IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Venetoclax (chronic lymphocytic leukaemia; combination with rituximab) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Venetoclax (chronische lymphatische Leukämie,* Kombination mit Rituximab*) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2019). Please note: This translation 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	Best supportive Care
CIT	chemoimmunotherapy
CLL	chronic lymphocytic leukaemia
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PALG	Polish Adult Leukaemia Group
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 venetoclax in combination with rituximab. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 22 November 2018.

Research question

The aim of this report was to assess the added benefit of venetoclax + rituximab compared with the appropriate comparator therapy (ACT) in adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

Two research questions resulted for the assessment in accordance with the G-BA's specification of the ACT. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of venetoclax + rituximab

Research question	Subindication	ACT[a]
1	Adult patients[b] with chronic lymphocytic leukaemia (CLL) without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated[c] and who have received at least one prior therapy	Individual chemoimmunotherapy in accordance with physician's choice under consideration of the general condition and the success and tolerability of the prior therapy[d]
2	Adult patients with CLL and at least one prior therapy who have either 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib or idelalisib + rituximab Best supportive care[f]

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment.
c: Referred to as CIT population in the assessment.
d: According to the G-BA, rituximab in combination with fludarabine and cyclophosphamide (FCR), rituximab in combination with bendamustine (BR) and rituximab in combination with chlorambucil (ClbR) are established and approved treatment options in the present therapeutic indication. For patients without 17p deletion and with at least 2 prior therapies, the drug combination ibrutinib/bendamustine/rituximab is comprised by the ACT.
e: Referred to as high-risk population in the assessment.
f: Best supportive Care (BSC) only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab; BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BR: rituximab in combination with bendamustine; CIT: chemoimmunotherapy; ClbR: rituximab in combination with chlorambucil; CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide; G-BA: Federal Joint Committee

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

Results

Research question 1: CIT population

For research question 1, the company used the randomized controlled trial (RCT) MURANO, which compared venetoclax + rituximab with bendamustine + rituximab. Data of this study are irrelevant for the present benefit assessment, because the decision on the treatment option in the comparator arm of the MURANO study presented by the company was not made on an individual basis, but all patients of the study received bendamustine + rituximab as uniform medication. The company presented no substantive arguments about why this combination was the individual treatment for all patients of the CIT population of the MURANO study.

In summary, the company presented no suitable data for the assessment of the added benefit in comparison with the ACT for adult patients with CLL without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated and who have received at least one prior therapy. This resulted in no hint of an added benefit of venetoclax + rituximab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: high-risk population

The company used the RCT MURANO also for research question 2. The data considered by the company permitted no conclusion on the added benefit of venetoclax + rituximab in comparison with the ACT for patients of the present research question.

In summary, the company presented no suitable data for the assessment of the added benefit of venetoclax + rituximab in comparison with the ACT for adult patients with CLL and at least one prior therapy who have either 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason. This resulted in no hint of an added benefit 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 the added benefit of venetoclax + rituximab.

[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: Venetoclax + rituximab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients[b] with CLL without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated[c] and who have received at least one prior therapy	Individual chemoimmunotherapy in accordance with physician's choice under consideration of the general condition and the success and tolerability of the prior therapy[d]	Added benefit not proven
2	Adult patients with CLL and at least one prior therapy who have either 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib or idelalisib + rituximab Best supportive care[f]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment.
c: Referred to as CIT population in the assessment.
d: According to the G-BA, rituximab in combination with fludarabine and cyclophosphamide (FCR), rituximab in combination with bendamustine (BR) and rituximab in combination with chlorambucil (ClbR) are established and approved treatment options in the present therapeutic indication. For patients without 17p deletion who have received at least 2 prior therapies, the drug combination ibrutinib/bendamustine/rituximab is comprised by the ACT.
e: Referred to as high-risk population in the assessment.
f: BSC only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab; BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BR: rituximab in combination with bendamustine; BSC: Best supportive Care; CIT: chemoimmunotherapy; ClbR: rituximab in combination with chlorambucil; CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of venetoclax + rituximab compared with the ACT in adult patients with CLL who have received at least one prior therapy.

Two research questions resulted for the assessment in accordance with the G-BA's specification of the ACT. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of venetoclax + rituximab

Research question	Subindication	ACT[a]
1	Adult patients[b] with CLL without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated[c] and who have received at least one prior therapy	Individual chemoimmunotherapy in accordance with physician's choice under consideration of the general condition and the success and tolerability of the prior therapy[d]
2	Adult patients with CLL and at least one prior therapy who have either 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib or idelalisib + rituximab Best supportive care[f]

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment.
c: Referred to as CIT population in the assessment.
d: According to the G-BA, rituximab in combination with fludarabine and cyclophosphamide (FCR), rituximab in combination with bendamustine (BR) and rituximab in combination with chlorambucil (ClbR) are established and approved treatment options in the present therapeutic indication. For patients without 17p deletion who have received at least 2 prior therapies, the drug combination ibrutinib/bendamustine/rituximab is comprised by the ACT.
e: Referred to as high-risk population in the assessment.
f: Best supportive Care (BSC) only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab; BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BR: rituximab in combination with bendamustine; CIT: chemoimmunotherapy; ClbR: rituximab in combination with chlorambucil; CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide; G-BA: Federal Joint Committee

The company followed the specification of the ACT for both research questions. The present assessment was conducted in comparison with the G-BA's ACT described in Table 4.

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

2.3 Research question 1: CIT population

2.3.1 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 venetoclax (status: 14 September 2018)
- bibliographical literature search on venetoclax (last search on 12 September 2018)
- search in trial registries for studies on venetoclax (last search on 14 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on venetoclax (last search on 11 December 2018)

The check of the completeness of the study pool produced no relevant studies on the comparison of venetoclax + rituximab versus the ACT. In contrast to this, the company identified RCT GO28667 [3-10] (hereinafter referred to as MURANO) for research question 1 and used this study for the assessment of an added benefit.

Study MURANO

The MURANO study is a randomized, active controlled, open-label and multicentre 2-arm phase 3 study. Included were adult patients with relapsed or refractory CLL independent of their 17p deletion or TP53 mutation status who had received at least one and at most 3 prior therapies. A total of 389 patients were randomly assigned to the 2 treatment arms venetoclax + rituximab and bendamustine + rituximab in a ratio of 1:1. For the derivation of the added benefit, the company created a subpopulation of research question 1 comprising patients without 17p deletion and without TP53 mutation who have a low risk status in accordance with the stratification factor of the study (recurrence more than 12 months after a chemotherapy or 24 months after a chemoimmunotherapy). These were 74 patients in the venetoclax + rituximab arm and 66 patients in the bendamustine + rituximab arm. Further characteristics of the MURANO study and information on the characteristics of the subpopulation created by the company can be found in Appendix A of the full benefit assessment.

No implementation of an individual chemoimmunotherapy in the MURANO study

The MURANO study was unsuitable for the assessment of the added benefit of venetoclax + rituximab in comparison with the ACT specified by the G-BA. The reason for this was that the decision on the treatment option in the comparator arm was not made on an individual basis, but all patients of this study arm received bendamustine + rituximab as uniform medication.

Besides bendamustine + rituximab, various treatment options are possible for adult patients with CLL without 17p deletion and/or TP53 mutation who have received at least one prior therapy and for whom chemoimmunotherapy is indicated. In accordance with the guidelines, treatment of relapses might include a repetition of the primary therapy in case of late recurrence and adequate response. Besides bendamustine + rituximab, the combination therapy with fludarabine + cyclophosphamide + rituximab, for instance, can be found in the guidelines as possible repeatedly applicable option [11-14]. The proportion of patients in the total population of the MURANO study who had already received bendamustine before (in combination with rituximab) is very small (less than 3% per study arm). However, about half of the patients in the total population had received the combination of fludarabine + cyclophosphamide + rituximab as prior CLL treatment. Thereby, 85% of the patients in each study arm were not refractory to fludarabine. A repetition of the primary therapy with fludarabine + cyclophosphamide + rituximab might also have been an option for these patients. The S3

guideline signals that fludarabine-based treatment can be switched to bendamustine-based treatment and vice versa [14]. However, none of the guidelines specifies bendamustine + rituximab to be the preferred choice over other treatment options for the target population mentioned in the guidelines.

The company justified the suitability of bendamustine + rituximab as individual treatment in accordance with physician's choice with the general suitability of the patients in the MURANO study for this treatment. In Module 4 A, it stated on the one hand that patients who had already been treated with bendamustine had to have responded adequately to this treatment for at least 24 months and had to be free of intolerances or contraindications to bendamustine and of hypersensitivity to rituximab. In Module 3 A, the company on the other hand justified the suitability of bendamustine + rituximab with the importance of this combination therapy according to the application frequency.

The company's arguments are not substantive. Even if there were no reasons against treatment with bendamustine + rituximab for the patients of the MURANO study, this does not imply, conversely, that this combination should be preferred over the other available treatment options. Nor does the application frequency of bendamustine + rituximab provide information on whether this therapy constitutes the individual treatment for the patients included in the MURANO study.

Overall, the company did not discuss in how far other principally suitable treatment options were not preferable under clinical aspects. These further treatment options were excluded in the comparator arm. Hence, the MURANO study allowed no comparison of venetoclax + rituximab with the ACT specified by the G-BA.

2.3.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit in comparison with the ACT for adult patients with CLL without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated and who have received at least one prior treatment. This resulted in no hint of an added benefit of venetoclax + rituximab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Since suitable data for the assessment of an added benefit in comparison with the ACT are not available for adult patients with CLL without 17p deletion and/or TP53 mutation and for whom chemoimmunotherapy is indicated and who have received at least one prior therapy, an added benefit of venetoclax + rituximab is not proven for this research question.

This deviates from the company's assessment, which derived an indication of considerable added benefit on the basis of a subpopulation of the MURANO study created by it.

2.3.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question 2: high-risk population

2.4.1 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 venetoclax (status: 14 September 2018)
- bibliographical literature search on venetoclax (last search on 12 September 2018)
- search in trial registries for studies on venetoclax (last search on 14 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on venetoclax (last search on 11 December 2018)

For research question 2, the company identified no relevant studies for the benefit assessment enabling a comparison with the ACT defined by the G-BA. The check also identified no relevant study.

Approach of the company

Data from the MURANO study

In Module 4 A (Section 4.3.1.1.4), the company refers to the MURANO study (see research question 1), which, from its point of view, included patients of the high-risk population. It explained that the ACT administered within the study (bendamustine + rituximab) did not correspond to the ACT specified by the G-BA (ibrutinib, idelalisib + rituximab or best supportive care [BSC]) and thus permitted no comparison with the ACT for the patient population of interest. In Module 4 A (Section 4.4.2), the company stated that it was still going to present the data of the high-risk population of the MURANO study as additional information. It described that the MURANO study presented an active comparison, which was to be considered as best available evidence. However, eventually the company provided no supplementary presentation and used the data from the MURANO study for the derivation of an added benefit instead.

The data considered by the company permitted no conclusion on the added benefit of venetoclax + rituximab in comparison with the ACT for patients of the present research question. The data presented by the company were therefore not used for the present assessment.

Comparison with ibrutinib

Moreover, the company noted that, according to guideline [11], the option “BSC” defined by the G-BA constituted a treatment option exclusively for patients who were not eligible for active

treatment due to severe comorbidities. According to the company, the guidelines [11,12,14] mention second-line treatment with ibrutinib in the first place. To enable a classification of the available evidence on venetoclax + rituximab for the high-risk population in comparison with ibrutinib, the company intended to compare the results on venetoclax + rituximab from the MURANO study descriptively with the results from several studies with ibrutinib. Information retrieval of the company identified 6 studies involving treatment with ibrutinib as monotherapy (RESONATE, RESONATE-17, CLL3002, NCT01500733, Compassionate Use Program of the Polish Adult Leukaemia Group (PALG), PCYC-1102-CA [15-23]). It conducted a descriptive comparison of the results on overall survival, progression-free survival (PFS), overall response and complete remission from these studies with the results from the MURANO study. The company justified this purely descriptive presentation with uncertainties regarding the homogeneity of the study populations to be compared and the operationalization of the outcomes.

Mere comparison of results from individual arms of different studies and, at the same time, non-consideration of the comparability of the study populations and the operationalizations of the outcomes is inadequate. The data presented by the company are thus unsuitable to prove an advantage or disadvantage of venetoclax + rituximab versus ibrutinib in patients of the high-risk population; they were not used for the present benefit assessment.

2.4.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of venetoclax + rituximab in comparison with the ACT for adult patients with CLL and at least one prior therapy who have either 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason. This resulted in no hint of an added benefit in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The data presented by the company for the assessment of the added benefit of venetoclax + rituximab in adult patients with CLL and at least one prior therapy who have either 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason, were unsuitable to derive an added benefit in comparison with the ACT. Hence, an added benefit of venetoclax + rituximab is not proven for these patients.

This deviates from the assessment of the company, which derived a hint of a non-quantifiable added benefit for patients of the high-risk population under consideration of the results of the MURANO study and a descriptive comparison of these results with those from the ibrutinib studies.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Probability and extent of added benefit – summary

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

Table 5: Venetoclax + rituximab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients[b] with CLL without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated[c] and who have received at least one prior therapy	Individual chemoimmunotherapy in accordance with physician's choice under consideration of the general condition and the success and tolerability of the prior therapy[d]	Added benefit not proven
2	Adult patients with CLL and at least one prior therapy who have either 17p deletion and/or TP53 mutation or for whom chemoimmunotherapy is not indicated for any other reason	Ibrutinib or idelalisib + rituximab Best supportive care[f]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment.
c: Referred to as CIT population in the assessment.
d: According to the G-BA, rituximab in combination with fludarabine and cyclophosphamide (FCR), rituximab in combination with bendamustine (BR) and rituximab in combination with chlorambucil (ClbR) are established and approved treatment options in the present therapeutic indication. For patients without 17p deletion who have received at least 2 prior therapies, the drug combination ibrutinib/bendamustine/rituximab is comprised by the ACT.
e: Referred to as high-risk population in the assessment.
f: BSC only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab; BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BR: rituximab in combination with bendamustine; BSC: Best supportive Care; CIT: chemoimmunotherapy; ClbR: rituximab in combination with chlorambucil; CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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