IQWiG Reports – Commission No. A19-78

Ibrutinib (Waldenström macroglobulinaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ibrutinib (Morbus Waldenström) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Ibrutinib (Waldenström macroglobulinaemia) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

2 September 2019

Internal Commission No.:

A19-78

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.

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Keywords: ibrutinib, rituximab, Waldenstrom macroglobulinemia, benefit 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
AE	adverse event
CXCR4	C-X-C motif chemokine receptor 4
ECOG PS	Eastern Cooperative Oncology Group – Performance Status
EMEA	Europe, Middle East and Africa
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	Matching Adjusted Indirect Comparison
PFS	progression-free survival
PHEDRA	EMEA Data for Real World Analysis
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 ibrutinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 September 2019.

Research question

The aim of the present report is the assessment of the added benefit of ibrutinib in combination with rituximab (hereinafter referred to as "ibrutinib + rituximab") in comparison with the appropriate comparator therapy (ACT), an individual treatment under consideration of the general condition and possible prior therapies in adult patients with Waldenström macroglobulinaemia.

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

Table 2: Research question of the benefit assessment of ibrutinib + rituximab

Research question	Subindication	ACT[a]
1	Adult patients with Waldenström macroglobulinaemia	Individual treatment under consideration of the general condition and possible prior therapies[b]

a: Presentation of the respective ACT specified by the G-BA.
b: For the present therapeutic indication, the company assumed that the patients were symptomatic and in need of treatment. Moreover, it is assumed that autologous or allogeneic stem cell transplantation was not indicated at the time point of treatment.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company specified an individual treatment under consideration of the general condition and possible prior therapies and thus followed the G-BA's specification.

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

Results

No direct or indirect comparisons

The company identified no randomized controlled trials (RCTs), neither for direct comparisons of ibrutinib + rituximab with the ACT, nor for adjusted indirect comparisons using the common comparator "rituximab" used by the company. It included the RCT PCYC-1127-CA (hereinafter referred to as iNNOVATE) to demonstrate the medical benefit of ibrutinib + rituximab, but explicitly not to assess the added benefit, and presents the results. The iNNOVATE study investigates ibrutinib + rituximab versus placebo + rituximab. For the

following reasons, the company did not use this study for the derivation of the added benefit versus the ACT.

All patients in comparator arm B of the iNNOVATE study received placebo + rituximab. However, the company could state neither that rituximab monotherapy presents a suitable individual therapy for all patients included in the comparator arm, nor can it identify a subpopulation to whom this applies. It is thus unclear whether and to which extent the ACT was implemented in the iNNOVATE study.

The iNNOVATE study is unsuitable for the derivation of the added benefit versus the ACT and is not used for the present benefit assessment.

Comparison of individual arms from different studies unsuitable

In the dossier, the company presented comparisons of individual arms from different studies. It compared the ibrutinib + rituximab arm A of the iNNOVATE study with an patient individual treatment or with ibrutinib monotherapy. To compare ibrutinib + rituximab with an individual treatment, the company presented data on the retrospective cohort studies Castillo 2018, Castillo 2019 and on the Platform for Haematology in EMEA (Europe, Middle East and Africa): Data for Real World Analysis (PHEDRA) data base. The company presented data on the single-arm study PCYC-1118E and on arm C of the iNNOVATE study for the comparison of ibrutinib + rituximab with ibrutinib monotherapy.

The comparisons of individual arms from different studies presented by the company were also unsuitable for the derivation of an added benefit, because the effect estimations were not sufficiently large that they could not be caused by systematic bias alone. In fact, no statistically significant results could be identified for patient-relevant outcomes. Moreover, the ACT was not implemented in study PCYC-1118E and in arm C of the iNNOVATE study. All patients in both study arms received ibrutinib monotherapy. The data presented by the company provide no information on whether ibrutinib monotherapy was the individually optimized treatment for the patients included in study PCYC-1118E and in arm C of the iNNOVATE study. Moreover, adverse events (AEs) were not recorded in the studies Castillo 2018, Castillo 2019 and the PHEDRA database. Therefore, adequate balancing of benefit and risk versus ibrutinib + rituximab is not possible for these studies.

For the reasons mentioned above, there are no suitable data for the assessment of ibrutinib + rituximab in the treatment of adult patients with Waldenström macroglobulinaemia. Hence, there was no hint of an added benefit of ibrutinib + rituximab 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 ibrutinib + rituximab.

Table 3: Ibrutinib + rituximab – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Adult patients with Waldenström macroglobulinaemia	Individual treatment under consideration of the general condition and possible prior therapies[b]	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: For the present therapeutic indication, the company assumed that the patients were symptomatic and in need of treatment. Moreover, it is assumed that autologous or allogeneic stem cell transplantation was not indicated at the time point of treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of ibrutinib in combination with rituximab (hereinafter referred to as "ibrutinib + rituximab") in comparison with the ACT, an individual treatment under consideration of the general condition and possible prior therapies in adult patients with Waldenström macroglobulinaemia.

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

Table 4: Research question of the benefit assessment of ibrutinib + rituximab

Research question	Subindication	ACT[a]
1	Adult patients with Waldenström macroglobulinaemia	Individual treatment under consideration of the general condition an possible prior therapies[b]
a: Presentation of the respective ACT specified by the G-BA. b: For the present therapeutic indication, the company assumed that the patients were symptomatic and in need of treatment. Moreover, it is assumed that autologous or allogeneic stem cell transplantation was not indicated at the time point of treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

[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].

The company specified an individual treatment under consideration of the general condition and possible prior therapies and thus followed the G-BA's specification.

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 ibrutinib + rituximab (status: 13 August 2019)
- bibliographical literature search on ibrutinib + rituximab (last search on 23 July 2019)
- search in trial registries for studies on ibrutinib + rituximab (last search on 19 July 2019)
- bibliographical literature search on ACTs (last search on 24 July 2019)
- search in trial registries for studies on ACTs (last search on 22 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ibrutinib (last search on 10 September 2019)

The check of the completeness of the study pool produced no relevant RCT on the direct comparison of ibrutinib + rituximab versus the ACT.

Approach of the company

The company also identified no RCTs, neither for direct comparisons of ibrutinib + rituximab with the ACT, nor for adjusted indirect comparisons using the common comparator "rituximab" used by the company. It included the RCT PCYC-1127-CA (hereinafter referred to as iNNOVATE) [3] to demonstrate the medical benefit of ibrutinib + rituximab, but explicitly not to assess the added benefit, and presents the results. The iNNOVATE study investigates ibrutinib + rituximab versus placebo + rituximab. In Section 4.3.1.2.1 of Module 4 B, the company stated that this study was not used for the derivation of the added benefit, because the comparator arm of the study neither corresponded to the ACT specified by the G-BA, nor could a subpopulation relevant for the research question be defined.

Since the company identified no RCTs for direct comparisons or adjusted indirect comparisons, it conducted a search for further studies and presented comparisons of individual arms from different studies (referred to as "historical comparison" or "indirect comparison" in the company's dossier). With its search, the company identified the studies Castillo 2018 [4], Castillo 2019 [5] and, by manual search, the Platform for Haematology in EMEA (Europe, Middle East and Africa): Data for Real World Analysis (PHEDRA) database [6] on the side of the ACT. It presented the mentioned studies as well as the single-arm study PCYC-1118E [7]

and arm C of the iNNOVATE study as supplementary information. On the intervention side, the company used arm A (ibrutinib + rituximab) of the iNNOVATE study and compared it with studies in which the patients were described as having received individual treatment (Castillo 2018, Castillo 2019, PHEDRA database) or ibrutinib monotherapy (study PCYC-1118E, arm C of the iNNOVATE study).

The data presented by the company are unsuitable for the derivation of an added benefit of ibrutinib + rituximab versus the ACT specified by the G-BA in the therapeutic indication. This is justified below. For this purpose, the data used by the company are first described. Then it is explained why the data presented permit no derivation of conclusions on the added benefit of ibrutinib + rituximab in comparison with the ACT.

Data presented by the company

iNNOVATE

The iNNOVATE study [3] is an RCT and the approval study for the new therapeutic indication "Waldenström macroglobulinaemia". The study included adult patients with untreated or pretreated Waldenström macroglobulinaemia. All study participants had a general condition from 0 to 2 according to the Eastern Cooperative Oncology Group – Performance Status (ECOG PS). A total of 150 patients were randomized. The patients in arm A received ibrutinib + rituximab, those in arm B were administered placebo + rituximab. In the non-randomized arm C, 31 patients who were refractory to prior rituximab-containing therapy and thus excluded from the randomized main study received ibrutinib monotherapy.

In the dossier, the company presented the results, but did not use the entire iNNOVATE study for the derivation of the added benefit, because the comparator arm of the study neither corresponds to the ACT specified by the G-BA, nor could a subpopulation relevant for the research question be defined. Moreover, the company used the results of the individual study arms A and C of the iNNOVATE study for its comparison of individual arms from different studies.

Castillo 2018

Castillo 2018 [4] is a retrospective cohort study investigating the response and survival of 182 adult patients with Waldenström macroglobulinaemia, who received primary therapy with different treatment regimens in the Dana-Farber Cancer Institute in Boston between 2005 and 2016. These regimens comprised therapies consisting of bendamustine + rituximab, cyclophosphamide + dexamethasone + rituximab and bortezomib + dexamethasone + rituximab. The majority of the patients additionally received maintenance treatment with rituximab after completed primary therapy. Results on the following outcomes are presented in the study: "overall survival", "progression-free survival (PFS)", and "response". Results on AEs were not reported.

Castillo 2019

The retrospective cohort study Castillo 2019 [5] investigates the impact of several C-X-C motif chemokine receptor 4 (CXCR4) mutations subtypes on the response and survival of 180 adult patients with Waldenström macroglobulinaemia who had been treated with ibrutinib in the Dana-Farber Cancer Institute in Boston between 2012 and 2017. The study presents results on the outcomes "overall survival", "PFS" and "response". Results on AEs were not reported.

PHEDRA

The PHEDRA database [6] is a retrospective secondary database, which is fed by individual patient data from various existing databases. Aim of the PHEDRA database is to understand the treatment patterns of the haematological diseases chronic lymphocytic leukaemia, mantle cell lymphoma and Waldenström macroglobulinaemia. The PHEDRA database comprises data of 2840 patients from the period 1990 to 2017.

The company presented analyses for 143 French patients with Waldenström macroglobulinaemia, who had been treated with therapy regimens which, according to the company, are relevant comparators. These therapies comprise rituximab + chlorambucil, bendamustine + rituximab, rituximab monotherapy, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone/prednisolone, rituximab + bortezomib, rituximab + cyclophosphamide + dexamethasone and ibrutinib monotherapy. The outcomes recorded in PHEDRA are "overall survival" and "PFS". Results on AEs were not reported.

PCYC-1118E

The study PCYC-1118E [7] is a single-arm, open-label study in which 63 adult patients with relapsed or refractory Waldenström macroglobulinaemia were treated with ibrutinib monotherapy. The following outcomes, among others, were investigated: "overall response rate", "overall survival", "PFS" and "AEs".

Data presented by the company are unsuitable for the derivation of the added benefit

RCT iNNOVATE

The company presented data on the RCT "iNNOVATE" in its dossier. However, for the following reasons, the company did not use this study for the derivation of the added benefit versus the ACT.

All patients in comparator arm B of the iNNOVATE study received placebo + rituximab. Despite the lack of approval in this therapeutic indication [8], rituximab monotherapy is mentioned in guidelines [9,10] as an alternative for elderly and comorbid patients. However, this treatment is associated with a lower response rates than combined chemoimmunotherapy. For patients with a good general condition, a combination therapy consisting of rituximab and chemotherapy is considered the standard both for primary therapy and for second-line treatment in Waldenström macroglobulinaemia [9]. According to statements of the company in Section

4.3.1.2.1 of Module 4 B, it must be assumed that another treatment than rituximab monotherapy would be an option for some of the patients in comparator arm B of the iNNOVATE study.

Moreover, the company considers a definition of the subpopulation relevant for the present benefit assessment to be impossible. The company justified this by stating that there was no definite age limit from which chemo-immunotherapy is no longer an option for the patients with Waldenström macroglobulinaemia. Moreover, comorbidities were not systematically recorded in the iNNOVATE study, which made it impossible to identify patients for whom rituximab monotherapy would be a suitable treatment option within the study.

Thus, the company could state neither that rituximab monotherapy presents a suitable individual therapy for all patients included in the comparator arm, nor can it identify a subpopulation to whom this applies. It is thus unclear whether and to which extent the ACT was implemented in the iNNOVATE study. Therefore, the company did not use the study for the derivation of an added benefit.

The argumentation of the company is adequate. The iNNOVATE study is unsuitable for the derivation of the added benefit versus the ACT and, concurring with the company, it is not used for the present benefit assessment.

Comparison of individual arms from different studies

In the dossier, the company presented comparisons of individual arms from different studies. It compared the ibrutinib + rituximab arm A of the iNNOVATE study with an individual treatment or with ibrutinib monotherapy.

In order to compare ibrutinib + rituximab with an individual treatment, the company presented data on the studies Castillo 2018, Castillo 2019 and the PHEDRA database.

The company presented data on the study PCYC-1118E and on arm C of the iNNOVATE study for the comparison of ibrutinib + rituximab with ibrutinib monotherapy. In order to compare ibrutinib + rituximab with the ibrutinib monotherapy from study PCYC-1118E, the company first tried to conduct a comparison using the Matching Adjusted Indirect Comparison (MAIC) method. In order to adjust the populations of the two studies, the company restricted the study population of the ibrutinib + rituximab arm A of the iNNOVATE study to pretreated patients. Nevertheless, when the MAIC was performed, imbalances in the baseline characteristics could not completely be eliminated. Due to possible bias, the company did not present the corresponding results in its dossier. Instead, it presented results from the naive comparison of two arms.

The data presented on the comparisons of individual arms from different studies are not suitable for deriving the added benefit versus the ACT for the following reasons:

No sufficiently large effect

When comparing individual arms from different studies, the uncertainty of results is high and conclusions on the added benefit are usually only possible if a very large effect is present. However, the effect estimations on the patient-relevant outcomes presented by the company were not sufficiently large that they could not be caused by bias alone. In fact, no statistically significant results could be identified for patient-relevant outcomes.

ACT not completely implemented

The ACT was not implemented in study PCYC-1118E and in arm C of the iNNOVATE study. All patients in both study arms received ibrutinib monotherapy. Ibrutinib monotherapy is approved for the therapeutic indication and is to be considered a treatment option within the framework of an individual treatment, but the data presented by the company provide no information on whether ibrutinib monotherapy was the individually optimized treatment for the patients included in study PCYC-1118E and in arm C of the iNNOVATE study. For the retrospective cohort studies Castillo 2018 and Castillo 2019 and the retrospective analyses from the PHEDRA database, however, it is assumed that the described therapies were individually tailored to the respective patients.

Adequate balancing of benefit and risk is not possible

AEs were not recorded in the studies Castillo 2018, Castillo 2019 and the PHEDRA database. Therefore, adequate balancing of benefit and risk versus ibrutinib + rituximab is not possible.

The company partly followed this assessment of the suitability of its presented comparisons of individual arms from different studies. From its point of view, the presented comparisons of individual arms from different studies allowed no derivation of an added benefit with sufficient certainty.

2.4 Results on added benefit

There are no suitable data for the assessment of ibrutinib + rituximab in the treatment of adult patients with Waldenström macroglobulinaemia. Hence, there was no hint of an added benefit of ibrutinib + rituximab in comparison with the ACT. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

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

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

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with Waldenström macroglobulinaemia	Individual treatment under consideration of the general condition and possible prior therapies[b]	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: For the present therapeutic indication, the company assumed that the patients were symptomatic and in need of treatment. Moreover, it is assumed that autologous or allogeneic stem cell transplantation was not indicated at the time point of treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above concurs with that of the company, which also rated an added benefit as not being proven in the present therapeutic indication.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company did not present any relevant data for the benefit assessment.

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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