IQWiG Reports – Commission No. A21-169

Zanubrutinib (Waldenström macroglobulinaemia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Zanubrutinib (Morbus Waldenström) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 March 2022). 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.

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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 one person.

IQWiG thanks the respondent for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
cLDA	constrained longitudinal data analysis
CXCR4	C-X-C chemokine receptor type 4
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed model repeated measures
MYD88	myeloid differentiation primary response 88
QLQ-C30	Quality of Life Questionnaire – Core 30
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 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 2021.

Research question

The aim of the present report was to assess the added benefit of zanubrutinib in comparison with the appropriate comparator therapy (ACT) in adult patients with Waldenström macroglobulinaemia who had received at least 1 prior therapy or as first-line therapy in patients who are not candidates for chemoimmunotherapy.

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 Waldenström macroglobulinaemia who have received at least 1 prior therapy, or as first-line treatment in patients unsuitable for chemoimmunotherapy	Individualized therapy[b] taking into account general health and any prior therapies as well as duration of remission after initial therapy

a. Presented is the ACT specified by the G-BA.
b. As ACTs, the drugs or drug combinations of bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are recommended in the guideline as well as in statements by the professional associations. With the exception of the combination of ibrutinib + rituximab, the drugs bortezomib and rituximab are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines and by professional associations. Within clinical trials, bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are deemed suitable comparators.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

However, in departure from the G-BA's specification, the company designated ibrutinib monotherapy as the ACT, reasoning that multiple treatment options might be deemed equally appropriate for the comparator therapy. From among these options it deems equally suitable, the company has selected ibrutinib monotherapy.

The company's reasoning is not appropriate. In the present therapeutic indication, guidelines specify that the treatment option should be selected taking into account patients' general health, any prior treatment, and duration of remission. Based on these clinical aspects, various individualized treatment options are available; these options might differ in value depending on

the patient's general health, any prior treatment, and remission duration and are therefore not to be deemed equally appropriate. The company did not submit any justification as to why ibrutinib constitutes individualized therapy for all patients within the therapeutic indication, irrespective of the above aspects.

The present benefit assessment has been compiled – contrary to the ACT of individualized therapy as defined by the company vis-a-vis the G-BA – under consideration of the clinical aspects mentioned in Table 2.

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

Results

The check for completeness of the study pool revealed no relevant studies comparing zanubrutinib versus the ACT of individualized therapy. The company, in contrast, identified the ASPEN study and used it in its assessment. The ASPEN study is unsuitable for assessing the benefit of zanubrutinib versus the ACT. The rationale is provided below.

Evidence presented by the company – ASPEN study

The ASPEN study is an ongoing, open, multicentre phase III study enrolling adult patients with Waldenström macroglobulinaemia. To be included in the study, treatment-experienced patients had to exhibit recurrent or refractory disease. Patients without prior therapy had to be unsuitable for chemoimmunotherapy in the treating physician's opinion.

Patients were assigned to 2 cohorts based on their myeloid differentiation primary response 88 (MYD88) mutation status. The active control cohort 1 of the study comprised patients with MYD88 mutation. Cohort 2 without comparator group comprised patients with either wild-type MYD88 or undetermined MYD88 mutation status.

The company used the active control cohort 1 of the ASPEN study in its benefit assessment. Cohort 1 randomized 102 patients to the intervention arm (zanubrutinib) and 99 to the comparator arm (ibrutinib). Randomization was stratified by C-X-C chemokine receptor type 4 (CXCR4) mutation status and the number of prior therapies for Waldenström macroglobulinaemia.

Treatment in the ASPEN study's intervention and comparator arms was in accordance with the Summaries of Product Characteristics (SPCs) for zanubrutinib and ibrutinib.

The study's primary outcome is response rate, measured as the proportion of participants achieving either complete response or very good partial response. Secondary outcomes are overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Individualized therapy not implemented in the ASPEN study

The ASPEN study is unsuitable for assessing any added benefit of zanubrutinib in comparison with the ACT specified by the G-BA. All patients in the study's comparator arm received ibrutinib monotherapy. The company did not provide any reasoning as to why ibrutinib would represent individualized therapy for ASPEN participants with Waldenström macroglobulinaemia, nor did it discuss why other available therapy options were not preferable individualized therapy in consideration of clinical aspects. The company's dossier does not supply sufficient information on clinical aspects to be taken into account when selecting the treatment option. Yet, the information available on treatment-experienced patients included in the study suggests that, for part of the study population, different treatment options might have been suitable. The ASPEN study, however, did not offer treating physicians any treatment options other than ibrutinib monotherapy for the comparator arm. Therefore, the study presented by the company does not allow comparing zanubrutinib with individualized therapy as the ACT specified by the G-BA.

Incomplete analyses submitted for the ASPEN study

Aside from the ASPEN study being unsuitable for the benefit assessment for the reasons described above, the ASPEN study's data analysis as presented in the dossier's Module 4 A suffers from substantial deficiencies. The dossier's Module 4 A exhibits shortcomings both in the analysis of the data on included patients and in the analysis of study results. In particular, the results of the ASPEN study presented in the company's dossier are incomplete. For instance, the analyses of the patient-reported outcomes surveyed in the study are incomplete for each of the 2 available data cut-offs. The dossier therefore does not allow an adequate assessment of the study results.

Results on added benefit

No suitable data for assessing the added benefit of zanubrutinib versus the ACT are available for adult patients with Waldenström macroglobulinaemia who have received at least 1 prior therapy or as first-line treatment in patients unsuitable for chemoimmunotherapy. This results in 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 presents 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

Table 3: Zanubrutinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with Waldenström macroglobulinaemia who have received at least one prior therapy, or as first-line treatment in patients unsuitable for chemoimmunotherapy	Individualized therapy[b] taking into account general health and any prior therapies as well as duration of remission after initial therapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The drugs or drug combinations of bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are recommended by the guideline as well as the professional associations as ACTs. With the exception of the combination of ibrutinib + rituximab, the drugs bortezomib and rituximab are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines and by professional associations. Within clinical trials, bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are deemed suitable comparators.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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].

2.2 Research question

The aim of the present report was to assess the added benefit of zanubrutinib in comparison with the ACT in adult patients with Waldenström macroglobulinaemia who have received at least 1 prior therapy, or as first-line treatment in patients unsuitable for chemoimmunotherapy.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of zanubrutinib

Therapeutic indication	**ACT[a]**
Adult patients with Waldenström macroglobulinaemia who have received at least 1 prior therapy, or as first-line treatment in patients unsuitable for chemoimmunotherapy	Individualized therapy[b] taking into account general health and any prior therapies as well as duration of remission after initial therapy

a. Presentation of the ACT specified by the G-BA.
b. The drugs or drug combinations of bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are recommended by the guideline as well as the professional associations as ACTs. With the exception of the combination of ibrutinib + rituximab, the drugs bortezomib and rituximab are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines and by professional associations. Within clinical trials, bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are deemed suitable comparators.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

However, in departure from the G-BA's specification, the company designated ibrutinib monotherapy as the ACT, reasoning that multiple treatment options might be deemed equally appropriate for the comparator therapy. Having deemed the options equally suitable, the company picked ibrutinib as the monotherapy substance.

The company's reasoning is not appropriate. The guidelines specify that in the present therapeutic indication, the treatment option should be selected in consideration of patients' general health, any prior treatment, and duration of remission [3,4]. Based on these clinical aspects, various individualized treatment options are available; these options might differ in value depending on the patient's general health, any prior treatment, and remission duration and are therefore not to be deemed equally appropriate. The company did not submit any justification for ibrutinib representing individualized therapy for all patients within the therapeutic indication, irrespective of the above aspects.

The present benefit assessment has been compiled – contrary to the ACT of individualized therapy as defined by the company vis-a-vis the G-BA – under consideration of the clinical aspects mentioned in Table 4.

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

2.3 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: 9 November 2021)
- bibliographical literature search on zanubrutinib (last search on 9 November 2021)
- search in trial registries / trial results databases for studies on zanubrutinib (last search on 9 November 2021)
- search on the G-BA website for zanubrutinib (last search on 9 November 2021)

To check the completeness of the study pool:

- search in trial registries for studies on zanubrutinib (last search on 28 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check for completeness of the study pool revealed no relevant studies comparing zanubrutinib versus the ACT of individualized therapy.

The company, in contrast, identified the ASPEN study [5-10] and used it in its assessment. The ASPEN study is unsuitable for assessing the benefit of zanubrutinib versus the ACT. The rationale is provided below.

Evidence provided by the company

The ASPEN study presented by the company compares zanubrutinib treatment versus ibrutinib, each as monotherapy. This study is unsuitable for the present benefit assessment because the information submitted by the company fails to demonstrate that, for the included patients, the employed comparator therapy of ibrutinib represented individualized therapy, taking into account general health, any prior treatment, and duration of remission after initial treatment.

Design of the ASPEN study

The ASPEN study is an ongoing, open, multicentre phase III study enrolling adult patients with Waldenström macroglobulinaemia. To be included in the study, treatment-experienced patients had to exhibit recurrent or refractory disease. Patients without prior therapy had to be deemed ineligible for chemoimmunotherapy by their treating physician. All included patients additionally had to exhibit at least 1 criterion for being indicated for therapy as defined by the consensus panel of the International Workshop on Waldenström Macroglobulinemia (IWWM)-7 [11].

Patients were assigned to 2 cohorts based on their MYD88 mutation status. The study's active control cohort 1 comprised patients with MYD88 mutation (N = 201). Cohort 2 without

comparator group comprised patients with wild-type MYD88 or undetermined MYD88 mutation status (N = 28).

The company used the active control cohort 1 of the ASPEN study in its benefit assessment. Results for cohort 2 are presented in Module 4 A as supplementary information. This cohort is not further discussed below because it does not comprise a control group and is therefore irrelevant for the comparison of zanubrutinib with the ACT.

Cohort 1 randomized 102 patients to the intervention arm (zanubrutinib) and 99 to the comparator arm (ibrutinib). Randomization was stratified by CXCR4 mutation status and the number of prior therapies for Waldenström macroglobulinaemia.

Treatment in the ASPEN study's intervention and comparator arms was in accordance with the SPCs for zanubrutinib [12] and ibrutinib [13]. Zanubrutinib is administered orally at a dosage of 160 mg twice daily and ibrutinib orally at a dosage of 420 mg once daily. In both arms, treatment was administered in 28-day cycles until progression or the occurrence of unacceptable toxicity. Both in the zanubrutinib arm and in the ibrutinib arm, patients in the first 2 cycles were eligible for plasmapheresis where clinically indicated.

The study's primary outcome is response rate, measured as the proportion of participants achieving either complete response or very good partial response. Secondary outcomes are overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Appendix B of the full dossier assessment contains further information on the ASPEN study, on the characterization of the study population as well as on antineoplastic prior therapies of patients with recurrent/refractory disease.

Individualized therapy not implemented in the ASPEN study

The ASPEN study is unsuitable for assessing any added benefit of zanubrutinib in comparison with the ACT specified by the G-BA. All patients in the study's comparator arm received ibrutinib monotherapy. However, the company's dossier provides no information to demonstrate that, for the patients included in the study, this treatment option represents the ACT of individualized therapy as specified by the G-BA.

For adult patients with Waldenström macroglobulinaemia who have received at least 1 prior therapy, or as first-line treatment in patients unsuitable for chemoimmunotherapy, the G-BA specified the ACT of individualized therapy, taking into account general health and any prior therapies as well as remission duration after initial therapy. Alongside ibrutinib monotherapy, the following therapy options are deemed suitable comparators within the context of clinical trials: bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab.

The company's dossier fails to discuss the extent to which the aspects of health status, any prior therapies, and remission duration were taken into account in patient enrolment in the ASPEN study, whose comparator arm offered ibrutinib monotherapy as the only treatment option. Furthermore, Module 4 A of the company's dossier does not analyse the available information on these aspects. The information available in the dossier likewise does not demonstrate that ibrutinib monotherapy represents individualized therapy for the patients included in the study, taking into account these aspects. The available information suggests that, for part of the study population, treatment options other than those listed above were potentially suitable.

For patients in good general health, the guidelines [3,4] specify combinations of rituximab and chemotherapy as treatment options of first choice for first-line treatment in patients with Waldenström macroglobulinaemia. In the ASPEN study, 94% of patients included in cohort 1 had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1, indicating that they were in good general health. The majority of the patients included in the study (82%) had received at least 1 prior therapy (see Table 11 in Appendix B of the full dossier assessment). Module 4 A of the company's dossier does not identify the patients' prior therapies. Although the information provided in the study documents shows that this patient group had already received a lot of prior treatment regimens at baseline, only 1 patient had received a combination of rituximab and chemotherapy as prior therapy (see Table 12 in Appendix B of the full dossier assessment). While a large proportion of treatment-experienced patients had received prior rituximab therapy (about 90%), contrary to guideline recommendations, this treatment was not administered in the form of a combination with chemotherapy, i.e., it was not administered in combination with either bendamustine or cyclophosphamide and dexamethasone. Likewise, none of the prior therapies involved rituximab in combination with bortezomib. Only 1 patient had received rituximab in combination with cyclophosphamide, doxorubicin hydrochloride, prednisone, and vincristine sulphate. This information seems implausible given the guideline recommendations concerning combinations of rituximab and chemotherapy. In all, it is questionable whether, for the patients included in the study's comparator arm, ibrutinib in fact represents the best possible individualized therapy or whether, in consideration of prior therapy, different treatment options, particularly combination regimens of rituximab and chemotherapy, would have been preferable for individual patients.

According to the guideline issued by the German Society for Haematology and Medical Oncology (DGHO), repeating the prior therapy would represent another option for patients in good general health who had a remission duration of ≥ 24 months after first-line therapy [4]. For treatment-experienced participants of the ASPEN study, the company's dossier does not provide any information on the duration of remission after first-line therapy. The study documents provide information only on the time from the end of the most recent therapy until the 1st dose of the study treatment (see Table 11 in Appendix B of the full dossier assessment). These data differ markedly between the 2 study arms: While the median time from the end of the most recent therapy until the 1st dose of the study drug was 14.2 months in the zanubrutinib arm, it equalled 30.6 months in the ibrutinib arm. These data suggest potential differences

between study arms regarding the duration of remission duration after first-line therapy, but only approximate analyses are possible. This is due, firstly, to the data not being exclusively based on treatment responders. Secondly, the data are based on all treatment-experienced patients, regardless of the number of prior courses of therapy they received. The available data therefore do not show whether ibrutinib represents individualized therapy for treatment-experienced patients in the study's comparator arm or whether in consideration of the duration of remission, repeating the first-line therapy might have been preferable for at least some of these patients.

In addition to treatment-experienced patients, the ASPEN study included a small proportion of first-line therapy patients who are unsuitable for chemoimmunotherapy (18%; 19 patients in the zanubrutinib arm and 18 in the ibrutinib arm). For these patients, the company likewise did not explain why ibrutinib represents a suitable individualized therapy. However, the guidelines specify BTK inhibitors such as ibrutinib, possibly in combination with rituximab, as the primary suitable treatment options for these patients who are unsuitable for chemoimmunotherapies [3,4].

In summary, the company neither provided a rationale as to why ibrutinib represented individualized therapy for ASPEN participants with Waldenström macroglobulinaemia, nor did it discuss the extent to which other, generally available treatment options were not preferable individualized therapy in consideration of clinical aspects. The company's dossier does not supply sufficient information on clinical aspects to be taken into account when selecting the treatment option. Yet, the information available on treatment-experienced patients included in the study suggests that for part of the study population, different treatment options might have been suitable. However, the ASPEN study did not provide treating physicians with any comparator arm options other than ibrutinib monotherapy. Therefore, the study presented by the company is not suitable for a comparison of zanubrutinib versus the ACT of individualized therapy.

Incomplete analyses submitted for the ASPEN study

Aside from the ASPEN study being unsuitable for the benefit assessment for the reasons described above, the ASPEN study's data analysis as presented in the dossier's Module 4 A suffers from substantial deficiencies. Alongside the described shortcomings in the data analysis for the included patients, Module 4 A of the dossier inadequately analyses the results of the study. In particular, the results of the ASPEN study presented in the company's dossier are incomplete. The dossier therefore does not allow an adequate assessment of the study results. The rationale is provided below.

Missing analyses on the 2nd data cut-off

Two data cut-offs are available for the ASPEN study. The 1st data cut-off from 31 August 2019 was predefined, being carried out ≥ 15 months after 90% of recurrent or refractory patients had been recruited. The 2nd data cut-off was conducted on 31 August 2020 upon request by the European Medicines Agency (EMA). The company presents analyses on the 1st data cut-off in

Module 4 A of the dossier and uses it for the benefit assessment. However, for this data cut-off, the company presents analyses only for a portion of the relevant patient-reported outcomes. In addition, the company does not present any complete subgroup analyses for this data cut-off. While Module 4 A descriptively presents results on the 2nd data cut-off, results on patient-reported outcomes are completely missing for this data cut-off. The results of the ASPEN study as presented in the company's dossier are therefore incomplete.

Incomplete data on patient-reported outcomes

The ASPEN study surveyed patient-reported outcomes on morbidity and health-related quality of life by means of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30). Furthermore, health status was surveyed with the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS). The company's dossier presents no analyses of these patient-reported outcomes at the 2nd data cut-off, reasoning that not all outcomes were evaluated at this non-predefined data cut-off, which was requested by the EMA.

The dossier template [14] generally specifies for complete analyses of all surveyed patient-relevant outcomes to be carried out and presented for the data cut-offs submitted by the company, even in cases where a data cut-off was originally planned for the analysis of only some of the outcomes. Further, in the current data constellation, the 31 August 2020 data cut-off presumably contains substantial amounts of additional data on patient-reported outcomes when compared to the 31 August 2019 data cut-off. This can be safely assumed since the ASPEN study followed up on patient-reported outcomes until treatment end, and according to information provided in the study documents on the 2nd data cut-off, 75% of patients in the zanubrutinib arm and 68% in the ibrutinib arm were still being treated and hence followed up at that time.

For the 1st data cut-off on 31 August 2019, Module 4 A of the company's dossier presents analyses on patient-reported outcomes, but even these analyses are incomplete since they included only some of the relevant patient-reported outcomes surveyed in the study. For EQ-5D VAS, Module 4 A does not present any results. For the EORTC QLQ-C30 questionnaire, the company presents analyses only on selected scales (4 symptom scales: fatigue, pain, appetite loss, diarrhoea; scale on global health status). The study documents show, however, that the ASPEN study surveyed all scales of EORTC QLQ-C30. The company did not justify its exclusion of analyses on further relevant aspects of symptoms and health-related quality of life, which are surveyed via the questionnaire, e.g. nausea and vomiting and physical, emotional, or social functioning. The results of the ASPEN study as presented by the company are therefore incomplete.

No complete subgroup analyses

Module 4 A of the company's dossier presents subgroup analyses only for the attribute of treatment status at baseline; related results from an interaction test are missing. The company justifies foregoing subgroup analyses for other potential effect modifiers and interaction testing

by arguing that the ASPEN study defined a priori subgroup analyses only for the primary outcome and for the attributes of sex, age, disease severity or stage as well as centre and country. The company further argues that these analyses showed no significant effect modification for the primary outcome by the investigated attributes and that it is therefore safe to assume that no effect modification can be expected in further outcomes either. This assumption by the company is inadequate. According to the dossier template, for studies conducted by the company, corresponding analyses must be submitted for all identified effect modifiers of all relevant outcomes in accordance with the criteria specified in the template and therefore must be carried out post hoc if necessary [14]. The company's approach regarding subgroup analyses is therefore not appropriate and leads to incomplete information being provided in the dossier.

Analysis of results inadequate overall

Irrespective of the fact that the company has not submitted complete results on either of the 2 data cut-offs available for the ASPEN study, the analyses presented by the company in Module 4 A have been insufficiently analysed. Further key points of criticism on the data analysis by the company in Module 4 A are described below:

- The results presented by the company on the selected symptom scales of the EORTC QLQ-C30 are based on constrained longitudinal data analysis (cLDA). For the global health status scale, the company additionally submitted the results of an analysis on the basis of the mixed model repeated measures (MMRM).

  The cLDA each seem to involve an analysis at the end of treatment, but for said end, all analyses presented in Module 4 A at the 1st data cut-off apparently contain data for only 4 patients in the intervention arm and 9 patients in the comparator arm. Although Module 4 A of the company's dossier does not supply any analyses of return rates for patient-reported outcomes at all analysis points, figures on the course of the study, which the company additionally presented, show that surveys were conducted for all presented scales, e.g. at cycle 19, in more than 60% of intervention arm patients and more than 50% of comparator arm patients. The MMRM analysis on global health status included almost all randomized patients (101 versus 99) with the surveys available from them. It remains unclear why the company has submitted an analysis on treatment end by means of the cLDA model which apparently included few patients instead of carrying out, e.g., an MMRM analysis for all scales, including all surveys for the entire study population.
- In addition to the described analyses by means of cLDA and MMRM, the company reports descriptively how many patients "improved" or "deteriorated" or remained "stable" by treatment end for the EORTC QLQ-C30 global health status. However, the company did not report the criteria used for these categorizations. While responder analyses were preferred for the benefit assessment, as explained in the IQWiG General Methods [1,15], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post hoc analyses, exactly 15% of the scale range; see G-BA Frequently Asked Questions regarding the special situation for the EORTC QLQ

C30 [16]). It remains unclear whether this is the case for the criteria applied by the company.

- Module 4 A of the company's dossier provides no information on outcome-specific follow-up durations or on antineoplastic subsequent therapies. Aside from the incompletely presented and inadequately analysed results, this issue further complicates the interpretation of study data.

2.4 Results on added benefit

No suitable data for assessing the added benefit of zanubrutinib versus the ACT are available for adult patients with Waldenström macroglobulinaemia who have received at least 1 prior therapy or as first-line treatment in patients unsuitable for chemoimmunotherapy. This results in no hint of an added benefit of zanubrutinib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of 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 Waldenström macroglobulinaemia who have received at least one prior therapy, or as first-line treatment in patients unsuitable for chemoimmunotherapy	Individualized therapy[b] taking into account general health and any prior therapies as well as duration of remission after initial therapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The drugs or drug combinations of bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are recommended by the guideline as well as the professional associations as ACTs. With the exception of the combination of ibrutinib + rituximab, the drugs bortezomib and rituximab are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines and by professional associations. Within clinical trials, bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab, and rituximab are deemed suitable comparators.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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

The G-BA decides on the added benefit.

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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