IQWiG Reports – Commission No. A22-13

Duvelisib (chronic lymphocytic leukaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Duvelisib (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 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

No feedback was received in the framework of the present 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
BR	bendamustine + rituximab
BSC	best supportive care
ClbR	chlorambucil + rituximab
CLL	chronic lymphocytic leukaemia
EMA	European Medicines Agency
FCR	fludarabine + cyclophosphamide + rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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 duvelisib. 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 2 February 2022.

Research question

The aim of the present report is to assess the added benefit of duvelisib in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least 2 prior therapies.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of duvelisib

Research question	Therapeutic indication	ACT[a]
Adult patients with relapsed or refractory CLL after at least 2 prior therapies		
1	Who have not previously received a BTK inhibitor and/or a BCL-2 inhibitor[b]	▪ Ibrutinib or ▪ venetoclax + rituximab or ▪ chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors[c])
2	After prior therapy with at least one BTK inhibitor[b]	Venetoclax + rituximab
3	After prior therapy with at least 1 BCL-2 inhibitor[b]	Ibrutinib
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL-2 inhibitor[b]	Individualized treatment selected from ▪ idelalisib in combination with rituximab ▪ BR, ▪ ClbR, and ▪ BSC[d]; taking into account comorbidities, general health, genetic risk factors[c] as well as the success of and tolerance to prior therapy

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to require treatment (e.g. Binet stage C), and allogeneic stem cell transplantation is presumed not to be indicated at the time of treatment.
c. According to the G-BA, "genetic risk factors according to the current state of medical knowledge" is defined as the presence of a 17p deletion/TP53 mutation.
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC is an option only for patients with a short life expectancy and in very poor general health.

BCL2: B-cell lymphoma 2; BR: bendamustine + rituximab; BSC: best supportive care; BTK: Bruton's tyrosine kinase; ClbR: chlorambucil + rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee

The company does not follow the G-BA's specification regarding the different research questions or regarding the ACT, but instead defines individualized treatment choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, fludarabine in combination with cyclophosphamide and rituximab (FCR), bendamustine in combination with rituximab (BR), chlorambucil in combination with rituximab (ClbR), ibrutinib in combination with BR as well as best supportive care (BSC) as the ACT in adult patients with CLL after at least 2 prior lines of treatment. In this regard, the company cites a previous procedure on the drug acalabrutinib. In addition, the company deems ofatumumab to be a relevant treatment option in the context of individualized therapy, reasoning that, in the DUO study, which was relevant for approval, ofatumumab was used as a comparator therapy and represented an approved treatment option at the time the study was conducted.

The company's departures from the research questions specified by the G-BA as well as from the respective ACTs are not appropriate. Rather than listing any arguments to support its

approach, the company exclusively cites the procedure on acalabrutinib. Further, the additional option of ofatumumab cited by the company lost approval for the treatment of CLL in 2019. The present assessment was conducted using the research questions and ACT specified by the G-BA.

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 relevant randomized controlled trials (RCTs) were found for assessing the added benefit of duvelisib in comparison with the ACT.

The company, in contrast, identified the DUO study (IPI-145-07), which it used to assess the added benefit of duvelisib. However, the DUO study is unsuitable for assessing any added benefit of duvelisib in comparison with the ACT specified by the G-BA. The comparator therapy used in the study, ofatumumab, does not correspond to the ACT for duvelisib for any of the research questions. In addition, ofatumumab is no longer approved for the treatment of CLL, as was also pointed out by the European Medicines Agency (EMA) during the approval procedure.

No suitable data are available for assessing the added benefit of duvelisib in comparison with the ACT in the treatment of adult patients with relapsed or refractory CLL after at least 2 prior therapies. This results in no hint of added benefit of duvelisib in comparison with the ACT for any of the research questions; an added benefit is therefore not proven for any of them.

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 duvelisib.

[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: Duvelisib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with relapsed or refractory CLL after at least 2 prior therapies			
1	Who have not previously received a BTK inhibitor and/or a BCL-2 inhibitor[b]	▪ Ibrutinib or ▪ venetoclax + rituximab or ▪ chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors[c])	Added benefit not proven
2	After prior therapy with at least 1 BTK inhibitor[b]	Venetoclax + rituximab	Added benefit not proven
3	After prior therapy with at least 1 BCL-2 inhibitor[b]	Ibrutinib	Added benefit not proven
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL-2 inhibitor[b]	Individualized treatment selected from ▪ idelalisib in combination with rituximab, ▪ BR, ▪ ClbR, and ▪ BSC[d]; taking into account comorbidities, general health, genetic risk factors[c] as well as the success of and tolerance to prior therapy	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to require treatment (e.g. Binet stage C), and allogeneic stem cell transplantation is presumed not to be indicated at the time of treatment.
c. According to the G-BA, "genetic risk factors according to the current state of medical knowledge" is defined as the presence of a 17p deletion/TP53 mutation.
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC is an option only for patients with a short life expectancy and in very poor general health.

BCL2: B-cell lymphoma 2; BR: bendamustine + rituximab; BSC: best supportive care; BTK: Bruton's tyrosine kinase; ClbR: chlorambucil + rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of duvelisib in comparison with the ACT in adult patients with relapsed or refractory CLL after at least 2 prior therapies.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of duvelisib

Research question	Therapeutic indication	ACT[a]
Adult patients with relapsed or refractory CLL after at least 2 prior therapies		
1	Who have not previously received a BTK inhibitor and/or a BCL-2 inhibitor[b]	▪ Ibrutinib or ▪ venetoclax + rituximab or ▪ chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors[c])
2	After prior therapy with at least 1 BTK inhibitor[b]	Venetoclax + rituximab
3	After prior therapy with at least 1 BCL-2 inhibitor[b]	Ibrutinib
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL-2 inhibitor[b]	Individualized treatment selected from ▪ idelalisib in combination with rituximab, ▪ BR, ▪ ClbR, and ▪ BSC[d]; taking into account comorbidities, general health, genetic risk factors[c] as well as the success of and tolerance to prior therapy

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to require treatment (e.g. Binet stage C), and allogeneic stem cell transplantation is presumed not to be indicated at the time point of treatment.
c. According to the G-BA, "genetic risk factors according to the current state of medical knowledge" is defined as the presence of a 17p deletion/TP53 mutation.
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC is an option only for patients with a short life expectancy who are in very poor general health.

BCL2: B-cell lymphoma 2; BR: bendamustine + rituximab; BSC: best supportive care; BTK: Bruton's tyrosine kinase; ClbR: chlorambucil + rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee

The company does not follow the G-BA's specification regarding the different research questions or regarding the ACT, but instead defines individualized treatment choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR, ibrutinib in combination with BR as well as BSC as the ACT in adult patients with CLL after at least 2 prior lines of treatment. In this regard, the company cites the procedure on acalabrutinib [3,4]. In addition, the company deems ofatumumab to be a relevant treatment option in the context of individualized therapy, reasoning that, in the DUO study, which was

relevant for approval, ofatumumab was used as a comparator therapy and represented an approved treatment option at the time the study was conducted.

The company's departures from the research questions specified by the G-BA as well as from the respective ACTs are not appropriate. Rather than listing any arguments to support its approach, the company exclusively cites the procedure on acalabrutinib. Further, the additional option of ofatumumab cited by the company stopped being approved for the treatment of CLL in 2019 [5]. The present assessment was conducted using the research questions and ACT specified by the G-BA.

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 lists on duvelisib (status: 15 December 2021)
- bibliographical literature search on duvelisib (last search on 15 December 2021)
- search in trial registries / trial results databases for studies on duvelisib (last search on 15 December 2021)
- search on the G-BA website for duvelisib (last search on 15 December 2021)

To check the completeness of the study pool:

- search in trial registries for studies on duvelisib (last search on 10 February 2022); for search strategies, see Appendix A of the full dossier assessment

The check found no relevant RCTs for assessing the added benefit of duvelisib in comparison with the ACT.

The company, in contrast, identified the DUO study (IPI-145-07) [6] comparing duvelisib with ofatumumab and used the study to assess the added benefit of duvelisib. However, the DUO study is unsuitable for assessing any added benefit of duvelisib in comparison with the ACT specified by the G-BA. This is explained below.

2.3.1 Evidence provided by the company

DUO study

The DUO study is a multicentre, randomized, open-label, active control phase III study comparing duvelisib with ofatumumab in the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL) whose disease is relapsed or refractory after at least 1 prior

therapy. The regulatory approval of duvelisib was based on this pivotal study. A total of 319 patients were included in the study. According to Module 4 A of the company's dossier, 196 of these patients had received at least 2 prior therapies. Patients were randomized at a 1:1 ratio to the treatment arms of duvelisib or ofatumumab. The primary outcome of the study was progression-free survival. Further outcomes included, among others, mortality and side effects outcomes.

Approach of the company

The company used the DUO study to assess the added benefit of duvelisib in the present therapeutic indication. The company reports that ofatumumab was an approved and valid treatment option at the time the study was conducted.

DUO study presented by the company is unsuitable for assessing added benefit

The approach of the company is not appropriate. The DUO study is unsuitable for assessing the added benefit of duvelisib in the present therapeutic indication. The comparator therapy used in the study, ofatumumab, does not correspond to the ACT for duvelisib for any of the research questions. In addition, ofatumumab is no longer approved for the treatment of CLL [5], as was also pointed out by the EMA during the approval procedure [7].

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of duvelisib in comparison with the ACT in the treatment of adult patients with relapsed or refractory CLL after at least 2 prior therapies. This results in no hint of added benefit of duvelisib in comparison with the ACT for any of the research questions; an added benefit is therefore not proven for any of them.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for duvelisib in comparison with the ACT.

Table 5: Duvelisib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with relapsed or refractory CLL after at least 2 prior therapies			
1	who have not previously received a BTK inhibitor and/or a BCL-2 inhibitor[b]	▪ Ibrutinib or ▪ venetoclax + rituximab or ▪ chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors[c])	Added benefit not proven
2	After prior therapy with at least 1 BTK inhibitor[b]	Venetoclax + rituximab	Added benefit not proven
3	After prior therapy with at least 1 BCL-2 inhibitor[b]	Ibrutinib	Added benefit not proven
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL-2 inhibitor[b]	Individualized treatment choosing from ▪ idelalisib in combination with rituximab, ▪ BR, ▪ ClbR, and ▪ BSC[d]; taking into account comorbidities, general health, genetic risk factors[c] as well as the success of and tolerance to prior therapy	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, patients are presumed to require treatment (e.g. Binet stage C), and allogeneic stem cell transplantation is presumed not to be indicated at the time of treatment.
c. According to the G-BA, "genetic risk factors according to the current state of medical knowledge" is defined as the presence of a 17p deletion/TP53 mutation.
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC is an option only for patients with a short life expectancy who are in very poor general health.

BCL2: B-cell lymphoma 2; BR: bendamustine + rituximab; BSC: best supportive care; BTK: Bruton's tyrosine kinase; ClbR: chlorambucil + rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which, irrespective of the research questions, derived a hint of non-quantifiable added benefit for adult patients with relapsed/refractory CLL after at least 2 prior therapies.

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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