IQWiG Reports – Commission No. A21-66

Obinutuzumab (follicular lymphoma, first line treatment) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Obinutuzumab (follikuläres Lymphom, Erstlinientherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 August 2021). 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.

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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
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, and prednisolone
ECOG	Eastern Cooperative Oncology Group
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FACT-LymS	Functional Assessment of Cancer Therapy-Lymphoma Subscale
FDA	Food and Drug Administration
FLIPI	Follicular Lymphoma International Prognostic Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GELF	Groupe d'Etude des Lymphomes Folliculaires (
IDMC	independent data monitoring committee
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PFS	progression-free survival
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	system organ class
WHO	World Health Organization

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 obinutuzumab. 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 14 May 2021.

Research question

The aim of this report is to assess the added benefit of obinutuzumab in combination with chemotherapy in patients with previously untreated advanced follicular lymphoma, followed by obinutuzumab maintenance therapy in treatment responders. This treatment is compared with the appropriate comparator therapy (ACT) of rituximab in combination with chemotherapy, followed by rituximab maintenance therapy in patients who responded to induction therapy.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of obinutuzumab

Indication	ACT[a]
Patients with previously untreated advanced follicular lymphoma[b,c]	Rituximab in combination with chemotherapy (preferably in combination with CHOP or CVP or bendamustine), followed by rituximab maintenance therapy in patients who responded to induction therapy
a. Presented is the ACT specified by the G-BA. b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b (as per WHO classification) since this subentity is typically classified as aggressive non-Hodgkin lymphoma. c. In the present therapeutic indication, the G-BA assumes patients to be 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 therefore assumes a watch & wait strategy not to be an option. Further, it assumes for immunochemotherapy to be an option for the patients due to their good general condition. ACT: appropriate comparator therapy; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CVP: cyclophosphamide, vincristine, and prednisolone; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; WHO: World Health Organization	

The company followed the G-BA's specification of the ACT.

According to the S3 Guideline on Follicular Lymphoma Diagnosis, Treatment, and Follow-Up, the therapeutic indication of advanced follicular lymphoma presented in Table 2 corresponds to Ann Arbor stages II (in the presence of large lymphoma conglomerates, known as bulky disease), III, and IV.

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

Study pool and study design

Study pool

The study pool used for the benefit assessment is consistent with the study pool used by the company, which submitted the GALLIUM study for deriving an added benefit of obinutuzumab in comparison with the ACT.

The GALLIUM study is viewed as generally relevant for answering the present research question. Therefore, it is included in the benefit assessment and characterized below. However, the study results presented in the company's dossier are incomplete and were inadequately compiled. This makes it impossible to adequately assess the study data, and consequently, none of the results of the GALLIUM study were included in the benefit assessment.

Study design

The GALLIUM study is an open-label, randomized controlled trial (RCT) which included patients with previously untreated, indolent non-Hodgkin lymphoma. The study population comprises patients with advanced follicular lymphoma and marginal zone lymphoma, where advanced follicular lymphoma was defined as Ann Arbor stages II (with bulky disease), III, and IV. The study compares obinutuzumab with rituximab. As induction therapy, both drugs were initially combined with a chemotherapy regimen. Patients with treatment response then continued to receive the drug in the form of monotherapy for a maximum of 2 years. The obinutuzumab arm of the study includes 702 patients, and the rituximab arm, 699.

The study combined either obinutuzumab or rituximab with one of the 3 chemotherapies of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), cyclophosphamide, vincristine, and prednisolone (CVP), or bendamustine. Both drugs were administered using largely identical treatment regimens in terms of their sequence of induction and maintenance therapies, combination partners, cycle number, cycle duration, and administration route. The study centres selected the chemotherapy regimen. Prior to randomization, the chemotherapy to be used was defined for all patients of each centre.

The company's dossier presents results only for the subpopulation of patients with follicular lymphoma, comprising 601 patients in each study arm. This is the study subpopulation relevant for the benefit assessment. Regarding the definition of need for treatment, the current S3 Guideline on Follicular Lymphoma Diagnosis, Treatment, and Follow-Up cites the criteria specified by the Groupe d'Etude des Lymphomes Folliculaires (GELF) by way of example. The operationalization used in the study largely covers these criteria. The study's inclusion criteria excluded patients with follicular lymphoma grade 3b as per the classification of the World Health Organization (WHO). At baseline, the majority of patients were in good general health.

Data cut-offs and analyses

GALLIUM is an ongoing study. At the time the benefit was assessed, 5 data cut-offs were available. The 24 October 2012, 20 February 2014, and 31 January 2016 data cut-offs were planned a priori. Two further data cut-offs were requested by the Food and Drug Administration (FDA), in particular for an analysis of side effects data (10 September 2016 and 3 March 2017).

Incomplete submitted results

The results of the GALLIUM study which were submitted with the company's dossier are incomplete and were inadequately compiled. It is therefore impossible to adequately assess the study data, and consequently, none of the results of the study are usable for the benefit assessment. The rationale is provided below.

Incomplete data on health-related quality of life

For the various outcome categories, Module 4 C of the company's dossier presents analyses from different data cut-offs. For health-related quality of life, the company submitted analyses only from the 31 January 2016 data cut-off, but no analyses from 3 March 2017, the most current available data cut-off. In departure from the specifications of the dossier template, complete analyses, i.e. analyses of all surveyed outcomes, are therefore not available for any of the listed data cut-offs, particularly not for the most current data cut-off. However, a substantial volume of additional data on health-related quality of life would presumably have become available at the 3 March 2017 data cut-off.

Irrespective of the fact that the company failed to submit any analyses of health-related quality of life from the most current available data cut-off, the results presented in Module 4 C of the dossier are also inadequately compiled. Only separate analyses are available for Functional Assessment of Cancer Therapy-General (FACT-G) and Functional Assessment of Cancer Therapy-Lymphoma Subscale (FACT-LymS). Despite the fact that they were specified by the protocol the company did not submit any analyses of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) total score. In addition, the responder analyses for FACT-G and the FACT-LymS submitted by the company are unsuitable.

Incomplete data on common AEs

The information provided by the company on common adverse events (AEs) is incomplete as well. The dossier template specifies that alongside the total rates of AEs, results must be provided on all AEs (operationalized as System Organ Class [SOC] and Preferred Terms [PT] as per Medical Dictionary for Regulatory Activities [MedDRA]), provided they meet a minimum prevalence threshold. However, Module 4 C of the company's dossier presents only a subset of these AEs, For the benefit assessment, this makes it impossible to present common AEs or to select specific AEs on the basis of the AEs which occurred in the GALLIUM study.

Final evaluation and consequences

Taken altogether, the above-described deficiencies of the dossier are deemed major. The presented data are incomplete, particularly due to the lack of results on patient-reported outcomes at the most current data cut-off and the presentation of common AEs differing from the dossier template.

Therefore, no usable data are available for the assessment of added benefit of obinutuzumab in combination with chemotherapy in patients with previously untreated advanced follicular lymphoma, followed by obinutuzumab maintenance therapy in treatment responders, in comparison with the ACT. Consequently, there is no hint of an added benefit of obinutuzumab 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 obinutuzumab.

Table 3: Obinutuzumab – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Patients with previously untreated advanced follicular lymphoma[b,c]	Rituximab in combination with chemotherapy (preferably in combination with CHOP or CVP or bendamustine) followed by rituximab maintenance therapy for patients who have responded to induction therapy	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 (as per WHO classification) since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. In the present therapeutic indication, the G-BA assumes patients to be 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 therefore assumes a watch & wait strategy not to be an option. Further, it assumes for immunochemotherapy to be an option due to patients being in good general condition.

ACT: appropriate comparator therapy; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CVP: cyclophosphamide, vincristine, and prednisolone; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; WHO: World Health Organization

The G-BA decides on the added benefit.

[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].

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2017, wherein the G-BA had found an unquantifiable added benefit of obinutuzumab. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization due to the special status of orphan drugs, regardless of the underlying data.

2.2 Research question

The aim of this report is to assess the added benefit of obinutuzumab in combination with chemotherapy in patients with previously untreated advanced follicular lymphoma, followed by obinutuzumab maintenance therapy in treatment responders. This treatment is compared with the ACT of rituximab in combination with chemotherapy, followed by rituximab maintenance therapy in patients who responded to induction therapy.

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 obinutuzumab

Indication	**ACT[a]**
Patients with previously untreated advanced follicular lymphoma[b,c]	Rituximab in combination with chemotherapy (preferably in combination with CHOP or CVP or bendamustine), followed by rituximab maintenance therapy in patients who responded to induction therapy

a. Presented is the ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b (as per WHO classification) since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. In the present therapeutic indication, the G-BA assumes patients to be 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 therefore assumes a watch & wait strategy not to be an option. Further, it assumes for immunochemotherapy to be an option due to patients being in good general condition.

ACT: appropriate comparator therapy; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CVP: cyclophosphamide, vincristine, and prednisolone; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; WHO: World Health Organization

The company followed the G-BA's specification of the ACT. The G-BA lists CHOP, CVP as well as bendamustine as preferable chemotherapy options for use in combination with rituximab. Instead of selecting a specific option from among these chemotherapies, the company assessed the added benefit of obinutuzumab in comparison with rituximab as a combination parter of the 3 listed options.

According to the S3 Guideline on Follicular Lymphoma Diagnosis, Treatment, and Follow-Up [3], the therapeutic indication of advanced follicular lymphoma presented in Table 4 corresponds to Ann Arbor stages II (in the presence of large lymphoma conglomerates, known as bulky disease), III, and IV.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted 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 cited by the company in the dossier:

- Study list on obinutuzumab (as of 16 February 2021)
- Bibliographic literature search on obinutuzumab (most recent search on 16 February 2021)
- Search in trial registries / study results databases on obinutuzumab (most recent search on 18 March 2021)
- Search on the G-BA website on obinutuzumab (most recent search on 15 March 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on obinutuzumab (most recent search on 31 May 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
BO21223 (GALLIUM[d])	Yes	Yes	No	No[e]	Yes [4,5]	Yes [6-18]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to using this short name.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the study report in Module 5 of the dossier.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool used for the benefit assessment is consistent with the study pool used by the company, which submitted the GALLIUM study for deriving an added benefit of obinutuzumab in comparison with the ACT.

The GALLIUM study is viewed as generally relevant for answering the present research question. Therefore, it is included in the benefit assessment and characterized below. However, the study results presented in the company's dossier are incomplete and were inadequately compiled. Therefore, it is impossible to adequately assess the study data, and consequently,

none of the results of the GALLIUM study were included in the benefit assessment (see Section 2.4.2).

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
GALLIUM	RCT, open-label, parallel-group	Previously untreated patients (≥ 18 years of age) with CD20-positive indolent non-Hodgkin lymphoma (follicular lymphoma or marginal zone lymphoma) (stage II with bulky disease, III or IV), ECOG-PS 0, 1, or 2 requiring therapy[b]	Obinutuzumab + chemotherapy[d] (N = 702) Rituximab + chemotherapy[d] (N = 699) Relevant subpopulation (patients with follicular lymphoma)[c]: Obinutuzumab + chemotherapy[d] (N = 601) Rituximab + chemotherapy[d] (N = 601)	Screening: 35 days Treatment: up to a maximum of 2 years after the end of chemotherapy or up to disease progression, unacceptable toxicity, or treatment discontinuation upon the physician's or patient's discretion Follow-up observation[e]: outcome-specific, maximally until death, discontinuation of study participation, or study end	177 centres in Australia, Belgium, Canada, China, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Japan, Russia, Spain, Sweden, Taiwan, United Kingdom, United States 07/2011–ongoing Data cut-off dates: 24/10/2012: futility for CR 20/02/2014: futility for PFS (111 events) 31/01/2016: primary analysis for PFS and health-related quality of life (248 events)[g] 10/09/2016; efficacy, tolerability[h] 03/03/2017: tolerability[h]	Primary: PFS (in patients with follicular lymphoma) Secondary: overall survival, health-related quality of life, AEs

Table 6: Characterization of the included study – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment. b. Disease requiring therapy, defined by the presence of at least 1 of the following: very large lymphoma conglomerates (≥ 7 cm , known as bulky disease), local complaints or organ dysfunction, presence of B symptoms, presence of symptomatic extranodal disease, cytopenia (absolute neutrophil count < 1.0 x 10^9/L, haemoglobin < 10 g/dL, and/or platelet count < 100 x 10^9/L), involvement of ≥ 3 lymph node regions (each with a diameter of ≥ 3 cm), symptomatic splenomegaly. c. No information available on the total population. d. Either CHOP, CVP, or bendamustine; defined before randomization by each study centre. e. Outcome-specific information is provided in Table 8. f. Investigation of CR rates after the induction phase for 170 patients with follicular lymphoma. g. Upon IDMC recommendation, the primary analysis for PFS, originally planned after 370 events, was carried out after only 245 events (originally planned interim analysis) because the significance level for PFS was not reached. h. Upon FDA request. AE: adverse event; CD20: cluster of differentiation 20; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone); CR: complete response; CVP: cyclophosphamide, vincristine, prednisone/prednisolone/methylprednisolone); ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FDA: Food and Drug Administration; IDMC: independent data monitoring committee; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial					

Table 7: Characterization of the intervention – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy (multipage table)

Study	Intervention	Comparison
GALLIUM	Induction therapy: Obinutuzumab 1000 mg i.v. on Days 1, 8, and 15 of Cycle 1 and on Day 1 of the subsequent cycles (6–8 cycles of 21 or 28 days each, depending on the combination partner)	Induction therapy: Rituximab 375 mg/m² body surface area (BSA) i.v. on Day 1 of each cycle (6–8 cycles of 21 or 28 days each, depending on the combination partner)
	Each in combination with one of the following chemotherapies: ▪ CHOP On Day 1 of each of six 21-day cycles (Cycles 7–8: only obinutuzumab/rituximab): ▫ Cyclophosphamide 750 mg/m² i.v. ▫ Doxorubicin 50 mg/m² i.v., maximum of 300 mg ▫ Vincristine 1.4 mg/m² i.v., maximum 2 mg Plus on Days 1–5 of Cycles 1–6: ▫ Prednisone or prednisolone / methylprednisolone 100 mg orally (80 mg i.v.) ▪ CVP On Day 1 of each of eight 21-day cycles ▫ Cyclophosphamide 750 mg/m² i.v. ▫ Vincristine 1.4 mg/m² i.v., maximum 2 mg Plus on Days 1–5 of Cycles 1–8: ▫ Prednisone or prednisolone / methylprednisolone 100 mg orally (80 mg i.v.) ▪ Bendamustine On Days 1 and 2 of each of six 21-day cycles 90 mg/m² i.v. Plus on Days 1–5 of Cycle 1: ▫ Prednisone or prednisolone / methylprednisolone 100 mg orally (80 mg i.v.)	
	Maintenance therapy in patients who responded to induction therapy: ▪ Obinutuzumab 1000 mg i.v. every 2 months until disease progression or for up to 2 years	▪ Rituximab 375 mg/m² BSA i.v. every 2 months until disease progression or for up to 2 years
	Permitted dose adjustments ▪ Permitted in case of toxicity within 72 hours before Day 1 of the subsequent treatment cycle[a]	
	Premedication before administration of the study drug ▪ Acetaminophen/paracetamol 30–60 minutes before each cycle ▪ Antihistamine, e.g. diphenhydramine ▪ Tumour lysis prevention with allopurinol (in case of high risk of tumour lysis syndrome) ▪ Antiemetic therapy (e.g. serotonin antagonist: dolasetron, ondansetron)	

Table 7: Characterization of the intervention – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy (multipage table)

Study	Intervention	Comparison
	Nonpermitted prior treatment ▪ Chemotherapy ▪ Radiotherapy ▪ Immunotherapy ▪ Antibiotics i.v. or hospitalization ≤ 4 weeks before the start of Cycle 1 **Permitted concomitant treatment** ▪ Corticosteroids ≤ 30 mg/day at a stable dose ≥ 4 weeks before randomization ▪ Methotrexate 7.5 mg up to ≤ 20 mg/week for treating rheumatoid arthritis ▪ Rasburicase for treating tumour lysis syndrome and for the prevention of hyperuricaemia ▪ Antibiotic and/or antiviral prophylaxis ▪ Paracetamol/acetaminophen (≥ 500 mg) and/or H1 and H2 receptor antagonists (e.g. diphenhydramine, ranitidine)[b] ▪ Treatment of severe infusion-related events (e.g. with oxygen, β2 agonists/epinephrine and/or corticosteroids) ▪ Myeloid growth factors for the prevention and treatment of febrile neutropenia ▪ Prophylactic mesna in case of treatment with CHOP or CVP **Nonpermitted concomitant treatment** ▪ Cytotoxic chemotherapy (except for bendamustine, cyclophosphamide, doxorubicin, and vincristine) ▪ Immunotherapy ▪ Hormone therapy	

a. The study protocol contains detailed guidelines regarding the adjustment or pausing of therapy for cardiotoxicity, hepatotoxicity, neurotoxicity, tumour lysis syndrome, hepatitis B reactivation, progressive multifocal leukoencephalopathy, other nonhaematological toxicity as well as haematological toxicity, depending on the severity of the event [6].
b. In the event of infusion-related hyperthermia (> 38.5°C) or symptoms

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone); CVP: cyclophosphamide, vincristine, predisone/prednisolone/methylprednisolone; i.v.: intravenous; RCT: randomized controlled trial

The GALLIUM study is an open-label RCT which included patients with previously untreated, indolent non-Hodgkin lymphoma. The study population comprises patients with advanced follicular lymphoma and marginal zone lymphoma, where advanced follicular lymphoma was defined as Ann Arbor stages II (with bulky disease), III, and IV. The study compares obinutuzumab with rituximab. As induction therapy, both drugs were initially combined with a chemotherapy regimen. Patients with treatment response then continued to receive the drug in the form of monotherapy for a maximum of 2 years. The obinutuzumab arm of the study includes 702 patients, and the rituximab arm, 699.

The study combined obinutuzumab or rituximab each with one of 3 chemotherapies, CHOP, CVP, or bendamustine. The treatment regimens of the two drugs, including the sequence of induction and maintenance therapy, combination partners, cycle number, cycle length as well as administration route, were largely identical. For obinutuzumab and rituximab as well as the

combination with the CHOP and CVP chemotherapies, treatment was in line with the SPCs [19-24]. The same applies to the combination of obinutuzumab and bendamustine, which was administered in compliance with the obinutuzumab SPC [19]. Regarding the combination of rituximab and bendamustine, it must be noted that the bendamustine SPC does not provide any information on first-line therapy of follicular lymphoma [25], nor does the rituximab SPC specify a bendamustine dosage. However, the combination is recommended by current guidelines and consensus recommendations, including at the dosage and cycle number used in the GALLIUM study [3,26-28].

The study centres selected the chemotherapy regimen. Prior to randomization, the chemotherapy to be used was defined for all patients of each centre. Randomization was stratified by chemotherapy. Further stratification factors were geographic region and severity of disease according to either the Follicular Lymphoma International Prognostic Index (FLIPI) for patients with follicular lymphoma or the International Prognostic Index for patients with non-follicular lymphoma.

The primary outcome of the study was progression-free survival (PFS). Secondary outcomes comprised overall survival as well as outcomes from the categories of health-related quality of life and side effects.

Relevant subpopulation

Module 4 C of the company's dossier presents results only for the subpopulation of patients with follicular lymphoma, of which there were 601 in each study arm. In agreement with the company, this study subpopulation was deemed relevant for the benefit assessment.

As per the study inclusion criteria, only follicular lymphoma patients requiring therapy were to be included. Need for therapy was established by the presence of at least 1 of the following criteria:

- Very large lymphoma conglomerates (≥ 7cm, known as bulky disease)
- Local complaints or organ dysfunction
- Presence of B symptoms
- Presence of symptomatic extranodal disease
- Cytopoenia (absolute neutrophil count < 1.0 x 10^9/L, haemoglobin < 10 g/dL, and/or platelet count < 100 x 10^9/L)
- Involvement of ≥ 3 lymph node regions (each ≥ 3 cm in diameter)
- Symptomatic splenomegaly

For the definition of need for treatment, the current S3 Guideline on Follicular Lymphoma Diagnosis, Treatment, and Follow Up cites, as an example, the GELF criteria [3]. These criteria are largely consistent with the operationalization used in the study. The study's inclusion

criteria excluded patients with follicular lymphoma grade 3b as per the classification of the World Health Organization (WHO). As per inclusion criteria, patients had to be in good to moderate general health (Eastern Cooperative Oncology Group Performance Status [ECOG] status 0 to 2), with the vast majority actually being in good general health at baseline (approx. 97% with ECOG 0–1, see Table 9).

All information below is based on the GALLIUM subpopulation of patients with follicular lymphoma, which is relevant for the present benefit assessment.

Data cut-offs and analyses

GALLIUM is an ongoing study. At the time the benefit was assessed, 5 data cut-offs were available (see Table 6). The 24 October 2012, 20 February 2014, and 31 January 2016 data cut-offs were planned a priori. Two further data cut-offs were requested by the Food and Drug Administration (FDA), in particular for an analysis of side effects data (10 September 2016 and 3 March 2017). For the various outcome categories, Module 4 C of the company's dossier presents analyses from different data cut-offs. In departure from the specifications of the dossier template [29], however, complete analyses, i.e. analyses of all surveyed outcomes, are not available for any of the listed data cut-offs, particularly not for the most current data cut-off (for a detailed description, see Section 2.4.2). As a result, the provided information is incomplete.

Treatment duration and follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned follow-up observation – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy

Study **Outcome category** **Outcome**	**Planned follow-up observation**
GALLIUM	
Mortality	
Overall survival	Until death, loss to follow-up, or study end (expected at about 10.2 years after study start)
Health-related quality of life (FACT-Lym)	Up to 5 years after the end of therapy[a]
Side effects	
AEs	Up to 28 days after the last dose of the study drug
Severe AEs (CTCAE grade ≥ 3)	Up to 6 months after the last dose of the study drug (infections: up to 24 months after the last dose of the study drug)
SAEs	Up to 12 months after the last dose of the study drug[b]
a. The study documents fail to clarify whether health-related quality of life is to be surveyed beyond disease progression or only until the 1st visit after progression. b. AEs related to the study drug are followed up without restrictions.	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; RCT: randomized controlled trial; SAE: serious adverse event	

Although the follow-up of health-related quality of life was not continued throughout the study, it was, at any rate, continued for up to 5 years after treatment end. It remains unclear, however, whether follow-up continued beyond disease progression.

The follow-up durations for the outcome category of side effects are systematically shortened since they were surveyed only for the period of treatment with the study drug (plus 28 days for adverse events [AEs]; for 6 to 24 months after the last dose for severe AEs and serious AEs [SAEs]). To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire period.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characterization of the study population – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy (multipage table)

Study Characteristic Category	**Obinutuzumab + chemotherapy N[a] = 601**	**Rituximab + chemotherapy N[a] = 601**
GALLIUM		
Age [years], mean (SD)	58 (12)	58 (12)
Sex [f/m], %	53/47	53/47
Geographic region, n (%)		
Western Europe	294 (49)	286 (48)
North America	75 (13)	77 (13)
Asia Pacific	152 (25)	155 (26)
Other	80 (13)	83 (14)
ECOG-PS, n (%)		
0–1	585 (98)	576 (96)
2	15 (3)	23 (4)
Disease duration: period from initial diagnosis to randomization, n (%)		
< 6 months	490 (82)	474 (79)
6–12 months	35 (6)	32 (5)
≥ 12 months	73 (12)	95 (16)
Ann-Arbor stage, n (%)		
I	10 (2)	8 (1)
II (without bulky disease)	14 (2)	14 (2)
II (with bulky disease)	27 (5)	30 (5)
III	208 (35)	209 (35)
IV	339 (56)	336 (56)
FLIPI, n (%)		
Low (0, 1)	128 (21)	125 (21)
Intermediate (2)	224 (37)	223 (37)
High (≥ 3)	249 (41)	253 (42)
Bone marrow involvement, n (%)		
Yes	318 (54)	295 (49)
No	266 (45)	291 (49)
Morphologically not determined	8 (1)	12 (2)
Extranodal involvement, n (%)		
Yes	392 (65)	396 (66)
No	209 (35)	205 (34)
≥ 1 B symptom at baseline, n (%)		
Yes	201 (33)	206 (34)
No	400 (67)	394 (66)

Table 9: Characterization of the study population – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy (multipage table)

Study Characteristic Category	Obinutuzumab + chemotherapy N[a] = 601	Rituximab + chemotherapy N[a] = 601
Lymphoma conglomerates > 7 cm (bulky disease), n (%)		
Yes	255 (43)	271 (45)
No	345 (58)	329 (55)
Chemotherapy regimen, n (%)		
CHOP	195 (32)	203 (34)
CVP	61 (10)	57 (10)
Bendamustine	345 (57)	341 (57)
Treatment discontinuation (induction)[b], n (%)	37 (6[d])	47 (8[d])
Maintenance therapy not started[c], n (%)	19 (3[d])	24 (4[d])
Treatment discontinuation (maintenance)[c], n (%)	120 (20[d])	134 (22[d])
Study discontinuation[c], n (%)	180 (30)[e]	226 (38)[e]

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. The study defined B symptoms as unexplained fever > 38°C, night sweat, unexplained weight loss of > 10% of body weight within 6 months before the diagnosis.
c. Data cut-off 3/03/2017.
d. IQWiG calculations.
e. Of which deaths: 16 vs. 20, i.e. 3% of the obinutuzumab arm vs. 3% of the rituximab arm.

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone (or prednisone/methylprednisolone); CVP: cyclophosphamide, vincristine, prednisolone (or prednisone/methylprednisolone); ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; FLIPI: Follicular Lymphoma International Prognostic Index; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The mean age of the relevant GALLIUM subpopulation was 58 years. Men and women were represented in approximately equal numbers. About half of participants were from Western Europe, a quarter from the Asian-Pacific area, and about 13% each from North America and from other regions.

At baseline, almost all patients were in good general health, i.e. had an ECOG Performance Status of 0 or 1. The initial diagnosis had been established less than half a year ago in more than 80% of patients. Most patients were in Ann Arbor stage III or IV. The risk of an unfavourable course of disease was high in slightly more than 40% of patients, intermediate in 37%, and low in 21%. Bone marrow involvement was found in slightly more than half of patients and extranodal involvement in 66%. At baseline, about a third of the study population exhibited B symptoms with at least 1 symptom, while 44% had lymphoma conglomerates > 7 cm (bulky disease).

The most frequently used chemotherapy was bendamustine at 57%, followed by CHOP at 33%, and CVP at only 10% of patients.

Treatment discontinuation or study discontinuation was slightly more common in the rituximab arm than in the obinutuzumab arm. Most treatment discontinuations occurred during the monotherapy maintenance phase (about 21% of patients). Study discontinuations occurred in 30% of patients in the obinutuzumab arm and 38% in the comparator arm.

Data on the course of the study

Table 10 shows the mean and median durations of patient treatment as well as the mean and median durations of follow-up observation for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: obinutuzumab + chemotherapy vs. rituximab + chemotherapy

Study **Duration of the study phase** **Outcome category**	**Obinutuzumab + chemotherapy**	**Rituximab + chemotherapy**
GALLIUM (data cut-off: 3 March 2017)		
Duration of induction therapy [weeks]	N = 595	N = 597
Median [min; max]	25.3 [3.3; 35.3]	25.1 [2.6; 32.3]
Mean (SD)	24.9 (3.8)	24.5 (3.6)
Duration of maintenance therapy[a] [weeks]	N = 540[b]	N = 526[b]
Median [min; max]	93.1 [4.1; 117.3]	93.1 [2.1; 117.7]
Mean (SD)	84.1 (25.2)	81.3 (28.3)
Follow-up observation duration [weeks]	N = 601	N = 601
Mean[c] [min; max]	197.8 [0.0; 286.5][d]	193.9 [0.4; 291.8][d]
Overall survival, health-related quality of life (FACT-Lym), side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. The information provided fails to clarify whether this is a combined figure for both induction and maintenance therapy.
b. Number of patients who started maintenance therapy.
c. The company reported this as the "average follow-up." Presumably, the company is referring to the mean. It did not indicate whether this information referred to a specific outcome.
d. IQWiG converted from months to weeks.

max: maximum; min: minimum; N: number of patients to whom the specified time applies; ND: no data; RCT: randomized controlled trial; SD: standard deviation

For the relevant subpopulation, the GALLIUM treatment arms are comparable in terms of treatment duration. However, Module 4 C of the company's dossier does not provide any information on outcome-specific follow-up duration. Therefore, it is impossible to definitively assess the extent to which the follow-up durations for the individual outcomes differ between study arms. If they materially diverge, binary outcomes may require time-to-event analyses instead of relative risk as an effect estimator.

Module 4 C of the company's dossier does not present any information on antineoplastic follow-up therapies. Therefore, no conclusion can be drawn about their relevance to the present assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Health-related quality of life
  - Surveyed using the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym)
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Infusion-related reactions
  - Infections
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 C).

Since the results presented by the company were disregarded in the benefit assessment (see Section 2.4.2), an assessment of the risk of bias at study and outcome levels for the GALLIUM study was foregone.

2.4.2 Usability of the study results for the benefit assessment

The results of the GALLIUM study which were submitted in the company's dossier are incomplete and were inadequately compiled. It is therefore impossible to adequately assess the study data, and consequently, none of the results of the study are usable for the benefit assessment. The rationale is provided below.

Incomplete data on health-related quality of life

Module 4 C of the company's dossier presents analyses on the different outcome categories from different data cut-offs. Table 11 presents the data cut-offs and their reported results for each outcome category.

Table 11: Analyses of the GALLIUM study as presented by the company per data cut-off and outcome category

Data cut-off	Mortality	Health-related quality of life	Side effects
31/01/2016[a]	x	x	–
10/09/2016[b]	–	–	–
03/03/2017[c]	x	–	x

a. Pre-defined interim analysis of PFS; due to failure to reach the significance level, primary analysis of PFS and health-related quality of life as recommended by IDMC.
b. Data cut-off requested by the FDA; submitted to the G-BA as part of the approval process in 2017.
c. Data cut-off requested by the FDA.

AE: adverse event; FDA: Food and Drug Administration; G-BA: Federal Joint Committee; IDMC: independent data monitoring committee; PFS: progression-free survival

The company reported the data cut-offs of 10 September 2016 and 3 March 2017 to have been carried out upon FDA request. The 31 January 2016 data cut-off was planned as the 3rd interim analysis. The company disclosed that at this data cut-off, the significance level for the primary outcome of PFS had not been reached in the patient population with follicular lymphoma and that the independent data monitoring committee (IDMC) recommended a complete analysis of the study data. Therefore, the company views the 3rd interim analysis to be the primary analysis of final or confirmatory value for the outcomes of PFS and health-related quality of life, but not for overall survival and AEs. For the most current data cut-off of 3 March 2017, Module 4 C of the company's dossier presents analyses only for overall survival and AEs. For health-related quality of life, surveyed using FACT-Lym, it presents analyses as of 31 January 2016, reasoning that this was the predefined final or confirmatory data cut-off for PFS. This approach is inadequate. It is unclear why the company decided against additionally submitting analyses of health-related quality of life for the most current data cut-off (3 March 2017). For the G-BA's assessment procedure as part of the approval process in 2017, the company had already submitted analyses from more current data cut-offs (10 September 2016) [13]; the G-BA took these analyses into account for the assessment at that time [15-17].

The dossier template [29] 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 had originally been timed for the analysis of only some of the outcomes. Further, given the current data constellation, the 3 March 2017 data cut-off presumably provides substantial additional data on health-related quality of life when compared to the 31 January 2016 and 10 September 2016 data cut-offs.

In the GALLIUM study, health-related quality of life is surveyed using FACT-Lym for up to 5 years after the end of study treatment. Module 4 C of the company's dossier shows that, by 31 March 2016, about 45% of patients had been observed for > 3 years. In contrast, the percentage of patients with an observation duration > 3 years is about 72% at the 10 September 2016 data cut-off [13] and 87% at 3 March 2017. For an observation duration of

> 4 years, the percentage of patients increases between data cut-offs from almost 10% (31 January 2016) to 30% (10 September 2016) [13] and 45% (3 March 2017). Therefore, the most current data cut-off of 3 March 2017 presumably adds a relevant volume of patient data on the outcome of health-related quality of life.

Inadequate presentation of the data on health-related quality of life

Irrespective of the fact that the company failed to submit any analyses of health-related quality of life from the most current available data cut-off, the results presented in Module 4 C of the dossier are also inadequately compiled.

The GALLIUM study surveyed health-related quality of life using the FACT-Lym questionnaire [30], which consists of 5 subscales: 4 subscales from the generic questionnaire Functional Assessment of Cancer Therapy – General (FACT-G, 27 items) and 1 subscale on lymphoma-specific symptoms (FACT-LymS, 15 items).

Module 4 C of the company's dossier presents only separate analyses on FACT-G and the FACT-LymS subscale. The company did not submit any analyses on the FACT-Lym total score, despite the fact that the protocol called for them. These analyses would be relevant for the benefit assessment, however.

The company carried out responder analyses for both FACT-G and FACT-LymS, but these analyses are unsuitable for assessing added benefit.

- FACT-G: Percentage of patients with an improvement or deterioration by ≥ 6 points by Day 1 of Cycle 3 and by Month 2 and Month 12 of the maintenance phase (on a scale of 0 to 108 points)
- FACT-LymS: Percentage of patients with an improvement or deterioration by ≥ 5 points by Day 1 of Cycle 3 and by Month 2 and Month 12 of the maintenance phase (on a scale of 0 to 60 points)

The company's analyses are unusable for the dossier assessment. As discussed in the IQWiG General Methods [1,31], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change which is perceivable for patients. This is not the case for the aforementioned response criteria.

In addition, the company has presented the submitted responder analyses only for selected analysis time points (Day 1 of Cycle 3 of induction therapy as well as Month 2 and Month 12 of maintenance therapy). The study, however, continued to survey FACT-Lym even after treatment end. The questionnaire was administered on Day 1 of both the 1st and 3rd chemotherapy cycle, at the end of the induction phase, in the 2nd and 12th month of maintenance therapy, at the end of therapy and observation in the maintenance phase as well as once annually until the end of the 5-year follow-up observation. It remains unclear, however,

whether FACT-Lym is surveyed even beyond disease progression. The company did not offer any reasoning as to why it submitted results only for selected analysis time points in the induction and maintenance phases. Regarding survey time points in the follow-up observation phase, Module 4 C of the company's dossier neither provides information on return rates, nor does it justify why surveys within the follow-up observation period were disregarded in its assessment.

Alongside responder analyses, Module 4 C of the company's dossier presents analyses from a mixed model for repeated measures (MMRM) for FACT-G and the FACT-LymS subscale. Since they cannot be definitively interpreted, these analyses are likewise unusable for the benefit assessment. The company fails to indicate both the percentage of surviving patients per treatment arm who turned in a usable questionnaire at each survey time point and whether or not all of these data were included in the analysis. Generally, all surveyed data should be included in the analysis. Interpretation of the MMRM analysis also requires explicit information as to the time point or time period applicable to the presented effect estimator. The company, however, has not provided any of this information for the analyses it submitted.

Overall, drawing any conclusions on added benefit requires the results on patient-reported outcomes at the most current data cut-off in the form of a suitable analysis, e.g. in the form of responder analyses during treatment and at the latest possible time point for which an adequate analysis is possible [1] or in the form of analyses of continuous data covering the entire study period. Responder analyses are preferred.

Incomplete data on common AEs

The information on common AEs provided by the company is incomplete as well. According to the dossier template, alongside the total rates of AEs, results on all AEs (operationalized as SOC and PT as per MedDRA) must be presented, provided they exceed a minimum prevalence [29]. A complete presentation of these common AEs (separately by AEs without further differentiation, SAEs, AEs differentiated by severity) is essential for assessing the side effects profiles as well as for selecting specific AEs [1].

However, Module 4 C of the company's dossier presents only a subset of these AEs. AEs are presented regardless of their severity, provided they occurred in ≥ 10% of patients in a study arm. For severe AEs as well as SAEs, the company submitted analyses on the threshold value of ≥ 5% of patients in a study arm. As per dossier template, all events which occurred in ≥ 10 patients and in ≥ 1% of patients in a study arm are to be additionally reported, without regard to severity [29]. Hence, the information on common AEs provided in the dossier's Module 4 C is incomplete. For the benefit assessment, this makes it impossible to present common AEs or to select specific AEs on the basis of the AEs which occurred in the GALLIUM study.

Further points of criticism

As already described in Section 2.3.2, Module 4 C of the dossier also lacks information on antineoplastic subsequent therapies as well as on outcome-specific follow-up durations. Additionally, as described above, the data on the return rates of the FACT-Lym questionnaire are incomplete regarding analysis time points. Alongside the incomplete and insufficiently compiled results, this problem further complicates the interpretation of study data because the company's MODULE 4 C presents binary analyses for the FACT-Lym responder analyses and outcomes of the side effects category (relative risk, odds ratio, absolute risk difference). Without outcome-specific data on observation durations or return rates for all analysis time points, it is impossible to definitively evaluate the adequacy of the analyses presented by the company.

Final evaluation and consequences

Taken altogether, the above-described deficiencies of the dossier are deemed major. The presented data are incomplete, particularly due to the lack of results on health-related quality of life at the most current data cut-off as well as the incomplete presentation of the AE results.

Due to the incomplete data, it is impossible to adequately weigh benefit and harm and hence to assess the added benefit of obinutuzumab in comparison with the ACT. A presentation of usable study results presented in the company's dossier is foregone as well.

No usable data are available for the assessment of added benefit of obinutuzumab in combination with chemotherapy in patients with previously untreated advanced follicular lymphoma, followed by obinutuzumab maintenance therapy in treatment responders in comparison with the ACT. Consequently, there is no hint of an added benefit of obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 12 presents a summary of the results of the benefit assessment of obinutuzumab in comparison with the ACT.

Table 12: Obinutuzumab – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Patients with previously untreated advanced follicular lymphoma[b,c]	Rituximab in combination with chemotherapy (preferably in combination with CHOP or CVP or bendamustine) followed by rituximab maintenance therapy for patients who have responded to induction therapy	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 (as per WHO classification) since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. In the present therapeutic indication, the G-BA assumes patients to be 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 therefore assumes a watch & wait strategy not to be an option. Further, it assumes for immunochemotherapy to be an option due to patients being in good general condition.

ACT: appropriate comparator therapy; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CVP: cyclophosphamide, vincristine, and prednisolone; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; WHO: World Health Organization

The assessment described above deviates from that by the company, which derived proof of considerable added benefit.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2017, wherein the G-BA had found an unquantifiable added benefit of obinutuzumab. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization due to the special status of orphan drugs, regardless of the underlying data.

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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