Zanubrutinib
(marginal zone lymphoma)

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

EXTRACT

Project: A22-131 Version: 1.0 Status: 13 March 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Zanubrutinib (Marginalzonenlymphom) – 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 (marginal zone lymphoma) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

15 December 2022

Internal Project No.

A22-131

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

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Christian Siebel
- Christiane Balg
- Benjamin Becker
- Simone Heß
- Michaela Florina Kerekes
- Stefan Kobza
- Katrin Nink
- Regine Potthast

Keywords

Zanubrutinib, Lymphoma – B-Cell – Marginal Zone, 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
CD	cluster of differentiation
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MZL	marginal zone lymphoma
RCT	randomized controlled trial
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. 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 the present report is to assess the added benefit of zanubrutinib in comparison with the appropriate comparator therapy (ACT) in adult patients with marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based 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 zanubrutinib

Therapeutic indication	**ACT**[a]
Adult patients with MZL who have received at least 1 prior anti-CD20-based therapy[b]	Individualized therapy taking into account prior therapy[c], the course of disease (including duration of remission since previous therapy), and general health[d,e]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to be 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 is not an option. Further, patients are presumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. According to the G-BA, patients are presumed to have received adequate prior therapy, where therapeutically indicated, depending on the respective entity, e.g. *Helicobacter pylori* eradication in gastric extranodal MZL, radiotherapy in case of nodal MZL, or splenectomy in splenic MZL. In this regard, the characteristic "previously treated MZL" is interpreted solely with regard to systemic antineoplastic therapy.
d. Some individual components of the combination therapies recommended by guidelines are not approved in the present therapeutic indication of MZL: fludarabine, idelalisib, ibrutinib, lenalidomide, obinutuzumab, rituximab. There is a discrepancy between the drugs approved for the therapeutic indication of MZL and those recommended in guidelines and used in practice. In accordance with the G-BA, the following therapies are deemed suitable comparators for individualized therapy in the context of clinical trials: bendamustine + rituximab/obinutuzumab; CHOP + rituximab; CVP + rituximab; FCM + rituximab; chlorambucil ± rituximab; cyclophosphamide ± rituximab; lenalidomide + rituximab; rituximab monotherapy; idelalisib; ibrutinib.
e. Patients responding to combination therapy of chemotherapy plus rituximab or chemotherapy plus obinutuzumab are to be offered maintenance therapy with rituximab or obinutuzumab, respectively. According to the G-BA, autologous stem cell transplantation is assumed not to be indicated in the present therapeutic indication at the time point of treatment with zanubrutinib.

ACT: appropriate comparator therapy; CD: Cluster of Differentiation; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; FCM: fludarabine + cyclophosphamide + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MZL: marginal zone lymphoma

The company followed the G-BA's specification of the ACT.

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

Results

Concurring with the company, the check for the completeness of the study pool produced no randomized controlled trials (RCTs) on the direct comparison of zanubrutinib versus the ACT.

The company conducted an information retrieval for other investigations with zanubrutinib and presents in the dossier data from the 2 single-arm studies BGB-3111-214 (hereinafter referred to as MAGNOLIA study) and BGB-3111-AU-003. The company conducted no information retrieval on other investigations with the ACT.

Evidence presented by the company – MAGNOLIA study

The MAGNOLIA study is an uncontrolled, multicentre phase-2 study on treatment with zanubrutinib in patients with recurrent or refractory MZL. The study enrolled adult patients with MZL requiring treatment who had received at least 1 prior treatment, including at least 1 CD20-based therapy, and who did not achieve at least partial response or had documented disease progression after the most recent systemic therapy. It enrolled patients with histologically confirmed splenic, nodal, and extranodal MZL. In total, the company presented analyses of 68 patients enrolled in the study. Participants had received a median of 2 prior systemic therapies. All patients received prior anti-CD20 therapy.

Evidence presented by the company – BGB-3111-AU-003 study

The BGB-3111-AU-003 study is an uncontrolled, multicentre phase 1/2 study on zanubrutinib treatment in patients with B-cell neoplasia. The study consists of 2 parts. In part 1 (dose escalation phase), the recommended phase-2 dose was determined. Part 2 (dose expansion phase) assessed zanubrutinib at the recommended phase-2 dosage in different histological subtypes of B-cell neoplasia, including 20 patients with MZL. All patients analysed by the company had received at least 1 prior systemic therapy. Prior rituximab-based chemotherapy was received by 19 patients (95%).

Submitted data unsuitable for drawing conclusions on added benefit

In concordance with the company, the data from the 2 single-arm studies MAGNOLIA and BGB-3111-AU-003 are unsuitable for assessing the added benefit of zanubrutinib because they do not allow a comparison with the ACT. Overall, the company has therefore presented no suitable data for deriving an added benefit in comparison with the ACT.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of zanubrutinib 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 zanubrutinib.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Zanubrutinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with MZL who have received at least 1 prior anti-CD20-based therapy[b]	Individualized therapy taking into account prior therapy[c], the course of disease (including duration of remission since previous therapy), and general health[d,e]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to be 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 is not an option. Further, patients are presumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. According to the G-BA, patients are presumed to have received adequate prior therapy, where therapeutically indicated, depending on the respective entity, e.g. *Helicobacter pylori* eradication in gastric extranodal MZL, radiotherapy in case of nodal MZL, or splenectomy in splenic MZL. In this regard, the characteristic "previously treated MZL" is interpreted solely with regard to systemic antineoplastic therapy.
d. Some individual components of the combination therapies recommended by guidelines are not approved in the present therapeutic indication of MZL: fludarabine, idelalisib, ibrutinib, lenalidomide, obinutuzumab, rituximab. There is a discrepancy between the drugs approved for the therapeutic indication of MZL and those recommended in guidelines and used in practice. In accordance with the G-BA, the following therapies are deemed suitable comparators for individualized therapy in the context of clinical trials: bendamustine + rituximab/obinutuzumab; CHOP + rituximab; CVP + rituximab; FCM + rituximab; chlorambucil ± rituximab; cyclophosphamide ± rituximab; lenalidomide + rituximab; rituximab monotherapy; idelalisib; ibrutinib.
e. Patients responding to combination therapy of chemotherapy plus rituximab or chemotherapy plus obinutuzumab are to be offered maintenance therapy with rituximab or obinutuzumab, respectively. According to the G-BA, autologous stem cell transplantation is assumed not to be indicated in the present therapeutic indication at the time point of treatment with zanubrutinib.

ACT: appropriate comparator therapy; CD: Cluster of Differentiation; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; FCM: fludarabine + cyclophosphamide + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MZL: marginal zone lymphoma

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 zanubrutinib in comparison with the ACT in adult patients with MZL who have received at least 1 prior anti-CD20-based 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 zanubrutinib

Therapeutic indication	**ACT[a]**
Adult patients with MZL who have received at least 1 prior anti-CD20-based therapy[b]	Individualized therapy taking into account prior therapy[c], the course of disease (including duration of remission since previous therapy), and general health[d,e]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to be 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 is not an option. Further, patients are presumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. According to the G-BA, patients are presumed to have received adequate prior therapy, where therapeutically indicated, depending on the respective entity, e.g. *Helicobacter pylori* eradication in gastric extranodal MZL, radiotherapy in case of nodal MZL, or splenectomy in splenic MZL. In this regard, the characteristic "previously treated MZL" is interpreted solely with regard to systemic antineoplastic therapy.
d. Some individual components of the combination therapies recommended by guidelines are not approved in the present therapeutic indication of MZL: fludarabine, idelalisib, ibrutinib, lenalidomide, obinutuzumab, rituximab. There is a discrepancy between the drugs approved for the therapeutic indication of MZL and those recommended in guidelines and used in practice. In accordance with the G-BA, the following therapies are deemed suitable comparators for individualized therapy in the context of clinical trials: bendamustine + rituximab/obinutuzumab; CHOP + rituximab; CVP + rituximab; FCM + rituximab; chlorambucil ± rituximab; cyclophosphamide ± rituximab; lenalidomide + rituximab; rituximab monotherapy; idelalisib; ibrutinib.
e. Patients responding to combination therapy of chemotherapy plus rituximab or chemotherapy plus obinutuzumab are to be offered maintenance therapy with rituximab or obinutuzumab, respectively. According to the G-BA, autologous stem cell transplantation is assumed not to be indicated in the present therapeutic indication at the time point of treatment with zanubrutinib.

ACT: appropriate comparator therapy; CD: Cluster of Differentiation; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; FCM: fludarabine + cyclophosphamide + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MZL: marginal zone lymphoma

The company followed the G-BA's specification of the ACT.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on zanubrutinib (status: 18 October 2022)
- bibliographical literature search on zanubrutinib (last search on 20 October 2022)
- search in trial registries / trial results databases for studies on zanubrutinib (last search on 19 October 2022)
- search on the G-BA website for zanubrutinib (last search on 19 October 2022)

To check the completeness of the study pool:

- search in trial registries for studies on zanubrutinib (last search on 21 December 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check for the completeness of the study pool produced no RCTs on the direct comparison of zanubrutinib versus the ACT.

The company has conducted an information retrieval on other investigations on zanubrutinib, and its dossier presents data from the 2 single-arm studies BGB-3111-214 (hereinafter referred to as MAGNOLIA study) [3,4] and BGB-3111-AU-003 [5,6] on the basis of which approval was granted in the present therapeutic indication. The company conducted no information retrieval on other investigations with the ACT.

A check for completeness of the study pool presented by the company for other investigations was foregone because the data submitted by the company under “Other investigations” are unsuitable for the benefit assessment due to the lack of comparison with the ACT. This is explained below.

I 3.1 Evidence provided by the company

MAGNOLIA study

The MAGNOLIA study is an uncontrolled, multicentre phase-2 study on treatment with zanubrutinib in patients with recurrent or refractory MZL. The study enrolled adult patients with MZL requiring treatment who had received at least 1 prior treatment, including at least 1 CD20-based therapy, and who did not achieve at least partial response or had documented disease progression after the most recent systemic therapy. It enrolled patients with histologically confirmed splenic, nodal, and extranodal MZL.

In total, the company presented analyses of 68 patients enrolled in the study. Participants had received a median of 2 prior systemic therapies. All patients received prior anti-CD20 therapy.

The study's primary outcome is the overall response rate according to the independent review committee. Secondary outcomes include outcomes from the categories of morbidity, health-related quality of life and side effects.

According to Module 4C, 2 data cutoffs were implemented for the study (on 18 January 2021 and 4 May 2022). In Module 4 C, the company presents the results of the individual outcomes at the respective current data cutoffs.

Study BGB-3111-AU-003

The BGB-3111-AU-003 study is an uncontrolled, multicentre phase 1/2 study on zanubrutinib treatment in patients with B-cell neoplasia.

The study consists of 2 parts. In part 1 (dose escalation phase), the recommended phase-2 dose was determined. Part 2 (dose expansion phase) assessed zanubrutinib at the recommended phase-2 dosage in different histological subtypes of B-cell neoplasia, including 20 patients with MZL.

All patients taken into account by the company had received at least 1 prior systemic therapy. Prior rituximab-based chemotherapy was received by 19 patients (95%).

Primary outcomes of the study's part 2 are outcomes from the side effects category. In addition, the overall response rate is the primary efficacy outcome for patients with MZL. Secondary outcomes are mortality as well as outcomes from the morbidity category.

According to Module 4 C, 2 data cutoffs are available for the study (2 October 2020 and 31 March 2021). The company's dossier presents analyses on the 31 March 2021 data cut-off.

Approach of the company

The company explains that no direct comparative studies are available for zanubrutinib in the treatment of adult patients with MZL who received at least 1 prior therapy with an anti-CD20 antibody. Therefore, the company then looked for other investigations with zanubrutinib, identifying the 2 single-arm studies MAGNOLIA and BGB-3111-AU-003. The company reported using both studies for deriving added benefit, and the dossier's Module 4 C (section on other investigations) presents the results of the 2 single-arm studies MAGNOLIA and BGB-3111-AU-003**.** The company did not present data on the ACT. From the company's perspective, the results of the 2 single-arm studies show a lasting response to zanubrutinib as well as good tolerability. Overall, the company argues that due to the lack of RCT-based

evidence and the missing comparison with the ACT, the added benefit of zanubrutinib is not proven in comparison with individualized therapy.

Submitted data unsuitable for drawing conclusions on added benefit

In concordance with the company, the data from the 2 single-arm studies MAGNOLIA and BGB-3111-AU-003 are deemed unsuitable for assessing the added benefit of zanubrutinib because they do not allow a comparison with the ACT. Overall, the company has therefore presented no suitable data for deriving an added benefit in comparison with the ACT.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of zanubrutinib in comparison with the ACT in the treatment of adult patients with MZL who have received at least 1 prior anti-CD-based therapy. This results in no hint of an added benefit of zanubrutinib 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 zanubrutinib in comparison with the ACT.

Table 5: Zanubrutinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with MZL who have received at least 1 prior anti-CD20-based therapy[b]	Individualized therapy taking into account prior therapy[c], the course of disease (including duration of remission since previous therapy), and general health[d,e]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to be 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 is not an option. Further, they are assumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. According to the G-BA, patients are presumed to have received adequate prior therapy, where therapeutically indicated, depending on the respective entity, e.g. *Helicobacter pylori* eradication in gastric extranodal MZL, radiotherapy in case of nodal MZL, or splenectomy in splenic MZL. In this regard, the characteristic "previously treated MZL" is interpreted solely with regard to systemic antineoplastic therapy.
d. Some individual components of the combination therapies recommended by guidelines are not approved in the present therapeutic indication of MZL: fludarabine, idelalisib, ibrutinib, lenalidomide, obinutuzumab, rituximab. There is a discrepancy between the drugs approved for the therapeutic indication of MZL and those recommended in guidelines and used in practice. In accordance with the G-BA, the following therapies are deemed suitable comparators for individualized therapy in the context of clinical trials: bendamustine + rituximab/obinutuzumab; CHOP + rituximab; CVP + rituximab; FCM + rituximab; chlorambucil ± rituximab; cyclophosphamide ± rituximab; lenalidomide + rituximab; rituximab monotherapy; idelalisib; ibrutinib.
e. Patients responding to combination therapy of chemotherapy plus rituximab or chemotherapy plus obinutuzumab are to be offered maintenance therapy with rituximab or obinutuzumab, respectively. According to the G-BA, autologous stem cell transplantation is assumed not to be indicated in the present therapeutic indication at the time point of treatment with zanubrutinib.

ACT: appropriate comparator therapy; CD: Cluster of Differentiation; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; FCM: fludarabine + cyclophosphamide + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; MZL: marginal zone lymphoma

The assessment described above concurs with that of the company.

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. 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.

2. 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.

3. BeiGene. A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma (MAGNOLIA); Clinical Study Report (data cut-off date: 04 May 2022) [unpublished]. 2022.

4. Opat S, Tedeschi A, Linton K et al. The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. Clin Cancer Res 2021; 27(23): 6323-6332. https://dx.doi.org/10.1158/1078-0432.CCR-21-1704.

5. BeiGene. A Phase 1/2, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Patients With B-Cell Lymphoid Malignancies (BGB-3111-AU-003); Clinical Study Report (data cut-off date: 31 March 2021) [unpublished]. 2021.

6. Phillips T, Chan H, Tam CS et al. Zanubrutinib monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma. Blood Adv 2022; 6(11): 3472-3479. https://dx.doi.org/10.1182/bloodadvances.2021006083.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-131.html.