplantation. After leukapheresis, optional bridging therapy and lymphodepletion with fludarabine and cyclophosphamide or bendamustine, the patients received an infusion of tisagenlecleucel. 94 of 98 enrolled patients who had received an infusion of tisagenlecleucel and had had measurable disease prior to the infusion were included in the analysis. Primary outcome of the study was complete response. The data cut-off of 29 March 2021 with a median follow-up of approx. 17 months was used for the CA082-092 study.

The single-arm study ZUMA-5 investigated axicabtagene ciloleucel in adult patients with histologically confirmed relapsed or refractory follicular lymphoma (grade 1, 2 and 3a) or marginal zone lymphoma. Patients with at least 2 prior lines of therapy were included. The prior therapies had to have included an anti-CD20 therapy combined with an alkylating agent. After leukapheresis, optional bridging therapy and lymphodepletion, the patients received axicabtagene ciloleucel. 124 out of 127 patients with relapsed or refractory follicular lymphoma included in the study received an infusion with axicabtagene-ciloleucel. Primary outcome of the study was the overall response rate. The data cut-off of 14 September 2020 with a median follow-up of approx. 24 and approx. 18 months (morbidity outcomes and outcomes on adverse events (AEs) was used for the CA082-09 study.

For the comparisons of lisocabtagene maraleucel of the TRANSCEND FL study with mosunetuzumab, tisagenlecleucel or axicabtagene-ciloleucel, the company presented both an unadjusted comparison (“naive” comparison) and matching-adjusted indirect comparison (MAIC) analyses without a common comparator as main and sensitivity analyses for the outcomes response, progression-free survival and individual specific AEs in Module 4 C. No analyses are available for the outcome overall survival, as, according to the company, these were not conducted due to the low number of events at the time of the data cut-off considered.

**Comment on a study presented by the company as supplementary information (study CA082-013)**

The company refers to the retrospective study CA082-013 submitted as supplementary information for the marketing authorization and investigating lisocabtagene maraleucel in patients with relapsed and refractory follicular lymphoma. The company excluded this study on the grounds that the comparator therapies included did not represent the current state of medical knowledge or the reality of treatment in this therapeutic indication and were therefore not to be considered part of the ACT. Accordingly, the company does not analyse in detail the study in Module 4 C, but nevertheless describes the results as supplementary information in the summarized description of the added benefit (Section 4.4.2 in Module 4 C) in order to classify the clinical relevance of lisocabtagene maraleucel in comparison with various treatment options, some of which the G-BA considers to be part of the ACT in the company's view.

The CA082-013 study compared individual patient data on lisocabtagene maraleucel from the single-arm study TRANSCEND FL by means of an indirect comparison without common comparator and propensity score-based methods with individual patient data from various databases and from the studies AUGMENT (CC-5013-NHL-007 [13]) and MAGNIFY (CC-5013-NHL-008 [14]). The comparator side (pooled data from the databases and from the studies

AUGMENT and MAGNIFY) includes therapies such as lenalidomide in combination with rituximab, rituximab as monotherapy, and bendamustine in combination with obinutuzumab.

In agreement with the company, the CA082-013 study was classified as unsuitable for the derivation of an added benefit of lisocabtagene maraleucel. Irrespective of a further methodological review of the adjustment procedure used, this is partly due to the potentially incomplete study pool on the comparator side (see explanations above). Moreover, no systematic confounder identification was described.

### I 3.2 Assessment of the evidence presented by the company

**TRANSCEND FL study**

The TRANSCEND FL study presented by the company is a single-arm study. The study is therefore unsuitable for deriving an added benefit of lisocabtagene maraleucel in comparison with the ACT specified by the G-BA.

**Study CA082-092**

The CA082-092 study presented by the company is unsuitable for deriving the added benefit of lisocabtagene maraleucel.

The comparison of lisocabtagene maraleucel with axicabtagene ciloleucel conducted in the study is not relevant for this benefit assessment, as this option does not correspond to the ACT.

The unsuitability of the comparisons of lisocabtagene maraleucel with mosunetuzumab and tisagenlecleucel is mainly due to the fact that MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment. Irrespective of this, there are further serious shortcomings in the company's approach:

- The study pool on the comparator side is potentially incomplete.
- The company’s approach for the identification of confounders is not appropriate. Systematic confounder identification was not carried out.
- In Module 4 C, the company does not present any patient-relevant outcomes for the outcome categories mortality, morbidity and health-related quality of life. It is therefore not possible to weigh up the positive and negative effects across all outcome categories for the comparison presented.

The mentioned points of unsuitability for the benefit assessment are explained below.

***Comparisons of individual arms of different studies are not suitable for the benefit assessment***

MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [1]. In case of non-randomized comparisons without a common comparator, meaningful comparisons for the confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data [15]. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data.

If such analyses are available, it must be examined whether there are effects for which it can be ruled out with sufficient certainty that they are not based solely on systematic bias due to confounders. In Module 4 C, however, the company does not present any results on patient-relevant outcomes. Regardless of this, there are no such effects for the outcomes considered by the company.

***Incomplete study pool on the comparator side***

Since, as described above, the company did not identify any RCT that allowed a direct comparison or an adjusted indirect comparison via a common comparator of lisocabtagene maraleucel versus the ACT, it conducted an information retrieval on further studies on the intervention side. The company did not conduct an information retrieval for the ACT. Overall, the study pool on the comparator side is therefore potentially incomplete.

***Identification and completeness of confounders not appropriate***

The necessary structural equality between the treatment groups is not guaranteed in non-randomized studies; therefore, group differences in possible confounders, i.e. factors which are related to both treatment and outcomes and can thus alter the estimation of the treatment effect, must be taken into account in the estimation. The first prerequisite for this is that relevant confounders are systematically identified [15,16] as described, for example, in Pufulete 2022 [16] and in the IQWiG working paper GA23-02 [17]. Then it must be ensured that the dataset used contains the necessary information on the identified confounders. Based on this, suitable adjustment methods (e.g. propensity score weighting) must be used to adequately take into account a potential distorting effect of confounders [15].

The company's approach for the identification of confounders is not appropriate. According to Module 4 C of the dossier, confounders relevant to the therapeutic indication were identified chiefly based on the inclusion and exclusion criteria and patient characteristics of the TRANSCEND FL, GO29781, ELARA and ZUMA-5 studies. In addition, according to the company, a targeted review of confounders reported in other MAIC analyses conducted in the therapeutic indication and in the underlying studies was conducted, and clinical experts were consulted.

According to the company, a total of 40 potentially relevant confounders were identified and ranked by clinical experts on the basis of their prognostic strength or the degree of modification of the treatment effect for the outcomes of interest, regardless of data availability. 6 clinical experts (2 per comparison) were involved in determining the ranking.

For each of the 3 comparisons, the factors to be considered were subsequently selected based on, among other things, the availability of data between the comparative studies. The information in the study report shows that the studies provided data only for a few (< 20) of the 40 factors potentially relevant for the comparisons. In addition, this data-driven approach considered different confounders for the three comparisons. For example, 9 confounders were considered for morbidity outcomes in the comparison of lisocabtagene maraleucel with mosunetuzumab, 12 in the comparison with tisagenlecleucel and 11 in the comparison with axicabtagene-ciloleucel.

Overall, the company's approach does not ensure systematic identification of the confounders. In addition, the steps taken to identify confounders are insufficiently documented. The lack of data availability on various confounders involves no consequences for the conduction of the analyses. A potentially data-driven adjustment was made for some of the potentially relevant confounders. This approach is not appropriate.

***An overall assessment of the positive and negative effects across all outcome categories not possible***

Among others, the company presents results on the outcomes overall response, progression-free survival and various specific AE outcomes in Module 4 C.

No results are available on patient-relevant outcomes in the categories mortality, morbidity and health-related quality of life (data cut-off TRANSCEND FL 27 January 2023).

Altogether, an overall assessment of the positive and negative effects of lisocabtagene maraleucel across all outcome categories is therefore not possible on the basis of the comparisons presented by the company, irrespective of the other points described above.

**Summary**

Overall, the data presented by the company are not suitable for the benefit assessment and do not allow an adequate comparison of lisocabtagene maraleucel with the ACT.

## I 4 Results on added benefit

The company has not submitted any suitable data for assessing the added benefit of lisocabtagene maraleucel in comparison with the ACT in adult patients with relapsed or refractory follicular lymphoma following 2 or more lines of systemic therapy. There is no hint of an added benefit of lisocabtagene maraleucel compared to 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 5.

Table 5: Lisocabtagene maraleucel – probability and extent of added benefit

| Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| Adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy | Individualized treatment[d, e] choosing from<br>▪ bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization<br>▪ lenalidomide + rituximab,<br>▪ rituximab monotherapy,<br>▪ mosunetuzumab,<br>▪ tisagenlecleucel and<br>▪ zanubrutinib in combination with obinutuzumab | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the therapeutic indication, when determining the ACT, the G-BA assumes that lisocabtagene maraleucel is not an option for the treatment of diagnosed grade 3b follicular lymphoma in this therapeutic indication. This subentity is not assigned to the indolent non-Hodgkin lymphomas. Accordingly, the new WHO classification 2022 [3] for lymphoid tumours uses the new term "follicular large cell lymphoma" to distinguish the entity formerly known as "follicular lymphoma grade 3b" from the classic follicular lymphomas (grades 1 to 3a).
c. For this therapeutic indication, the G-BA assumes that for patients with follicular lymphoma, due to a correspondingly advanced stage of the disease particularly with regard to a symptomatic course (e.g. according to the GELF criteria), there is an indication for systemic antineoplastic therapy and therefore, among other things, a watchful waiting strategy is not an option. Further, patients are presumed not to be therapeutically indicated for radiotherapy at the time of treatment with lisocabtagene maraleucel. For this therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time point of treatment with lisocabtagene maraleucel.
d. The treatment decision is made in particular taking into account the prior therapy, the course of the disease and the patient's general condition.
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualised treatment decisions (multi-comparator study). The initial individualized treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; WHO: World Health Organization

The assessment described above deviates from that by 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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