Axicabtagene ciloleucel (follicular lymphoma)

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

EXTRACT

Project: A23-63 Version: 1.0 Status: 27 September 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Axicabtagen-Ciloleucel (follikuläres Lymphom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Axicabtagene ciloleucel (follicular lymphoma) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

3 July 2023

Internal Project No.

A23-63

Address of publisher

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

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

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

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 one person.

IQWiG thanks the respondent and the German Leukaemia and Lymphoma Aid (Deutsche Leukämie- und Lymphom-Hilfe e.V.) for participating in the written exchange and for their support. The respondent and the German Leukaemia and Lymphoma Aid were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Annette Christoph
- Christiane Balg
- Tobias Effertz
- Claudia Kapp
- Petra Kohlepp
- Katrin Nink
- Regine Potthast
- Anke Schulz

Keywords

Axicabtagene Ciloleucel, Lymphoma – Follicular, Benefit Assessment

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[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
BSG	Bundessozialgericht (Federal Social Court)
CAR	chimeric antigen receptor
CD	cluster of differentiation
CI	confidence interval
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
FL	follicular lymphoma
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMR	standardized mortality ratio
SPC	Summary of Product Characteristics
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug axicabtagene ciloleucel. 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 3 July 2023.

Research question

The aim of the present report is to assess the added benefit of axicabtagene ciloleucel in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory follicular lymphoma (FL) after 3 or more lines of systemic therapy.

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

Table 2: Research question of the benefit assessment of axicabtagene ciloleucel (multipage table)

Therapeutic indication[a]	**ACT**[b,c,d]
Adult patients with relapsed or refractory follicular lymphoma[e] after 3 or more lines of systemic therapy	Individualized therapy taking into account prior therapy, course of disease, and general health, selecting from ▪ bendamustine ▪ CHOP ▪ CVP ▪ chlorambucil ▪ cyclophosphamide ▪ MCP ▪ FCM in combination with rituximab each followed by rituximab maintenance therapy in case of induction therapy response ▪ bendamustine in combination with obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization ▪ lenalidomide in combination with rituximab ▪ rituximab monotherapy ▪ [^{90}Y]-radiolabelled ibritumomab tiuxetan

Table 2: Research question of the benefit assessment of axicabtagene ciloleucel (multipage table)

Therapeutic indication[a]	**ACT**[b,c,d]
a. In terms of the present therapeutic indication, it is assumed as per G-BA that patients with follicular lymphoma are therapeutically indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch-and-wait strategy, among others, is not an option. In terms of the present therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time of treatment and that radiotherapy is not therapeutically indicated. b. Presented is the ACT specified by the G-BA. c. For the implementation of individualized therapy in a direct comparative study, the investigator is expected as per G-BA to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment 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. In single-comparator studies, benefit assessments are used, in part, to ascertain the extent to which conclusions can be drawn about a subpopulation. d. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of recurrent or refractory follicular lymphoma grades 1 to 3a. Drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not deemed by the G-BA as ACTs in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R). e. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the approved therapeutic indication, the present determination of the ACT according to the G-BA refers to relapsed or refractory grade 1 to 3a follicular lymphoma. According to the generally recognized state of medical knowledge, grade 3b follicular lymphoma is not classified as indolent non-Hodgkin's lymphoma and is treated in the same way as diffuse large B-cell lymphoma (DLBCL). The new WHO classification 2022 [1] 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). ACT: appropriate comparator therapy; BSG: Federal Social Court; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; FCM: fludarabine, cyclophosphamide, mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MCP: mitoxantrone, chlorambucil, prednisone; SGB: Social Code Book; WHO: World Health Organization	

In the context of the specification of the ACT, the G-BA points out that in the available guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of recurrent or refractory follicular lymphoma grades 1 to 3a. Drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered by the G-BA as ACT in the narrower sense of § 2 (para. 1, sentence 3) §12 SGB V, according to the Federal Social Court (BSG) comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R).

The present assessment was conducted in comparison with the ACT specified by the G-BA. Deviating from the ACT specified by the G-BA, the company lists a number of other possible treatment options. A complete list can be found in Module 3A of the dossier. The company's deviation from the ACT specified by the G-BA is not further discussed below because the company did not present any suitable data for the benefit assessment – neither in comparison with a comparator therapy named by the company nor in comparison with the ACT specified by the G-BA.

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

Results

Concurring with the company, the check for completeness of the study pool revealed no randomized controlled trials (RCTs) which allows either a direct comparison with the ACT or an adjusted indirect comparison via a common comparator of axicabtagene ciloleucel versus the ACT specified for the G-BA for the research question.

For the benefit assessment, the company presents a comparison of individual arms from different studies, consisting of patient-specific data from the single-arm study ZUMA-5 (intervention side) and patient-specific data from the retrospective study SCHOLAR-5 (comparison side). The company carries out an analysis using standardized mortality ratio (SMR) weighting for the comparison of the individual arms.

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

Evidence provided by the company

ZUMA-5 study

The ongoing ZUMA-5 study is a single-arm, multicentre phase II study on treatment with axicabtagene ciloleucel. The study included adult patients with histologically confirmed indolent non-Hodgkin's B-cell lymphoma, with the histological subtype being limited to grade 1, 2, or 3a follicular lymphoma or marginal zone lymphoma (as per 2016 World Health Organization [WHO] classification). Patients with follicular lymphoma of histological grade 3b or with transformed follicular lymphoma or transformed marginal zone lymphoma were excluded from study participation.

Patients had to have refractory or relapsed disease after at least 2 prior therapies, including a monoclonal anti-cluster-of-differentiation (CD) 20 drug in combination with an alkylating agent. Patients with stable disease (without recurrence) more than 1 year after the end of the last therapy were excluded from the study population. Patients were also excluded in case of previous treatment with allogeneic stem cell therapy, autologous stem cell therapy less than

6 weeks before the planned axicabtagene ciloleucel infusion, chimeric antigen receptor (CAR) T-cell therapy, other genetically modified T-cell therapy, or with targeted anti-CD19 therapy. To be enrolled in the study, patients had to exhibit an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1 and at least 1 measurable lesion as per Lugano criteria.

For the present benefit assessment, the company took into account exclusively the subpopulation of patients with refractory or relapsed follicular lymphoma after 3 or more systemic therapies, and it accordingly used data from 75 of the total of 157 patients included in the ZUMA-5 study.

SCHOLAR-5 study

The SCHOLAR-5 study is a retrospective, multicentre study based on electronic patient records enrolling patients with relapsed or refractory indolent non-Hodgkin's lymphoma. The SCHOLAR-5 study analyses the data of a control cohort of the SCHOLAR-5 study (hereinafter referred to as the SCHOLAR-5 cohort) and compares them with the data of the patients in the ZUMA-5 study.

For the SCHOLAR-5 cohort, the company used data from several data sources. These were data from the 2 databases IQVIA and Vanderbilt University Medical Centre as well as data from the DELTA study.

The inclusion and exclusion criteria for the SCHOLAR-5 cohort from these data sources are based on selected criteria used in the ZUMA-5 clinical study. According to these criteria, patients aged 18 years and older with a histologically confirmed diagnosis of relapsed or refractory indolent non-Hodgkin's lymphoma with a histological subtype of grade 1, grade 2, or grade 3a follicular lymphoma or marginal zone lymphoma were taken into account.

In accordance with the therapeutic indication in question, only patients with 3 or more previous lines of therapy were included in the analyses. Furthermore, patients with marginal zone lymphoma were excluded from the analyses presented.

Presented comparison unsuitable for the benefit assessment

To derive the added benefit of axicabtagene ciloleucel compared to the ACT, the company presented a comparison of individual arms from different studies. On the axicabtagene ciloleucel side, this consists of patient-specific data from the single-arm ZUMA-5 study, and on the comparator side, of patient-specific data from the retrospective SCHOLAR-5 study.

The comparison presented by the company is not suitable for the derivation of an added benefit of axicabtagene ciloleucel in comparison with the ACT specified by the G-BA. This is mainly due to the following aspects:

- For the present therapeutic indication, the company presents comparative data on patient-relevant outcomes only for the outcome of overall survival. It is therefore not possible to weigh the benefits versus harms for the presented comparison.
- The ACT defined by the G-BA is not implemented in the presented comparison.
- The study pool on the comparator side is potentially incomplete.
- The information provided on the identification of the confounders collected does not allow an assessment of whether the company has identified and taken into account all relevant confounders. No systematic confounder identification is described.
- The information available in the dataset on the variables identified as relevant by the company is incomplete, which is why some of the relevant variables were not considered in the model estimating the propensity score, without the company drawing any conclusions from this.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of axicabtagene ciloleucel 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 axicabtagene ciloleucel.

[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 [2,3].

Table 3: Axicabtagene ciloleucel – probability and extent of added benefit (multipage table)

Therapeutic indication[a]	**ACT**[b,c,d]	**Probability and extent of added benefit**
Adult patients with relapsed or refractory follicular lymphoma[e] after 3 or more lines of systemic therapy	Individualized therapy taking into account prior therapy, course of disease, and general health, selecting from ▪ bendamustine ▪ CHOP ▪ CVP ▪ chlorambucil ▪ cyclophosphamide ▪ MCP ▪ FCM in combination with rituximab each followed by rituximab maintenance therapy if there is a response to induction therapy ▪ bendamustine in combination with obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization ▪ lenalidomide in combination with rituximab ▪ rituximab monotherapy ▪ [^{90}Y]-radiolabelled ibritumomab tiuxetan	Added benefit not proven

a. In the present therapeutic indication, it is assumed as per G-BA that patients with follicular lymphoma are therapeutically indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch-and-wait strategy, among others, is not an option. In terms of the present therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time of treatment and that radiotherapy is not therapeutically indicated.
b. Presented is the ACT specified by the G-BA.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment 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. In single-comparator studies, the extent to which conclusions can be drawn about a subpopulation is examined as part of the benefit assessment.
d. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of recurrent or refractory follicular lymphoma grades 1 to 3a. Drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered by the G-BA as ACTs in the narrower sense of § 2 (para. 1, sentence 3) § 12 SGB V, according to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R).
e. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the approved therapeutic indication, the present determination of the ACT according to the G-BA refers to relapsed or refractory grades 1 to 3a follicular lymphoma. According to the generally recognized state of medical knowledge, grade 3b follicular lymphoma is not classified as indolent non-Hodgkin's lymphoma and is treated in the same way as diffuse large B-cell lymphoma (DLBCL). The new WHO classification 2022 [1] 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).

Table 3: Axicabtagene ciloleucel – probability and extent of added benefit (multipage table)

Therapeutic indication[a]	**ACT**[b,c,d]	**Probability and extent of added benefit**
ACT: appropriate comparator therapy; BSG: Federal Social Court; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; FCM: fludarabine, cyclophosphamide, mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MCP: mitoxantrone, chlorambucil, prednisone; SGB: Social Code Book; WHO: World Health Organization		

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of axicabtagene ciloleucel in comparison with the ACT in adult patients with relapsed or refractory FL after 3 or more lines of systemic therapy.

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

Table 4: Research question of the benefit assessment of axicabtagene ciloleucel (multipage table)

Therapeutic indication[a]	**ACT**[b,c,d]
Adult patients with relapsed or refractory follicular lymphoma[e] after 3 or more lines of systemic therapy	Individualized therapy taking into account prior therapy, course of disease, and general health, selecting from ▪ bendamustine ▪ CHOP ▪ CVP ▪ chlorambucil ▪ cyclophosphamide ▪ MCP ▪ FCM in combination with rituximab each followed by rituximab maintenance therapy in case of induction therapy response ▪ bendamustine in combination with obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization ▪ lenalidomide in combination with rituximab ▪ rituximab monotherapy ▪ [^{90}Y]-radiolabelled ibritumomab tiuxetan

Table 4: Research question of the benefit assessment of axicabtagene ciloleucel (multipage table)

Therapeutic indication[a]	**ACT**[b,c,d]
a. In the present therapeutic indication, it is assumed as per G-BA that patients with follicular lymphoma are therapeutically indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch-and-wait strategy, among others, is not an option. In terms of the present therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time of treatment and that radiotherapy is not therapeutically indicated. b. Presented is the ACT specified by the G-BA. c. For the implementation of individualized therapy in a direct comparative study, the investigator is expected as per G-BA to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment 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. In single-comparator studies, the extent to which conclusions can be drawn about a subpopulation is examined as part of the benefit assessment. d. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of recurrent or refractory follicular lymphoma grades 1 to 3a. Drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered by the G-BA as ACTs in the narrower sense of § 2 (para. 1, sentence 3) § 12 SGB V, according to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R). e. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the approved therapeutic indication, the present determination of the ACT according to the G-BA refers to relapsed or refractory grades 1 to 3a follicular lymphoma. According to the generally recognized state of medical knowledge, grade 3b follicular lymphoma is not classified as indolent non-Hodgkin's lymphoma and is treated in the same way as diffuse large B-cell lymphoma (DLBCL). The new WHO classification 2022 [1] 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). ACT: appropriate comparator therapy; BSG: Federal Social Court; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; FCM: fludarabine, cyclophosphamide, mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MCP: mitoxantrone, chlorambucil, prednisone; SGB: Social Code Book; WHO: World Health Organization	

In the context of the specification of the ACT, the G-BA points out that in the available guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a (para. 7, sentence 4) SGB V list both approved and unapproved drug therapies for the treatment of recurrent or refractory follicular lymphoma grades 1 to 3a. Drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered by the G-BA as ACT in the narrower sense of § 2 (para. 1, sentence 3) § 12 SGB V, according to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R).

The present assessment was conducted in comparison with the ACT specified by the G-BA. Deviating from the ACT specified by the G-BA, the company lists a number of other possible treatment options. A complete list can be found in Module 3A of the dossier. The company's deviation from the ACT specified by the G-BA is not further discussed below because the company did not present any suitable data for the benefit assessment – neither in comparison with a comparator therapy named by the company nor in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented 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 list on axicabtagene ciloleucel (status: 3 April 2023)
- bibliographical literature search on axicabtagene ciloleucel (last search on 3 April 2023)
- search in trial registries / trial results databases for studies on axicabtagene ciloleucel (last search on 3 April 2023)
- search on the G-BA website for axicabtagene ciloleucel (last search on 5 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on axicabtagene ciloleucel (last search on 12 July 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool revealed no RCTs which allow either a direct comparison with the ACT or an adjusted indirect comparison via a common comparator of axicabtagene ciloleucel versus the ACT specified for the G-BA for the research question.

It should be noted that an open-label, randomized phase 3 study (ZUMA-22 study) is currently ongoing which investigates axicabtagene ciloleucel versus standard therapy in patients with follicular lymphoma (grades 1-3a) who have either received at least 2 prior lines of systemic therapy or who have relapsed after first-line chemoimmunotherapy [4,5]. It cannot be ruled out that a subpopulation of this study is potentially relevant for the present benefit assessment. However, no results of this study are available at this time. According to the ClinicalTrials.gov trial registry, the study is expected to be completed in July 2029 [4]. No further information is available on when the first analyses can be expected.

Since the company did not identify any RCTs which allowed a direct comparison or an adjusted indirect comparison via a common comparator for axicabtagene ciloleucel versus the ACT, it additionally conducted an information retrieval on further studies with axicabtagene ciloleucel. It identified the single-arm study ZUMA-5 [6]. In the course of this search for axicabtagene ciloleucel, the company also identified the SCHOLAR-5 study. In the bibliographic search, the company identified the studies Ghione 2022 [7] and Palomba 2023 [8]. In both studies, the results of the single-arm ZUMA-5 study are compared with the results of patients from the retrospective SCHOLAR-5 study [7-11].

In Module 4A, the company did not provide any information on the information retrieval on further studies on the ACT side. Accordingly, there is a lack of information on whether the company conducted such an information retrieval. Due to the missing data on the information retrieval for further investigations for the ACT, the study pool is potentially incomplete on the comparator side.

The check for completeness of the study pool on the intervention side identified no additional relevant studies. The completeness of the study pool on the ACT side was not checked. Irrespective of the potential incompleteness of the company's study pool, the data submitted by the company are unsuitable for drawing any conclusions on the added benefit of axicabtagene ciloleucel in comparison with the ACT for patients in the present therapeutic indication. This is explained in the following sections.

I 3.1 Evidence provided by the company

For the benefit assessment, the company presents a comparison of individual arms from different studies, consisting of patient-specific data from the single-arm study ZUMA-5 (intervention side) and patient-specific data from the retrospective study SCHOLAR-5 (comparison side) which include the data from 2 databases as well as 1 study (see below for details on the data sources).

The company carries out an analysis using SMR weighting for the comparison of the individual arms.

The comparison presented by the company is not suitable for the derivation of an added benefit of axicabtagene ciloleucel in comparison with the ACT specified by the G-BA. This is mainly due to the following aspects:

- With respect to the present therapeutic indication, the company presents comparative data on patient-relevant outcomes only for the outcome of overall survival. It is therefore not possible to weigh the benefits versus harms for the presented comparison.
- The ACT defined by the G-BA is not implemented in the presented comparison.
- The study pool on the comparator side is potentially incomplete.
- The information provided on the identification of the confounders collected does not allow an assessment of whether the company has identified and taken into account all relevant confounders. No systematic confounder identification is described.
- The information available in the dataset on the variables identified as relevant by the company is incomplete, which led to partial disregard of relevant variables in the model for propensity score estimation, without the company drawing any conclusions from this.

Below, the evidence presented by the company is described, and the reasons for its unsuitability for the benefit assessment are provided.

I 3.1.1 Evidence on axicabtagene ciloleucel

ZUMA-5 study

The ongoing ZUMA-5 study is a single-arm, multicentre phase II study on treatment with axicabtagene ciloleucel. The study included adult patients with histologically confirmed indolent non-Hodgkin B-cell lymphoma, with the histological subtype being limited to grade 1, 2, or 3a follicular lymphoma or marginal zone lymphoma (according to the 2016 WHO classification 2016 [12]). Patients with follicular lymphoma of histological grade 3b or with transformed follicular lymphoma or transformed marginal zone lymphoma were excluded from study participation.

Patients had to have refractory or relapsed disease after at least 2 prior therapies, including a monoclonal anti-CD20 drug in combination with an alkylating agent. Patients with stable disease (without recurrence) more than 1 year after the end of the last therapy were excluded from the study population. Patients were also excluded if they were previously treated with either allogeneic stem cell therapy, autologous stem cell therapy less than 6 weeks before the planned axicabtagene ciloleucel infusion, CAR T-cell therapy, other genetically modified T-cell therapy, or with targeted anti-CD19 therapy. To be enrolled in the study, patients had to exhibit an ECOG-PS ≤ 1 and at least 1 measurable lesion as per Lugano criteria [13].

Prior to treatment, the study required conducting preparations for the patient-specific production of the CAR T-cell preparation, starting with leukapheresis (for details see Figure 1 in I Appendix B of the full dossier assessment). Leukapheresis for the collection of peripheral blood mononuclear cells for the production of axicabtagene ciloleucel should be conducted within 4 weeks after the first screening visit and within 5 days after a patient fulfils the inclusion criteria. The start of leukapheresis was also regarded as the start of the study for the patients. The median time between leukapheresis and infusion in all patients with follicular lymphoma in the ZUMA-5 study was 27 days. Within this period, patients were allowed to receive anti-cancer treatment for disease control (bridging) if needed. On the 5^{th} to 3^{rd} day before treatment with axicabtagene ciloleucel, the patients received chemotherapy consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, each administered intravenously over 3 days, for lymphodepletion.

The study provided for the use of axicabtagene ciloleucel at a dose of 2 x 10^6 anti-CD19 CAR T-cells per kg body weight. Axicabtagene ciloleucel treatment was administered in accordance with the Summary of Product Characteristics (SPC) [14]. In addition, a second treatment with axicabtagene ciloleucel was possible under certain conditions [15].

The primary outcome of the study was the centrally assessed objective response rate. For this purpose, the scans are sent to a central imaging provider and reviewed by 2 independent central reviewers using the Lugano classification. Secondary outcomes include overall survival and outcomes on side effects.

Data cutoffs and analysis population of the ZUMA-5 study

At the time of the benefit assessment, the results of different predefined data cutoffs were available. These are the primary analysis (12 March 2020 cutoff date), the 1st follow-up analysis at Month 18 (14 September 2020 cutoff date) and the 2nd follow-up analysis at Month 24 (31 March 2021 cutoff date). The European marketing authorization was granted based on the data from the 2nd follow-up analysis [16]. It was conducted after the first 80 patients with follicular lymphoma had been followed up for 24 months after infusion of axicabtagene ciloleucel.

In Module 4A of the dossier, the company presents results on the data cutoff of a 3rd follow-up analysis at Month 36 (31 March 2022 cutoff date). This follow-up analysis was not predefined and was conducted when the median follow-up time after axicabtagene ciloleucel infusion for treated patients with follicular lymphoma had reached 36 months. According to the study documents, this analysis was not planned in the protocol but was conducted to observe the long-term effectiveness and safety of axicabtagene ciloleucel. Beyond that, no information is available as to what specific reason led to this analysis. The company justifies the presentation of this data cutoff by stating that this analysis is the most recent data cutoff with the longest evidence and the greatest information content. However, it should be noted that the results for the patient-relevant outcome of overall survival at Month 24 and Month 36 are almost identical.

For the present benefit assessment, the company took into account only the subpopulation of patients with refractory or relapsed follicular lymphoma after 3 or more systemic therapies. Patients with subsequently centrally confirmed nonfollicular lymphoma were excluded. Accordingly, the company drew on data from 75 of the total of 157 patients included in the ZUMA-5 study.

I 3.1.2 Evidence for the comparator therapy

SCHOLAR-5 study

The SCHOLAR-5 study is a retrospective, multicentre study based on electronic patient records which enrolled patients with relapsed or refractory indolent non-Hodgkin's lymphoma. Patients with relapsed or refractory follicular lymphoma (grades 1-3a) or marginal zone lymphoma who had received 2 or more prior lines of therapy were included.

On the one hand, this study aims to characterize the clinical and demographic characteristics and treatment patterns of these patients in routine care, and on the other, it is intended to form an external comparator group (hereinafter referred to as the SCHOLAR-5 cohort) which is comparable to the patient population of the single-arm ZUMA-5 study on axicabtagene ciloleucel in terms of disease characteristics.

For the SCHOLAR-5 study, data from patients with relapsed or refractory indolent non-Hodgkin's lymphoma from various oncological practices (sites) in the United States, the United Kingdom, France, and Spain who were treated outside of a clinical trial were to be collected as per study protocol.

SCHOLAR-5 cohort

In the SCHOLAR-5 study reports, the data of a control cohort (hereinafter referred to as the SCHOLAR-5 cohort) are analysed and compared with the data of the above-described subpopulation of ZUMA-5 participants.

For the SCHOLAR-5 cohort, the company used data from several data sources. These were data from the 2 databases IQVIA and Vanderbilt University Medical Centre as well as data from the DELTA study [17] (see below for details on these data sources). The use of the IQVIA database was provided for in the study protocol. According to the statistical analysis plan (SAP), data from the DELTA study were also used. The information in the study reports shows that patient records from the Vanderbilt University Medical Centre were also included.

The inclusion and exclusion criteria for the SCHOLAR-5 cohort from these data sources are based on selected criteria used in the ZUMA-5 clinical study. According to these criteria, patients aged 18 years and older with a histologically confirmed diagnosis of indolent non-Hodgkin's lymphoma with a histological subtype of grade 1, grade 2 or grade 3a follicular lymphoma or marginal zone lymphoma were analysed, but data of patients with marginal zone lymphoma were excluded in the analysis phase. Patients also had to have relapsed or refractory disease and have started the 3rd or a higher line of therapy. According to the inclusion criteria, treatment with an anti-CD20 antibody in combination with alkylating chemotherapy had to have taken place in order to count as a treatment line. Data from patients who had previously received CAR T-cell therapy or another genetically modified T-cell therapy were excluded. Patients with grade 3b follicular lymphoma or transformed follicular lymphoma were likewise excluded.

The study reports initially analysed only patients of either study with 3 or more previous lines of therapy, as per the present therapeutic indication, and patients with subsequently centrally confirmed non-follicular lymphoma were excluded from the ZUMA-5 study. Furthermore, patients with marginal zone lymphoma were excluded from the analyses presented.

In the available study reports, the data from the SCHOLAR-5 cohort are compared with the data of the patients from the ZUMA-5 study at the 2nd follow-up analysis at Month 24 or at the 3rd follow-up analysis at Month 36.

Data sources for the SCHOLAR-5 cohort

IQVIA and Vanderbilt University Medical Centre

Patient data from 6 centres in the United Kingdom, France, Spain, Portugal, and the United States were used from the IQVIA database. The fully anonymized database of electronic patient records at Vanderbilt University Medical Centre was used as a further data source.

For the comparison in the 2 study reports, the company used data from both databases only for patients with a potential observation period of at least 12 months. In addition, a fourth-line therapy or a higher line of therapy had to have been started on 23 July 2014 or later. This date corresponds to the approval date of idelalisib. The company justified the choice of this date by stating that, in its view, there was no significant change in the treatment regimen for the present therapeutic indication after idelalisib approval. The survey period lasted from July 2014 to December 2020 at the latest, depending on the centre.

The SCHOLAR-5 cohort includes 56 patients from the IQVIA database. Data from 2 patients were added from the Vanderbilt University Medical Centre database.

The company intends to optimally harmonize the number of prior treatment lines between the participants of the SCHOLAR-5 cohort and the ZUMA-5 study. For each patient in the SCHOLAR-5 cohort, the company therefore selects a therapy from all permissible therapy lines (index therapy line), the start of which represents the start of the study for the respective patient. For the patients from the 2 databases, the company randomly selects an index therapy line for each patient with a 4th and higher therapy line.

DELTA study

The DELTA study is a single-arm, open-label, multicentre phase II study of idelalisib treatment which included 125 patients with indolent non-Hodgkin's lymphoma. Patients had to have failed to respond to at least 2 prior therapies (including the monoclonal anti-CD20 antibody rituximab and an alkylating agent) or have relapsed within 6 months of receiving these therapies.

For the formation of the SCHOLAR-5 study's control cohort, the company analyses only patients from the subpopulation of 72 DELTA participants with grades 1 to 3a follicular lymphoma who had received the fourth or higher line of therapy following the idelalisib study treatment.

The company defined the first treatment after the end of therapy with the study medication of idelalisib as the index date. If no data are available for the first treatment after the use of idelalisib, the patient is excluded from the analysis. Any prior treatment with a monoclonal anti-CD20 antibody had to have been administered in combination with an alkylating agent to count as a line of therapy. This results in 24 patients from the DELTA study being included in the control cohort of the SCHOLAR-5 study.

Analysis population

For the present benefit assessment, the 3 data sources for the control cohort resulted in a total of 82 patients with different treatment options on the ACT side (I Appendix C, Table 6 of the full dossier assessment, see also the following section).

I 3.2 The company's approach

To derive the added benefit of axicabtagene ciloleucel compared to the ACT, the company presented a comparison of individual arms from different studies. On the axicabtagene ciloleucel side, this consists of patient-specific data from the single-arm ZUMA-5 study and, on the comparator side, of patient-specific data from the retrospective SCHOLAR-5 study. In the SCHOLAR-5 cohort, data from 2 databases (IQVIA, Vanderbilt University Medical Centre) and the DELTA study are analysed (see above).

In order to equalize the differences between the data from the ZUMA-5 study and the external comparator group, the inclusion and exclusion criteria for the SCHOLAR-5 cohort were based on selected criteria used in the ZUMA-5 clinical study. For the analyses, patients with 3 or more prior lines of therapy were taken into account, and patients with subsequently centrally confirmed non-follicular lymphomas were excluded from the ZUMA-5 study. Furthermore, patients with marginal zone lymphoma were excluded from the analyses presented. In addition, the company conducted a weighted analysis according to SMR weighting. According to the company, the use of a propensity score method is intended to ensure that the differences observed between the treatment groups can be attributed to the axicabtagene ciloleucel intervention.

I 3.3 Assessment of the evidence presented by the company

The comparison presented by the company is not suitable for deriving an added benefit of axicabtagene ciloleucel in comparison with the ACT specified by the G-BA. Irrespective of a further methodological examination of the adjustment procedure used by SMR weighting on the basis of propensity scores, this is mainly due to the following points.

No weighing of benefit and risk possible

With respect to the present therapeutic indication, the company presents comparative data on patient-relevant outcomes only for the outcome of overall survival. Given the currently

available data, the observed effects are small enough to be explicable solely by systematic bias due to the inadequate application of the selected propensity score analysis (see below) (2nd follow-up analysis at Month 24: hazard ratio: 0.35; 95% confidence interval [CI]: [0.18; 0.66]; p-value: p = 0.001; 3rd follow-up analysis at Month 36: hazard ratio: 0.36; 95% CI: [0.20; 0.64]; p-value: p < 0.001; each in the weighted comparison of the full analysis set with leukapheresis as the start time).

Furthermore, no comparative results are available for other patient-relevant outcomes. According to the study documents, the SCHOLAR-5 study was originally to survey patient-reported outcomes, but insufficient data were available for an analysis because not enough appropriate data had been collected. No information is available on the volume of the available data. Adverse events were surveyed in the ZUMA-5 study, but according to the company's Module 4A (contrary to information provided in the SAP), they were not surveyed in the SCHOLAR-5 cohort.

Overall, it is therefore impossible to weigh the benefits and harms of axicabtagene ciloleucel on the basis of the comparison presented by the company.

ACT not implemented

The company reports that 3 data sources, i.e. data from 2 databases (IQVIA, Vanderbilt University Medical Centre) and data from the DELTA study, were used to generate data on the comparison side.

As described above, for forming the SCHOLAR-5 cohort, data from the 2 databases for patients who had started fourth-line therapy or a higher line of therapy on 23 July 2014 or later were included. For the patients from the IQVIA and Vanderbilt University Medical Centre databases, a decision was therefore necessary as to which treatment line was to be deemed the start of the study for each patient. In each patient, 1 therapy was randomly selected from all permitted therapy lines, and the start of this therapy was counted as the start of the study. According to the company, this ensures an optimally balanced number of previous treatment lines between the patients in the ZUMA-5 study and the SCHOLAR-5 cohort. In the DELTA study – which included patients with 2 prior therapies – the first treatment after the end of the study medication of idelalisib was selected in each case.

The company's Module 4A (I Appendix C, Table 6 of the full dossier assessment) presents the treatment pattern resulting from the selection of a randomized treatment line for the 82 patients of the final SCHOLAR-5 cohort included in the company's analysis. However, one issue is that information is available largely on drug classes rather than the specific drugs used. It is therefore not clear whether the drugs or combinations of drugs specified as the ACT by the G-BA were used. Another issue is that the treatment options used include a larger

proportion of experimental therapies (20 of the 82 [24%] patients, see I Appendix C, Table 6 of the full dossier assessment).

Overall, the available data allow deducing only that a maximum of 25 of the 82 (30.5%) patients in the SCHOLAR-5 cohort received a treatment option in accordance with the ACT, but on the basis of the available data, it cannot be verified to what extent these were administered in accordance with the respective SPCs. The ACT defined by the G-BA has therefore not been appropriately implemented in the SCHOLAR-5 cohort.

Completeness of study pool on the comparator side not ensured

Since, as described above, the company did not find any RCT that allowed a direct comparison or an adjusted indirect comparison via a common comparator for axicabtagene ciloleucel versus the ACT, it additionally conducted an information retrieval on further studies on the intervention side. However, Module 4A does not include any information indicating that the company also conducted an information search for further studies on the ACT side. The study pool is therefore potentially incomplete on the comparator side.

Confounders: lacking appropriate identification and completeness

Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies, group differences in possible confounders, i.e. factors which are related to both the 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 [18,19] as described, for example, in Pufulete 2022 [19]. 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 [18].

The company’s approach for the identification of confounders is not appropriate. According to Module 4 A of the dossier, clinical advice was sought to determine the propensity scores prior to data availability in order to determine which characteristics should ideally be balanced between the treatment groups at baseline and in which hierarchical order the covariates should be prioritized as prognostic values. However, no information is available on how the clinical advice was specifically obtained and how the hierarchy of the variables analysed was determined. Furthermore, there is no evidence of a systematic (literature) research having been conducted. Consequently, it is unclear whether the company’s approach is suitable for the systematic identification of relevant confounders.

The study protocol [11] contains a list of 26 variables without a description of how they were selected. In the SAP (version 2.0) [10], a total of 20 variables are predefined, whose importance (high, medium, low) was assessed by clinical experts and which are to be used for

the propensity score estimation model. These variables were reduced to 9 potential confounders. The information provided in Module 4A and the study documents do not clearly show how the company specifically proceeded with the reduction of the number of confounders, as the information in the two sources differs and is furthermore insufficiently detailed.

Finally, as per Module 4A, the propensity score model comprises the following 9 variables:

- disease progression within 24 months since start of first treatment with monoclonal anti-CD20 antibody in combination with chemotherapy
- number of prior lines of therapy
- relapsed or refractory status
- previous stem cell therapy
- tumour burden measured by the diameter of the largest lesion (due to the high proportion of missing data, as a substitute for the previously planned criteria of the Groupe d'Etude des Lymphomes Folliculaires [GELF])
- time since the last therapy line
- best response to most recent line of therapy
- age
- previous combination therapy with an anti-CD20 antibody in combination with an alkylating agent

The 20 variables originally listed in the SAP (version 2.0) include the variables Follicular Lymphoma International Prognostic Index (FLIPI) total score and bone marrow involvement, which were assessed as being of high and medium importance, respectively, according to clinical expertise. According to Module 4A of the company's dossier, these are not included in its list of variables for determining the propensity scores shown in Module 4A due to the high proportion of missing data in the data sources used for the SCHOLAR-5 cohort. They are therefore excluded from the final selection of variables for the propensity score estimation model. The company does not draw any inferences for the benefit assessment from the exclusion of these variables assessed as relevant according to clinical expertise. This is not appropriate because it thus failed to address the potential effect of the missing information regarding relevant confounders on the certainty of results and on the observed effects of the outcome of overall survival in the SCHOLAR-5 study. For example, no evaluation is provided of how the lack of adjustment for these potentially relevant confounders might affect the effect estimate for this outcome.

Summary

Overall, the data presented by the company are not suitable for the benefit assessment and do not allow an adequate comparison of axicabtagene ciloleucel versus the ACT.

I 4 Results on added benefit

The company has not submitted any suitable data for assessing the added benefit of axicabtagene ciloleucel in comparison with the ACT in adult patients with recurrent or refractory follicular lymphoma following 3 or more systemic therapies. There is no hint of an added benefit of axicabtagene ciloleucel in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for axicabtagene ciloleucel in comparison with the ACT.

Table 5: Axicabtagene ciloleucel – probability and extent of added benefit (multipage table)

Therapeutic indication[a]	**ACT**[b,c,d]	**Probability and extent of added benefit**
Adult patients with relapsed or refractory follicular lymphoma[e] after 3 or more lines of systemic therapy	Individualized therapy taking into account prior therapy, course of disease, and general health, selecting from ▪ bendamustine ▪ CHOP ▪ CVP ▪ chlorambucil ▪ cyclophosphamide ▪ MCP ▪ FCM in combination with rituximab each followed by rituximab maintenance therapy in case of induction therapy response ▪ bendamustine in combination with obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization ▪ lenalidomide in combination with rituximab ▪ rituximab monotherapy ▪ [^{90}Y]-radiolabelled ibritumomab tiuxetan	Added benefit not proven

Table 5: Axicabtagene ciloleucel – probability and extent of added benefit (multipage table)

Therapeutic indication[a]	ACT[b,c,d]	Probability and extent of added benefit
a. In terms of the present therapeutic indication, it is assumed as per G-BA that patients with follicular lymphoma are therapeutically indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch-and-wait strategy, among others, is not an option. In terms of the present therapeutic indication, it is assumed that stem cell transplantation is not indicated at the time of treatment and that radiotherapy is not therapeutically indicated. b. Presented is the ACT specified by the G-BA. c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment 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. In single-comparator studies, the extent to which conclusions can be drawn about a subpopulation is examined as part of the benefit assessment. d. Present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a para. 7, sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of recurrent or refractory follicular lymphoma grades 1 to 3a. Drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not deemed as ACTs in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R). e. Irrespective of the fact that grade 3b follicular lymphoma is formally covered by the approved therapeutic indication, the present determination of the ACT according to the G-BA refers to relapsed or refractory grades 1 to 3a follicular lymphoma. According to the generally recognized state of medical knowledge, grade 3b follicular lymphoma is not classified as indolent non-Hodgkin's lymphoma and is treated in the same way as diffuse large B-cell lymphoma (DLBCL). The new WHO classification 2022 [1] 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). ACT: appropriate comparator therapy; BSG: Federal Social Court; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; DLBCL: diffuse large B-cell lymphoma; FCM: fludarabine, cyclophosphamide, mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MCP: mitoxantrone, chlorambucil, prednisone; SGB: Social Code Book; WHO: World Health Organization		

The assessment described above deviates from that by the company, which derived a hint of considerable 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.

1. Alaggio R, Amador C, Anagnostopoulos I et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022; 36(7): 1720-1748. https://dx.doi.org/10.1038/s41375-022-01620-2.

2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

3. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

4. Kite, a Gilead Company. Study of Axicabtagene Ciloleucel Versus Standard of Care Therapy in Participants With Relapsed/Refractory Follicular Lymphoma [online]. 2023 [Accessed: 19.07.2023]. URL: https://classic.clinicaltrials.gov/show/NCT05371093.

5. Kite Pharma. A Phase 3 Randomized, Open-Label, Multicenter Study Evaluating the Efficacy of Axicabtagene Ciloleucel Versus Standard of Care Therapy in Subjects with Relapsed/Refractory Follicular Lymphoma [online]. [Accessed: 12.07.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-003260-28.

6. Jacobson CA, Chavez JC, Sehgal AR et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2021; 23(1): 91-103. https://dx.doi.org/10.1016/S1470-2045(21)00591-X.

7. Ghione P, Palomba ML, Patel AR et al. Comparative effectiveness of ZUMA-5 (axi-cel) vs SCHOLAR-5 external control in relapsed/refractory follicular lymphoma. Blood 2022; 140(8): 851-860. https://dx.doi.org/10.1182/blood.2021014375.

8. Palomba ML, Ghione P, Patel AR et al. A 24-month updated analysis of the comparative effectiveness of ZUMA-5 (axi-cel) vs. SCHOLAR-5 external control in relapsed/refractory follicular lymphoma. Expert Rev Anticancer Ther 2023; 23(2): 199-206. https://dx.doi.org/10.1080/14737140.2023.2171994.

9. Kite, a Gilead Company. A Comparison of Clinical Outcomes from Zuma-5 (Axicabtagene Ciloleucel) and the International Scholar-5 External Control Cohort in Relapsed/Refractory Follicular Lymphoma (r/r FL): 36-Month Follow-Up for Patients with Three or More Prior Lines of Therapy, Excluding Patients with Centrally Confirmed Non-Follicular Lymphoma, Addendum to Modules 5.3.5.2 Zuma-5 Clinical Study Report (28 October 2022); SCHOLAR-5 Final Study Report [unpublished]. 2022.

10. Delta Hat, Kite, a Gilead Company. Statistical Analysis Plan; KTE-INHL-RW2020; real-world response/survival and treatment patterns among patients with relapsed/refractory indolent non-hodgkin lymphoma in USA, UK, France, Spain, and Portugal oncology practices; v2.0 [unpublished]. 2021.

11. Kite Pharma. Real-World Response/Survival and Treatment Patterns among Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma in USA, UK, France, and Spain Oncology Practices; SCHOLAR-5 protocol [unpublished]. 2020.

12. Swerdlow SH, Campo E, Pileri SA et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127(20): 2375-2390. https://dx.doi.org/10.1182/blood-2016-01-643569.

13. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32(27): 3059-3068. https://dx.doi.org/10.1200/JCO.2013.54.8800.

14. Gilead. Yescarta [online]. 2022 [Accessed: 04.07.2023]. URL: https://www.fachinfo.de.

15. Kite Pharma. A Phase 2 Multicenter Study Of Axicabtagene Ciloleucel In Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5); Clinical Study Protocol KTE-C19-105 (ZUMA-5) Amendment #6 [unpublished]. 2020.

16. European Medicines Agency. Yescarta; Assessment report [online]. 2022 [Accessed: 23.08.2023]. URL: https://www.ema.europa.eu/documents/variation-report/yescarta-h-c-004480-ii-0042-epar-assessment-report-variation_en.pdf.

17. Gopal AK, Kahl BS, de Vos S et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014; 370(11): 1008-1018. https://dx.doi.org/10.1056/NEJMoa1314583.

18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a19-43_versorgungsnahe-daten-zum-zwecke-der-nutzenbewertung_rapid-report_v1-1.pdf.

19. Pufulete M, Mahadevan K, Johnson TW et al. Confounders and co-interventions identified in non-randomized studies of interventions. J Clin Epidemiol 2022; 148: 115-123. https://dx.doi.org/10.1016/j.jclinepi.2022.03.018.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-63.html.