Zanubrutinib (follicular lymphoma)

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

EXTRACT

Project: A23-130 Version: 1.0 Status: 13 Mar 2024 DOI: 10.60584/A23-130_en

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Zanubrutinib (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

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

Commissioning agency

Federal Joint Committee

Commission awarded on

15 December 2023

Internal Project No.

A23-130

DOI-URL

https://doi.org/10.60584/A23-130_en

Address of publisher

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Gerhard Kreutzer.

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

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Keywords

Zanubrutinib, Lymphoma – Follicular, Benefit Assessment

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group-Performance Score
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GELF	Groupe d'Étude des Lymphomes Folliculaires
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone
RCT	randomized controlled trial
R-CVP	rituximab in combination with cyclophosphamide, vincristine, prednisone/prednisolone
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

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 zanubrutinib in combination with obinutuzumab. 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 15 December 2023.

Research question

The aim of this report was to assess the added benefit of zanubrutinib in combination with obinutuzumab (hereinafter referred to as zanubrutinib + obinutuzumab) in comparison with the appropriate comparator therapy (ACT) in patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies.

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

Table 2: Research questions of the benefit assessment of zanubrutinib + obinutuzumab

Therapeutic indication	**ACT**[a]
Adult patients with refractory or relapsed follicular lymphoma who have received at least 2 prior systemic therapies[b, c]	Individualized treatment[d] selected from bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization lenalidomid + rituximab rituximab monotherapy mosunetuzumab tisagenlecleuceld taking into account prior therapy, course of disease, and general health
a. Presented is the ACT specified by the G-BA. b. In terms of the present therapeutic indication, it is assumed as per G-BA that zanubrutinib in combination with obinutuzumab is not an option for the treatment of diagnosed grade 3b follicular lymphomas. c. 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. Further, patients are presumed not to be therapeutically indicated for radiotherapy or stem cell transplantation at the time of therapy. d. For the implementation of individualized therapy in a study of direct comparison, 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). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GELF: Groupe d'Étude des Lymphomes Folliculaires	

The company deviates from the ACT specified by the G-BA by adding further individualized therapy options:

- rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone (R-CHOP)
- rituximab in combination with cyclophosphamide, vincristine, prednisone/prednisolone (R-CVP)
- idelalisib

The company's deviation from the G-BA's ACT is of no consequence, as it presented no data on the ACT named by it or specified by the G-BA. The present assessment was conducted 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 provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Results

The check for completeness of the study pool revealed no relevant studies comparing zanubrutinib + obinutuzumab with the ACT specified by the G-BA.

The company, in contrast, identified the RCT ROSEWOOD and used it in its assessment. The ROSEWOOD study is not suitable for the benefit assessment because it does not allow a comparison with the ACT.

In agreement with the company, the MAHOGANY study was identified, for which, however, no results were available at the time of the present benefit assessment.

Evidence presented by the company – ROSEWOOD study

The ROSEWOOD study is an ongoing, open-label, randomized phase 2 study comparing zanubrutinib + obinutuzumab with obinutuzumab as monotherapy in follicular lymphoma after at least 2 prior systemic therapies. The main inclusion criteria for the study were histologically confirmed follicular lymphoma of WHO Grade 1 to 3a, prior administration of chemo-immunotherapy (with a CD20 antibody and a combination therapy based on alkylating agents) and disease progression after the most recent, at least 2nd line of treatment. The lack of response to this latest line of therapy, in terms of at least partial remission, also qualified for inclusion in the study. Patients with significantly impaired general health (Eastern Cooperative Oncology Group Performance Score [ECOG PS] 3 or higher) were excluded.

A total of 217 patients were randomized in a 2:1 ratio into the study (145 in the intervention arm and 72 in the comparator arm).

The study medication in the intervention arm was applied according to the specifications of the Summary of Product Characteristics. The study medication used in the comparator arm is

not approved for the current therapeutic indication, the dosage of obinutuzumab as monotherapy was administered similarly to the intervention arm.

The study's primary outcome was overall response. Secondary outcomes include overall survival, progression-free survival, morbidity and health-related quality of life outcomes, and adverse events.

No implementation of the ACT in the ROSEWOOD study

The G-BA defined the ACT as an individualized treatment with a choice of bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy, lenalidomide + rituximab, rituximab monotherapy, mosunetuzumab and tisagenlecleucel, taking into account the prior therapy, the course of the disease and the general health. Additionally, the G-BA points out that in a directly comparative study, 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).

The ROSEWOOD study presented is a single-comparator study in which all comparator arm participants received obinutuzumab as monotherapy. Treatment with obinutuzumab as monotherapy does not correspond to any of the options specified in the ACT as part of individualized treatment. Individualized treatment taking into account prior therapy, course of disease, and general health was also not possible in the study. Thus, the ROSEWOOD study did not implement the ACT. The ROSEWOOD study is therefore unsuitable for assessing any added benefit of zanubrutinib + obinutuzumab in comparison with the ACT specified by the G-BA.

Results on added benefit

No suitable data are available for the assessment of the added benefit of zanubrutinib + obinutuzumab for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies in comparison with the ACT. This is no hint of an added benefit of zanubrutinib + obinutuzumab 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 probability and extent of the added benefit of zanubrutinib + obinutuzumab.

[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

Table 3: Zanubrutinib + obinutuzumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with refractory or relapsed follicular lymphoma who have received at least 2 prior systemic therapies[b, c]	Individualized treatment[d] selected from bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization lenalidomid + rituximab rituximab monotherapy mosunetuzumab tisagenlecleuceld taking into account prior therapy, course of disease, and general health	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In terms of the present therapeutic indication, it is assumed as per G-BA that zanubrutinib in combination with obinutuzumab is not an option for the treatment of diagnosed grade 3b follicular lymphomas.
c. 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. Further, patients are presumed not to be therapeutically indicated for radiotherapy or stem cell transplantation at the time of therapy.
d. For the implementation of individualized therapy in a study of direct comparison, 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).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GELF: Groupe d'Étude des Lymphomes Folliculaires

(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].

I 2 Research question

The aim of this report was to assess the added benefit of zanubrutinib in combination with obinutuzumab (hereinafter referred to as zanubrutinib + obinutuzumab) in comparison with the ACT in patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies.

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

Table 4: Research questions of the benefit assessment of zanubrutinib + obinutuzumab

Therapeutic indication	**ACT[a]**
Adult patients with refractory or relapsed follicular lymphoma who have received at least 2 prior systemic therapies[b, c]	Individualized treatment[d] selected from bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization lenalidomid + rituximab rituximab monotherapy mosunetuzumab tisagenlecleuceld taking into account prior therapy, course of disease, and general health
a. Presented is the ACT specified by the G-BA. b. In terms of the present therapeutic indication, it is assumed as per G-BA that zanubrutinib in combination with obinutuzumab is not an option for the treatment of diagnosed grade 3b follicular lymphomas. c. 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. Further, patients are presumed not to be therapeutically indicated for radiotherapy or stem cell transplantation at the time of therapy. d. For the implementation of individualized therapy in a study of direct comparison, 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). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GELF: Groupe d'Étude des Lymphomes Folliculaires	

The company deviates from the ACT specified by the G-BA by adding the following options to the individualized treatment:

- rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone (R-CHOP)
- rituximab in combination with cyclophosphamide, vincristine, prednisone/prednisolone (R-CVP)
- Idelalisib

The company's deviation from the G-BA's ACT is of no consequence, as it presented no data on the ACT named by it or specified by the G-BA. The present assessment was conducted 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 provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on zanubrutinib (status: 18 October 2023)
- bibliographical literature search on zanubrutinib (last search on 16 October 2023)
- search in trial registries/trial results databases for studies on zanubrutinib (last search on 18 October 2023)
- search on the G-BA website for zanubrutinib (last search on 18 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on zanubrutinib (last search on 21 December 2023); for search strategies, see I Appendix A of the full dossier assessment

The check for completeness of the study pool revealed no relevant studies comparing zanubrutinib + obinutuzumab with the ACT specified by the G-BA.

The company, in contrast, identified the RCT ROSEWOOD [3] and used it in its assessment. The ROSEWOOD study is not suitable for the benefit assessment because it does not allow a comparison with the ACT (for rationale, see Sections I 3.1 and I 3.2).

Ongoing study identified

In agreement with the company, the MAHOGANY study [4] was identified, for which no results were available at the time of the present benefit assessment. This study is a 4-arm randomized, open-label Phase III study comparing, among other things, zanubrutinib in combination with obinutuzumab versus lenalidomide in combination with rituximab in relapsed or refractory follicular lymphoma after at least one prior therapy. Thus, this study potentially includes a subpopulation with at least 2 previous therapies that is relevant for the present research question. The company is the sponsor of this study. According to Module 4A, the study has been in the recruitment phase since May 2023. It appears from the study protocol that the number of events required for the first interim analysis is expected to be reached approximately 5.5 years after inclusion of the first patient.

I 3.1 Evidence presented by the company – ROSEWOOD study

The ROSEWOOD study is an ongoing, open-label, randomized phase 2 study comparing zanubrutinib + obinutuzumab with obinutuzumab as monotherapy in Patients with follicular lymphoma who have received at least 2 prior systemic therapies. The main inclusion criteria for the study were histologically confirmed follicular lymphoma of WHO Grade 1 to 3a, prior

administration of chemo-immunotherapy (with a CD20 antibody and a combination therapy based on alkylating agents) and disease progression after the most recent, at least 2nd line of treatment. The lack of response to this latest line of therapy, in terms of at least partial remission, also qualified for inclusion in the study. Patients with significantly impaired general health (ECOG PS 3 or higher) were excluded.

A total of 217 patients were included into the study and randomized in a 2:1 ratio (145 in the intervention arm and 72 in the comparator arm). Stratification factors were region (China versus non-China), number of prior therapies (2 to 3 versus more than 3) and refractory status to rituximab (yes versus no).

The study medication in the intervention arm was applied according to the specifications of the Summary of Product Characteristics [5,6]. The study medication used in the comparator arm is not approved for the current therapeutic indication, the dosage of obinutuzumab as monotherapy was administered similarly to the intervention arm. Treatment was administered until disease progression or occurrence of unacceptable side effects. At the discretion of the investigator, it is possible for patients in the comparator arm to receive treatment with zanubrutinib + obinutuzumab if the disease progresses or there is no at least partial response to therapy after twelve cycles.

The study's primary outcome was overall response. Secondary outcomes include overall survival, progression-free survival, morbidity and health-related quality of life outcomes, and adverse events.

The ROSEWOOD study is still ongoing. A total of 2 data cut-offs were conducted, on 21 October 2021 (planned interim analysis) and on 25 June 2022 (requested by the Federal Drug Administration in the approval process, according to the company). In Module 4A, the company presents analyses of the 2nd data cut-off.

I 3.2 Assessment of the evidence presented by the company

No implementation of the ACT in the ROSEWOOD study

The G-BA defined the ACT as an individualized treatment with a choice of bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy, lenalidomide + rituximab, rituximab monotherapy, mosunetuzumab and tisagenlecleucel, taking into account the prior therapy, the course of the disease and the general health. Additionally, the G-BA points out that in a directly comparative study, 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).

The ROSEWOOD study presented is a single-comparator study in which all comparator arm participants received obinutuzumab as monotherapy. Treatment with obinutuzumab as

monotherapy does not correspond to any of the options specified in the ACT as part of individualized treatment. Individualized treatment taking into account prior therapy, course of disease, and general health was also not possible in the study. Thus, the ROSEWOOD study did not implement the ACT. The ROSEWOOD study is therefore unsuitable for assessing any added benefit of zanubrutinib + obinutuzumab in comparison with the ACT specified by the G-BA.

Therapeutic indication questionable in the patients included in the study

Irrespective of the implementation of the appropriate therapy in the ROSEWOOD study, it is questionable whether all patients included were therapeutically indicated for for systemic therapy. According to the G-BA, it is assumed that patients in this therapeutic indication are therapeutically indicated for systemic antineoplastic therapy due to an advanced stage of the disease, particularly with regard to a symptomatic course or a high tumour load (e.g. according to the criteria of the Groupe d'Étude des Lymphomes Folliculaires [GELF]), and that a watch-and-wait strategy is therefore not an option (see Table 4). However, the presence of a therapeutic indication was not an inclusion criterion for the ROSEWOOD study. The patient population included also reflects this: At randomization, only 57% of patients met at least one GELF criterion as a therapeutic indication. This means that the therapeutic indication is questionable for a relevant proportion of the study population. These patients would therefore not fall under the present research question.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of zanubrutinib + obinutuzumab for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies in comparison with the ACT. This is no hint of an added benefit of zanubrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

The result of the assessment of the added benefit of zanubrutinib + obinutuzumab in comparison with the ACT is summarized in Table 5.

Table 5: Zanubrutinib + obinutuzumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with refractory or relapsed follicular lymphoma who have received at least 2 prior systemic therapies[b, c]	Individualized treatment[d] selected from bendamustine + obinutuzumab followed by obinutuzumab maintenance therapy as per marketing authorization lenalidomid + rituximab rituximab monotherapy mosunetuzumab tisagenlecleuceld taking into account prior therapy, course of disease, and general health	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In terms of the present therapeutic indication, it is assumed as per G-BA that zanubrutinib in combination with obinutuzumab is not an option for the treatment of diagnosed grade 3b follicular lymphomas.
c. 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. Further, patients are presumed not to be therapeutically indicated for radiotherapy or stem cell transplantation at the time of therapy.
d. For the implementation of individualized therapy in a study of direct comparison, 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).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GELF: Groupe d'Étude des Lymphomes Folliculaires

The assessment described above departs from that by the company, which, based on the results of the ROSEWOOD study, derived a hint of a minor added benefit for zanubrutinib + obinutuzumab compared with obinutuzumab.

The G-BA decides on the added benefit.

I 5 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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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-130.html.