IQWiG Reports – Commission No. A22-14

Duvelisib (follicular lymphoma) –

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 (follikuläres Lymphom) – 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
CHOP	cyclophosphamide + doxorubicin + vincristine + prednisone
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 patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies.

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

Table 2: Research question of the benefit assessment of duvelisib

Therapeutic indication	**ACT[a]**
Adult patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies[b, c]	Individualized therapy taking into account prior therapy, course of disease, and general health[d]

a. Presented is the respective ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. The G-BA assumes that patients with follicular lymphoma are indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch & wait strategy is not an option. Additionally, it assumes that, at the time of therapy, patients are indicated for neither radiotherapy nor autologous or allogeneic stem cell transplantation.
d. According to the G-BA, the following therapies are deemed suitable comparators in the context of a clinical study:
bendamustine + rituximab/obinutuzumab, CHOP + rituximab/obinutuzumab, CVP + rituximab/obinutuzumab, FCM + rituximab/obinutuzumab, chlorambucil + rituximab, cyclophosphamide + rituximab, FM + rituximab/obinutuzumab, ICE + rituximab/obinutuzumab, MCP + rituximab/obinutuzumab, DHAP + rituximab/obinutuzumab, lenalidomide + rituximab, rituximab monotherapy, [^{90}Y]-radiolabelled ibritumomab tiuxetan, idelalisib. Some individual components of these combination therapies recommended by guidelines are not approved in the present indication of follicular lymphoma: carboplatin, cisplatin, doxorubicin, fludarabine, ifosfamide. In the present therapeutic indication, obinutuzumab is approved only in combination with bendamustine. There is a discrepancy between the drugs approved for the therapeutic indication of follicular lymphoma and those recommended in guidelines and used in practice. Patients responding to a combination therapy of chemotherapy plus rituximab or chemotherapy plus obinutuzumab are to be offered maintenance therapy with rituximab or obinutuzumab, respectively.

ACT: appropriate comparator therapy; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; DHAP: dexamethasone + ara-C/cytarabine + cisplatin; FCM: fludarabine + cyclophosphamide + mitoxantrone; FM: fludarabine + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; ICE: ifosfamide + carboplatin + etoposide; MCP: mitoxantrone + chlorambucil + prednisone

The company has stated that, based on previous procedures used for the therapeutic indication, it will designate an individualized therapy as the ACT, taking into account prior therapy and type and duration of response, and the company has listed the active therapies it deems to qualify for this purpose.

The present assessment was conducted in comparison with the ACT specified by the G-BA. The G-BA specified individualized therapy as the ACT for the present therapeutic indication. However, the G-BA designated a greater number of suitable comparators than did the company. The company's deviation from the ACT specified by the G-BA is of no consequence for the assessment because, concurring with the company, no randomized controlled trial (RCT) was found.

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 RCTs were found for assessing the added benefit of duvelisib in comparison with the ACT. Because the company likewise identified no RCTs, it conducted an information retrieval for other studies, where it identified the single-arm study DYNAMO (IPI-145-06) and used it to assess added benefit. The company has neither presented any data on the ACT nor conducted a comparison with the ACT. Based on the non-comparative data from the DYNAMO study, the company derived a hint of non-quantifiable added benefit.

This approach is not appropriate. The DYNAMO study is a single-arm study which does not allow a comparison versus the ACT specified by the G-BA. Departing from the company's evaluation, the DYNAMO study is therefore unsuitable for assessing the added benefit of duvelisib.

No suitable data are available for assessing the added benefit of duvelisib in comparison with the ACT in the treatment of patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies. This results in no hint of an added benefit of duvelisib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of 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

Table 3: Duvelisib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies[b, c]	Individualized therapy taking into account prior therapy, course of disease, and general health[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. The G-BA assumes that patients with follicular lymphoma are indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch & wait strategy is not an option. Additionally, it assumes that, at the time of therapy, patients are indicated for neither radiotherapy nor autologous or allogeneic stem cell transplantation.
d. According to the G-BA, the following therapies are deemed suitable comparators in the context of a clinical study:
bendamustine + rituximab/obinutuzumab, CHOP + rituximab/obinutuzumab, CVP + rituximab/obinutuzumab, FCM + rituximab/obinutuzumab, chlorambucil + rituximab, cyclophosphamide + rituximab, FM + rituximab/obinutuzumab, ICE + rituximab/obinutuzumab, MCP + rituximab/obinutuzumab, DHAP + rituximab/obinutuzumab, lenalidomide + rituximab, rituximab monotherapy, [^{90}Y]-radiolabelled ibritumomab tiuxetan, idelalisib. Some individual components of these combination therapies recommended by guidelines are not approved in the present indication of follicular lymphoma: carboplatin, cisplatin, doxorubicin, fludarabine, ifosfamide. In the present therapeutic indication, obinutuzumab is approved only in combination with bendamustine. There is a discrepancy between the drugs approved for the therapeutic indication of follicular lymphoma and those recommended in guidelines and used in practice. Patients responding to a combination therapy of chemotherapy plus rituximab or chemotherapy plus obinutuzumab are to be offered maintenance therapy with rituximab or obinutuzumab, respectively.

ACT: appropriate comparator therapy; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; DHAP: dexamethasone + ara-C/cytarabine + cisplatin; FCM: fludarabine + cyclophosphamide + mitoxantrone; FM: fludarabine + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; ICE: ifosfamide + carboplatin + etoposide; MCP: mitoxantrone + chlorambucil + prednisone

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 is to assess the added benefit of duvelisib in comparison with the ACT in patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies.

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

Table 4: Research question of the benefit assessment of duvelisib

Therapeutic indication	**ACT[a]**
Adult patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies[b, c]	Individualized therapy taking into account prior therapy, course of disease, and general health[d]

a. Presented is the respective ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. The G-BA assumes that patients with follicular lymphoma are indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch & wait strategy is not an option. Additionally, it assumes that, at the time of therapy, patients are not indicated for radiotherapy or autologous or allogeneic stem cell transplantation.
d. According to the G-BA, the following therapies are deemed suitable comparators in the context of a clinical study:
bendamustine + rituximab/obinutuzumab, CHOP + rituximab/obinutuzumab, CVP + rituximab/obinutuzumab, FCM + rituximab/obinutuzumab, chlorambucil + rituximab, cyclophosphamide + rituximab, FM + rituximab/obinutuzumab, ICE + rituximab/obinutuzumab, MCP + rituximab/obinutuzumab, DHAP + rituximab/obinutuzumab, lenalidomide + rituximab, rituximab monotherapy, [^{90}Y]-radiolabelled ibritumomab tiuxetan, idelalisib. Some individual components of these combination therapies recommended by guidelines are not approved in the present indication of follicular lymphoma: carboplatin, cisplatin, doxorubicin, fludarabine, ifosfamide. In the present therapeutic indication, obinutuzumab is approved only in combination with bendamustine. There is a discrepancy between the drugs approved for the therapeutic indication of follicular lymphoma and those recommended in guidelines and used in practice. Patients responding to a combination therapy of chemotherapy plus rituximab or chemotherapy plus obinutuzumab are to be offered maintenance therapy with rituximab or obinutuzumab, respectively.

ACT: appropriate comparator therapy; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; DHAP: dexamethasone + ara-C/cytarabine + cisplatin; FCM: fludarabine + cyclophosphamide + mitoxantrone; FM: fludarabine + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; ICE: ifosfamide + carboplatin + etoposide; MCP: mitoxantrone + chlorambucil + prednisone

The company has stated that, based on previous procedures used for the therapeutic indication, it will designate an individualized therapy as the ACT, taking into account prior therapy and the type and duration of response. The company explains that, in its view, this includes only active therapies, not treatment with best supportive care. According to the company, guidelines provide for the following treatment options for patients with prior recurrence: obinutuzumab and bendamustine, idelalisib as well as lenalidomide and rituximab. In addition, the company lists other treatment regimens which medical societies reportedly favoured in the procedure on obinutuzumab and bendamustine as first-line therapy: rituximab and bendamustine, rituximab and cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP), obinutuzumab and CHOP

as well as obinutuzumab and bendamustine. In addition, the company lists rituximab monotherapy as another treatment option.

The present assessment was conducted in comparison with the ACT specified by the G-BA. The G-BA specified individualized therapy as the ACT for the present therapeutic indication. However, more suitable comparators were designated by the G-BA than by the company. The deviation between the ACT specified by the G-BA and that used by the company is of no consequence for the assessment because concurring with the company, no RCT was found (see section below).

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 15 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not reveal any relevant RCTs for assessing the added benefit of duvelisib in comparison with the ACT. Since the company likewise identified no RCTs, it conducted an information retrieval for other studies with duvelisib. As other investigations, the company identified the single-arm study DYNAMO (IPI-145-06) [3] (see Section 2.3.1) and used it for assessing added benefit. The company conducted no information retrieval for other investigations with the ACT.

A check of the completeness of the study pool presented by the company for other investigations was foregone because the study submitted by the company is not suitable for deriving added benefit of duvelisib due to the lack of comparison with the ACT. This is explained below.

2.3.1 Evidence provided by the company

DYNAMO study

The DYNAMO study is a multicentre, uncontrolled, open-label phase II study on duvelisib for the treatment of adult patients with indolent non-Hodgkin lymphoma who exhibited disease progression and whose disease was refractory to both rituximab and chemotherapy or radioimmunotherapy. The regulatory approval of duvelisib was based on this study as pivotal study. The study enrolled a total of 129 patients with follicular lymphoma, marginal zone lymphoma, or small-cell lymphocytic lymphoma. Of the enrolled patients, 83 had follicular lymphoma, with 81% of these cases being refractory to at least 2 prior therapies. The study's primary outcome was the overall response rate. Further outcomes include, among others, mortality and side effects outcomes.

The company's approach

The company uses the DYNAMO study to assess the added benefit of duvelisib, and the company's dossier presents results on duvelisib treatment of patients with follicular lymphoma. The company has neither carried out an information retrieval on other investigations with the ACT nor provided a comparison with the ACT. The company explains that the present therapeutic indication represents a severe chronic disease with limited treatment alternatives, resulting in a therapeutic need. Based on the non-comparative data from the DYNAMO study, the company has derived a hint of non-quantifiable added benefit.

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

The company's approach of deriving added benefit for duvelisib on the basis of the DYNAMO study is not appropriate. The DYNAMO study is a single-arm study which does not allow a comparison versus the ACT specified by the G-BA. Departing from the company's evaluation, the DYNAMO study is therefore unsuitable for assessing the added benefit of duvelisib.

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 patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies. This results in no hint of an added benefit of duvelisib 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 for duvelisib in comparison with the ACT.

Table 5: Duvelisib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with follicular lymphoma which is refractory to at least 2 prior systemic therapies[b, c]	Individualized therapy taking into account prior therapy, course of disease, and general health[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. The G-BA assumes that patients with follicular lymphoma are indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and that a watch & wait strategy is not an option. Additionally, it assumes that, at the time of therapy, patients are indicated for neither radiotherapy nor autologous or allogeneic stem cell transplantation.
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ACT: appropriate comparator therapy; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; CVP: cyclophosphamide + vincristine + prednisone; DHAP: dexamethasone + ara-C/cytarabine + cisplatin; FCM: fludarabine + cyclophosphamide + mitoxantrone; FM: fludarabine + mitoxantrone; G-BA: Federal Joint Committee; GELF: Groupe d'Etude des Lymphomes Folliculaires; ICE: ifosfamide + carboplatin + etoposide; MCP: mitoxantrone + chlorambucil + prednisone

The assessment described above deviates from the assessment by the company, which derived a hint of a non-quantifiable added benefit on the basis of noncomparative data.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-14.html.