Loncastuximab tesirine (relapsed or refractory diffuse large B-cell lymphoma); requirement of routine practice data collection and evaluations

Resolution of: 17 July 2025
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Requirement of routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient loncastuximab tesirine:

Therapeutic indication (according to the marketing authorisation of 20 December 2022):

Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

Therapeutic indication for the requirement of routine practice data collection and evaluations (resolution of 17 July 2025):

Treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy, who are not eligible for CAR-T cell therapy and stem cell transplantation.

1. Requirements for routine practice data collection and evaluations

With reference to the justification for the necessity of routine practice data collection for the active ingredient loncastuximab tesirine for the purpose of the benefit assessment, which forms the basis of the procedure-initiating resolution on the requirement of a routine practice data collection of 16 January 2025, the following requirements arise:

1.1 Research question according to PICO scheme

Population	Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy, who are not eligible for CAR-T cell therapy and stem cell transplantation.
Intervention	▪ Loncastuximab tesirine The marketing authorisation and the dosage information in the product information for loncastuximab tesirine must be taken into account.
Comparator	Individualised therapy with selection of ▪ polatuzumab vedotin + bendamustine + rituximab, ▪ tafasitamab + lenalidomide, ▪ odronextamab, ▪ epcoritamab and

	▪ glofitamab The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.
Outcome	Mortality ▪ Overall survival Morbidity ▪ Patient-reported symptomatology, measured with a validated instrument Health-related quality of life, measured with a validated instrument Side effects ▪ Serious adverse events (SAEs), operationalised as adverse events which lead to hospitalisation or prolong an existing hospitalisation, or lead to death; overall rate ▪ Discontinuation due to adverse events (overall rate) ▪ Specific adverse events (with indication of the respective severity grade)

1.2 Type and methods of data collection

Taking into account the research question of the routine practice data collection and the methodological limitations of non-randomised comparisons, the following requirements are placed on the study design and the data source for the present routine practice data collection.

1.2.1 Requirements for the study design

- Non-randomised, prospective comparison of loncastuximab tesirine with the listed comparator
    - Preferably as an adaptive platform registry study
    - Otherwise, as a comparative registry study,
    - If both of the above options are not feasible, a comparator study should be carried out using a data platform specifically designed for the present routine practice data collection (study-specific data collection).
    - For the enrolment in the study and the start of observation of the patients, the time of the treatment decision should be chosen based on an intention-to-treat principle.

1.2.2 Data source requirement

- Use of registries or a data platform to be set up specifically for the present routine practice data collection as a data source, which meet the requirements of routine practice data collection and fulfil at least the following quality criteria[1]:
    - Detailed registry description or description of the data platform (protocol)

[1]IQWiG A25-06: RPDC concept – Loncastuximab tesirine (DLBCL)

- Exact definition or operationalisation of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints and confounders
- Use of standard classifications and terminologies
- Use of validated standard data collection tools (questionnaire, scales, tests)
- Training courses on data collection and recording
- Implementation of a consensus disease-specific core data set
- Use of exact dates for the patient, the disease, important examinations and treatments/ interventions
- Clearly defined inclusion and exclusion criteria for patients in particular for the demarcation of the patient population that is not eligible for CAR-T cell therapy and stem cell transplantation
- Strategies to avoid selection bias in patient inclusion to achieve representativeness
- Specifications to ensure completeness of data per data collection time point and completeness of data collection time points
- Source data verification for 100% of patients per data collection site for the primary endpoint and for at least 10% of randomly selected patients per data collection site for all other endpoints over the period since the start of data collection
- When using a registry: Ensuring scientific independence and transparency

- Use of a registry or a data platform to be set up specifically for the present routine practice data collection, in which treatment of diffuse large B-cell lymphoma is carried out in accordance with German daily care or is sufficiently similar to care in Germany

1.2.3 Primary data source and integration of further data sources

- GLA and RUBIN registries, provided that the quality criteria specified in section 1.2.2 are met

- It is also possible to integrate other registries, taking into account all the data source requirements mentioned in section 1.2.2

1.3 Duration and scope of data collection

Considering the fact that it should be possible to recognise a clear effect on overall survival after 24 months, the following duration of observation should be implemented during routine practice data collection:

- 24 months

The available data on loncastuximab tesirine and the comparator therapies do not provide adequate information for an indicative sample size estimate. Therefore, an indicative consideration of sample size scenarios is carried out, in which effect sizes are shown for a routine practice data collection for the active ingredient loncastuximab tesirine, which can be detected on the basis of the available patient numbers and taking into account the shifted null hypothesis.

- Assumptions for the indicative consideration of the sample size scenarios:
  - Power of 80%

- Sample sizes: N = 500, N = 600 and N = 700
- Event percentages of the control group: 70%, 82.5% and 95% at month 36; percentage of events in the intervention group: 5% to 70%, up to 80% or up to 90%
- Significance level α = 2.5 % (1-sided test)
- Shifted null hypothesis (H0: HR ≥ 0.5)
- Recruitment ratios: 1:1, 1:3 and 1:5)

- Approx. 525 to 700 patients to be expected in the therapeutic indication
- Detectable effects for the endpoint of overall survival: Hazard ratio = 0.32 to 0.40 to the advantage of epcoritamab over the comparator therapy

On the basis of this orientating consideration of sample size scenarios, it can be assumed that a routine practice data collection for the present research question can be realised with a high degree of probability, taking into account the patients that can be recruited in the therapeutic indication. The final sample size planning is part of the study documents to be prepared (statistical analysis plan, study protocol; see section 1.5).

1.4 Evaluations of the data for the purpose of the benefit assessment

The pharmaceutical company shall submit the following evaluations to the G-BA:

- Interim analyses

  Evaluations of two interim analyses shall be presented. The relevant times for the performance of the interim analyses shall be the times specified in section 2.3.
  The interim analyses shall be performed according to the specifications in the study protocol and statistical analysis plan. In the process, a check for discontinuation due to futility must also be carried out for each interim analysis.

  Implementation of the final sample size estimate in interim analyses:

  Based on the first interim analysis, a final sample size estimate will be made on the basis of the more precise effect assumptions that are then possible, insofar as this is already possible on the basis of the recruited subjects. If a final sample size estimate cannot be made at the time of the first interim analysis, this must be explained and justified in a comprehensible manner. In these cases, the final sample size estimate can be presented with the interim analysis in which sufficient recruitment has been achieved for a final sample size estimate. For each further interim analysis in which a final sample size estimate cannot yet be made, the reasons for this must be clearly explained. At the latest at the time of the last interim analysis, a final sample size estimate must be presented on the basis of the more precise effect assumptions that are then possible.

  If applicable, the final sample size estimate can also be carried out at the time of its submission on the basis of endpoints other than those mentioned in the present resolution and taking into account a shifted hypothesis boundary in accordance with the procedure in IQWiG's concept.

The interim analyses shall be prepared on the basis of Module 4 of the dossier template, providing the full texts and study documents.

- Final evaluations for the purpose of the renewed benefit assessment

The final evaluations shall be carried out according to the specifications in the study protocol and statistical analysis plan. For the transmission of the final evaluations to the G-BA, the time specified in section 3 applies.

The final evaluations shall be prepared in a dossier in accordance with the provisions of Section 9 paragraphs 1 to 7 of the Rules of Procedure of the G-BA.

1.5 Requirements for the preparation of the study protocol and statistical analysis plan

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out routine practice data collection and evaluations.

With regard to the evaluation of the data, the following information in particular must be presented in advance in the study protocol and statistical analysis plan:

- Information on the statistical methods and models used, as well as naming the procedures and the criteria used in model selection and adaptation
- Information on the expected scope and reasons for missing data, as well as measures to avoid missing data and evaluation strategies to deal with missing data
- Information on dealing with implausible data and outliers
- Information on planned sensitivity analyses
- Information on the start of observation of the patients
- Information on the identification, as well as the adequate, pre-specified adjustment for confounders
- Information on the investigation of potential effect modifiers
- Information on interim analyses taking into account the requirements under section 1.4 and the specifications under section 2.3
- Information on discontinuation criteria due to futility
- Information on the criteria for the selection of the specific line of therapy for the inclusion of patients in the RPDC depending on the fulfilment of the inclusion and exclusion criteria

2. Specifications for reviewing whether the pharmaceutical company have fulfilled their obligation to carry out routine practice data collection and evaluations

2.1 Submission of a study protocol as well as the statistical analysis plan for coordination with the G-BA

The final drafts for a study protocol and for a statistical analysis plan prepared by the pharmaceutical company are to be submitted to the G-BA for approval by 17 December 2025 at the latest.

The G-BA, with the involvement of IQWiG, carries out a review of the study protocol and the statistical analysis plan and usually communicates the result to the pharmaceutical company in writing within 12 weeks.

Before submitting the requested documents to the G-BA, the pharmaceutical company have the option to request a consultation with the G-BA according to Section 35a, paragraph 7 SGB V in conjunction with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The subject of such consultation is, in particular, the drafts for a study protocol as

well as for a statistical analysis plan. In order to enable the pharmaceutical company to adequately consider the aspects addressed in the consultation when preparing the study protocol and statistical analysis plan, the request for consultation must be submitted to the G-BA by 14 August 2025 at the latest.

If the G-BA determines during the first submission of the study protocol and statistical analysis plan that the requirements of routine practice data collection and evaluations are inadequately implemented, the pharmaceutical company is given the opportunity to revise the study documents once. The G-BA shall adopt a declaratory resolution in this regard in the procedure for routine practice data collection and evaluations, which shall set out the necessary need for adaptation of the study documents. The deadline for submission of the revised statistical analysis plan and study protocol is 4 weeks, unless otherwise specified in the declaratory resolution.

The G-BA may come to the conclusion that the routine practice data collection can be carried out on the basis of the submitted study protocol and statistical analysis plan under the condition that further adaptations to the study documents deemed mandatory for the implementation of the requirements from this resolution must be made.

2.2 Submission of information on the course of data collection (in particular information on the status of recruitment)

6 months, 18 months and 36 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, the pharmaceutical company shall provide the G-BA in particular with the information on

- the number and the respective medicinal treatment of the patients included so far,
- patient-related observation periods, and
- any deviations regarding the expected number of recruits

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2.3 Submission of interim analyses

At the following time points after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, interim analyses shall be carried out and corresponding evaluations shall be submitted to the G-BA, taking into account the requirements specified in section 1.4:

- 18 months after the start of routine practice data collection
- 36 months after the start of routine practice data collection

The G-BA carries out a review of the interim analyses with the involvement of the IQWiG.

3. Deadline for the submission of evaluations of the data collected as part of the routine practice data collection

For the performance of a new benefit assessment, the evaluations of data collected as part of the routine practice data collection must be submitted by 17 January 2031 at the latest.

The submission of these evaluations must be made in the form of a dossier in accordance with the provisions of Chapter 5 Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA, taking into account the requirements of this resolution in accordance with Chapter 5 Section 58 of the Rules of Procedure of the G-BA.