Horizon Scanning in Oncology

Obinutuzumab (Gazyvaro®) in combination with bendamustine for the treatment of relapsed/ refractory follicular lymphoma (FL)

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1 Research questions

The EUnetHTA HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to predefined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is obinutuzumab?
A0022	Who manufactures obinutuzumab?
A0007	What is the target population in this assessment?
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C0005	What are the susceptible patient groups that are more likely to be harmed through the use of obinutuzumab?
A0021	What is the reimbursement status of obinutuzumab?

2 Drug description

Generic/Brand name/ATC code:

Obinutuzumab/Gazyvaro®/Gazyva®/L01XC15

B0001: What is obinutuzumab?

anti-CD20 antibody

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered type II anti-CD20 antibody of the IgG1 subclass. It specifically targets the CD20 antigen expressed on the surface of non-malignant and malignant pre-B and mature B lymphocytes. Obinutuzumab mediates B-cell lysis through engaging immune effector cells, by activating the intracellular death-signalling pathways and by activating the complement cascade. Included in the immune effector cell mechanisms are antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis [2, 3].

Obinutuzumab is available as single-use vials containing 1,000 mg/40 ml (25 mg/ml). It should be administered as an intravenous infusion but not as an intravenous push or bolus. Furthermore, premedication for infusion reactions and tumour lysis syndrome is recommended [2, 3].

cycle 1:
1,000 mg x day 1, 8, 15
cycles 2–6:
1,000 mg day 1
1,000 mg/2 M[1]/2 Y[2]

The recommended dosage for the treatment of follicular lymphoma (FL) is 1,000 mg on day 1, followed by 1,000 mg on days 8 and 15 of cycle 1. In cycles 2–6 1,000 mg are recommended on the respective day 1. Subsequently, 1,000 mg should be administered every 2 months for 2 years [2].

A0022: Who manufactures obinutuzumab?

Roche Registration Ltd

3 Indication

A0007: What is the target population in this assessment?

obinutuzumab-bendamustine for relapsed/refractory FL

Obinutuzumab in combination with bendamustine, followed by obinutuzumab monotherapy, is indicated for the treatment of FL patients who relapsed after or are refractory to a rituximab-containing regimen.

[1] M = months

[2] Y = years

4 Current regulatory status

A0020: For which indications has obinutuzumab received marketing authorisation?

approved by the EMA since 2014 for CLL

positive opinion by the CHMP for the treatment of FL in April 2016

Obinutuzumab was initially approved in July 2014 by the European Medicines Agency (EMA) as combination therapy with chlorambucil for the treatment of patients with untreated chronic lymphocytic leukaemia (CLL), with comorbidities making them unsuitable for full-dose fludarabine-based therapy [3]. In April 2016, the Committee for Human Medicinal Products (CHMP) adopted a positive opinion for the following indication: obinutuzumab as a combination therapy with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL who did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen [4].

approved by the FDA since 2013 for CLL

approved for the treatment of FL since 2016

In November 2013, the US Food and Drug Administration (FDA) approved obinutuzumab in combination with chlorambucil for the treatment of previously untreated CLL. In February 2016, obinutuzumab received marketing authorisation for combination therapy with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL who relapsed after or are refractory to a rituximab-containing regimen. This approval was based on results of a phase III study, GADOLIN, which is available in abstract form only [2, 5].

5 Burden of disease

A0002: What is FL?

FL is the most common subtype of indolent B-cell NHL

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of diseases that arise from distinct lymphocyte types, B or T/NK cells [6, 7]. They can be indolent (slow-growing) or aggressive (fast-growing). The two commonest forms of NHL in adults are diffuse large B-cell lymphomas, which are typically aggressive and follicular lymphomas (FL), which are typically indolent [8].

A0004: What is the natural course of FL?

bidirectional feedback mechanism between cancer cells and reactive cells

FL tumour cells are malignant equivalents of normal germinal centre B cells (centrocytes and centroblasts). In combination with a group of cells like macrophages, follicular dendritic cells, fibroblasts, endothelial cells and T lymphocytes, they create a disease-specific microenvironment. This enables a bidirectional feedback mechanism among cancer cells and the network of reactive cells [9, 10]. Malignant B cells can influence the microenvironment through the following mechanisms: skewing the differentiation of immune cells, attracting regulatory T cells/suppressive monocytes, and secreting cytokines that promote an immunosuppressive environment [11].

often late diagnosis

The substantial majority of FL patients are diagnosed at an advanced stage [9]. Progression of FL alters from person to person and is contingent on the speed of tumour's growth as well as the involvement of other organs [12]. Some people with FL remain asymptomatic for years, although they have advanced-stage disease [9, 12]. Over time, some FL patients develop a transformed lymphoma, such as a diffuse large B-cell lymphoma [12, 13].

A0006: What are the consequences of FL for the society?

A0023: How many people belong to the target population?

1,265 new NHL cases in Austria

In Austria, 1,265 patients were newly diagnosed with NHL in 2015, equalling an incidence rate of 9.0 cases per 100,000 persons. It is estimated that 617 people are dying due to the disease per year. Age-standardised rates from 2015 show that incidence (10.7 vs 7.6) and mortality (4.4 vs 2.5) are higher in men than in women [14]. NHL is commonly diagnosed in people aged 65–74, which results in a median age of 66 years [15].

sixth most common cancer in Europe

FL is the sixth most common cancer in Europe, accounting for approximately 3% of all cancers. FL represents about 25% of all NHLs and is the second most common subtype of lymphoma in western Europe [16].

A0005: What are the symptoms and the burden of FL?

initial symptom: painless swelling of lymph nodes

The initial symptoms of FL are painless swelling of lymph nodes in the neck, arm pits, and/or groin [12, 16]. The compression of vital organs can cause symptoms like abdominal/back pain due to affected deep lymph nodes. Other signs and symptoms of FL may include fatigue, infections, and sometimes bleeding. Fever, night sweats as well as unintentional weight loss are known as B-symptoms, which are particularly important during the staging process [16].

A0003: What are the known risk factors for FL?

no increased risk in relatives of FL patients

The probability for developing FL is affected by age, gender, and ethnicity. FL is less common among Asians and Blacks than among other ethnicities. As FL is not an inherited disease, the substantial risk of developing FL is not increased in siblings and children of patients [12].

Other factors that have been associated with the occurrence of FL are lifestyle, environmental factors and previous medical conditions; however, their influence is not yet clear [16].

A0024: How is FL currently diagnosed according to published guidelines and in practice?

tissue biopsy of the lymph nodes for diagnosis of FL

An excisional tissue biopsy is necessary for the diagnosis of FL, in most instances from a lymph node. To further strengthen a suspected diagnosis, an additional histological examination (immunophenotypic and molecular genetic studies) is required. While the majority of patients have systematic follicular lymphoma, three additional clinical variants of FL were classified by the WHO in 2008 [10]:

- paediatric FL
- intrafollicular neoplasia
- primary intestinal FL

staging according to involved lymph nodes or the number of centroblasts

To determine which stage of disease is present and which parts of the body have been affected, different tests are available, e.g. blood tests, bone marrow biopsy, computed tomography (CT) scan, positron emission tomography (PET) scan. One way to stage FL is dependent on how much of the lymphatic system is affected at the time of diagnosis [10]:

- Stage I – one lymph node region/structure is involved.
- Stage II – two or more lymph node regions/structures on the same side of the diaphragm are involved.
- Stage III – lymph node regions/structures on both sides of the diaphragm are involved.
- Stage IV – disseminated involvement of several organs or tissues other than lymph node regions/structures, like bone marrow.

Each stage includes an additional letter (A or B) that indicates whether B-symptoms are present (B) or not (A). Another staging system of the WHO (2008) classifies FL into three grades: FL1–2, FL3A and FL3B, based on the number of centroblasts [17].

6 Current treatment

A0025: How is FL currently managed according to published guidelines and in practice?

for the determination of treatment options several factors have to be taken into account

To determine a treatment strategy for a patient with FL, the following factors have to be taken into account: the extent and size of disease, the establishment of the precise histologic subtype, the general health/performance status and the patient's age.

treatment options for early-stage FL: RT, observation, chemmoimmunotherapy

Since FL is commonly indolent, it can take years for the disease to progress. During that time it may not be necessary to apply any therapies, instead, a „watch and wait" approach (close observation) can be used [12, 18]. Treatment options for patients who suffer from early-stage disease (I and contiguous II) are radiation therapy (RT), observation, and chemoimmunotherapy/immunotherapy (rituximab) [18, 19].

first-line treatment options for advanced FL

Patients with advanced disease/stage but a low burden may also be observed or receive rituximab as a first-line therapy, while the following treatment options are available for patients who are suffering from a high burden [7, 20]:

- monotherapy with rituximab/an alkylating agent
- chemoimmunotherapy (bendamustine plus rituximab, R-CHOP[3] or R-CVP[4])
- maintenance therapy with rituximab or consolidation therapy with radio-immunotherapy

[3] R-CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab

[4] R-CVP = cyclophosphamide, vincristine, and prednisone plus rituximab

no standard therapies for refractory/relapsed FL available

No standard therapies are available for the treatment of relapsed or refractory FL. However, there are several potential therapies that can be applied, like rituximab as monotherapy (poor performance status) or in combination with chemotherapy (good performance status). Another option is chemoimmunotherapy with R-CVP[4], R-CHOP[3], rituximab plus bendamustine, or idelalisib as monotherapy for rituximab-refractory patients. However, it should be mentioned that idelalisib monotherapy is currently monitored due to severe AEs [17, 21, 22].

7 Evidence

search in 5 databases

273 references in total

A literature search was conducted on 11 May 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were „Obinutuzumab", „Gazyva", „ga101", „r7159", „ro5072759", „Lymphoma and Non-Hodgkin". Overall, 275 references were identified through systematic literature search. The manufacturer was contacted as well but did not respond to our request. Eligible for inclusion were phase III trials (full texts, abstracts) and phase II studies published as full text, as well as other study designs like results from compassionate-use programmes or meta-analyses. After applying these inclusion criteria, 1 phase III trial available in abstract form and 1 phase I/II trial were included in this report. Additionally, FDA approval documents and 24 references identified through manual search were included.

included:
1 phase III study
1 phase I/II study

7.1 Clinical efficacy and safety – phase III studies

GADOLIN: randomised phase III study

GADOLIN [2, 23] was an open-label, multicentre, randomised, phase III study comparing obinutuzumab combined with bendamustine to bendamustine monotherapy in patients with rituximab-refractory, indolent NHL. Reported are the efficacy results of the study's FL population (n = 321) and the safety data based on 392 indolent NHL patients, of whom 81% had FL, 12% had marginal zone lymphoma, and 7% had small lymphocytic lymphoma. The trial was discontinued at the planned interim analysis.

comparison of obinutuzumab-bendamustine vs bendamustine monotherapy

Rituximab-refractory, CD20-positive patients with indolent NHL were randomised in a 1:1 ratio to receive either obinutuzumab (cycle 1: 1,000 mg on days 1, 8 and 15; cycles 2–6: 1,000 mg on day 1 followed by 1,000 mg every 2 months for up to 2 years) plus bendamustine (cycles 1–6: 90 mg/m^2/day on days 1 and 2), and after complete response (CR), partial response (PR), or stable disease (SD), patients received obinutuzumab maintenance therapy (1,000 mg every two months for two years or until progression); or bendamustine (cycles 1–6: 120 mg/m^2/day on days 1 and 2). The stratification of randomisation was based on the rituximab-refractory type (refractory to prior rituximab monotherapy vs rituximab in combination with chemotherapy) and the number of prior therapies (≤ 2 vs > 2).

Enrolled patients were at least 18 years or older with a median age of 63 (ranging from 34 to 87 years). 95% of patients had an ECOG performance status of 0–1 at baseline. The median number of prior therapies was 2, ranging from 1 to 10. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 3.

median age 63 years and ECOG performance status of 0–1

The primary outcome of GADOLIN was progression-free survival (PFS) measured by an independent radiology facility (IRF); secondary outcomes included PFS assessed by an investigator, overall survival (OS), best overall response (OR), safety outcomes including adverse events (AEs) and health-related quality of life (HRQoL; assessed by the 42-item Functional Assessment of Cancer Treatment-Lymphoma questionnaire).

primary outcome: PFS
secondary outcomes: OS, OR, AEs and HRQoL

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of obinutuzumab on mortality?

The secondary study endpoint, OS, was not yet reached either by the obinutuzumab-bendamustine group or in the bendamustine arm.

OS was reached by neither study group

D0006: How does obinutuzumab affect progression (or recurrence) of FL?

The primary endpoint, PFS assessed by an independent radiology facility (PFS-IRF), was significantly improved ($p < 0.0001$) in the obinutuzumab-bendamustine group compared to the bendamustine arm. Median PSF-IRF was 13.8 months in the bendamustine group and was not reached in the obinutuzumab-bendamustine arm. The hazard ratio (HR) for disease progression for obinutuzumab-bendamustine compared to bendamustine alone was 0.48 (95% CI 0.34–0.68).

primary endpoint: PFS-IRF

median PFS-IRF was not reached in the intervention group

Median PFS assessed by an investigator (PFS-IA) was 13.7 months in the bendamustine group compared to 29.2 months in the obinutuzumab-bendamustine arm. PFS-IA was significantly ($p < 0.0001$) different between the two randomised groups. The HR for disease progression assessed by an investigator for obinutuzumab-bendamustine compared to bendamustine alone was 0.48 (95% CI 0.35–0.67).

median PFS-IA:
O-B arm: 29.2 months
B arm: 13.7 months

D0005: How does obinutuzumab affect symptoms and findings (severity, frequency) of FL?

The overall response (OR) rates were 78.7% (obinutuzumab-bendamustine) and 74.7% (bendamustine); a complete response (CR) was achieved in 15.5% of patients in the obinutuzumab-bendamustine group and in 18.7% of patients in the bendamustine arm. Partial response (PR) rates were 63.2% and 56.0% in patients receiving obinutuzumab-bendamustine and in patients receiving bendamustine alone respectively.

OR was not significantly improved
O-B: 78.7%
B: 74.7%

D0011: What is the effect of obinutuzumab on patients' body functions?

Neutropenia, thrombocytopenia as well as pneumonia can occur in patients treated with obinutuzumab. Detailed description of adverse events can be found in the section 'Safety'.

D0012: What is the effect of obinutuzumab on generic health-related quality of life?

D0013: What is the effect of obinutuzumab on disease-specific quality of life?

similar mean baseline scores between the two study arms

The obinutuzumab-bendamustine group and the bendamustine arm showed similar mean baseline scores in all individual FACT-Lym[5] subscales, and composite FACT-G[6], FACT-TOI[7], and FACT total scores. During the treatment period as well as during follow-up, no differences could be noted in the average scores between the study arms regarding any of the FACT-Lym[5] subscales. The median time to ≥ 6 point worsening from baseline on FACT-TOI[7] was 8.0 months (95% CI, 5.8–15.1) in the obinutuzumab-bendamustine arm and 4.6 months (95% CI, 3.8-6.4) in the bendamustine arm (HR = 0.74, 95% CI 0.56–0.98) [24].

Table 1: Efficacy results based on the FL population of the GADOLIN trial

Descriptive statistics and estimate variability	Treatment group	Obinutuzumab-bendamustine	Bendamustine
	Number of subjects	155	166
	Median PFS-IRF[8] (95% CI), months	NR	13.8
	Median PFS-IA[9] (95% CI), months	29.2	13.7
	OS	NR	NR
	Best OR[10], % CR PR	78.7 15.5 63.2	74.7 18.7 56.0
	Median duration of DOR, months	NR	11.6
Effect estimate per comparison	Comparison groups		Obinutuzumab-bendamustine vs bendamustine
	PFS-IRC[8]	HR	0.48
		95% CI	0.34–0.68
		Log-rank test p value	< 0.0001
	PFS-IA[9]	HR	0.48
		95% CI	0.35–0.67
		Log-rank test p value	< 0.0001

Abbreviations: CI = confidence interval, CR = complete response, DOR = duration of response, HR = hazard ratio, OR = overall response, OS = overall survival, PFS = progression-free survival, PR = partial response

[5] FACT-Lym = Functional Assessment of Cancer Therapy – for patients with NHL

[6] FACT-G = Functional Assessment of Cancer Therapy – general

[7] FACT-TOI = Functional Assessment of Cancer Therapy – Trial Outcome Index

[8] PFS-IRF = PFS determined by an independent radiology facility

[9] PFS-IA = PFS assessed by an investigator

[10] best OR = best response of CR/PR within 12 months of study start

7.1.2 Safety

C0008: How safe is obinutuzumab in relation to the comparator(s)?

most common AEs in both treatment groups: neutropenia, thrombocytopenia, infusion-related reactions

The most common grade 3–4 AEs in both the obinutuzumab-bendamustine group and in the bendamustine group were neutropenia (33% vs 26.3%), thrombocytopenia (10.8% vs 16.2%), and infusion-related reactions (10.8% vs 5.6%). Serious AEs that were most frequently reported in both treatment arms were febrile neutropenia (obinutuzumab-bendamustine 4.1%; bendamustine: 3.0%) and pneumonia (obinutuzumab-bendamustine: 2.9%; bendamustine: 5.1%).

discontinuation due to AEs:
O-B: 11.3%
B: 15.7%

During obinutuzumab maintenance treatment, the most common haematological grade 3–4 laboratory abnormalities were lymphopenia (52%), leukopenia (20%) and neutropenia (27%). Chemistry grade 3–4 laboratory abnormalities occurred in 8% (hypophosphataemia and hyponatraemia) of patient during obinutuzumab monotherapy. Treatment discontinuation due to AEs occurred in 11.3% (obinutuzumab-bendamustine) and 15.7% (bendamustine) of patients. Grade 5 AEs were not reported, treatment-related grade 1–4 AEs can be found in Table 2.

C0002: Are the harms related to dosage or frequency of applying obinutuzumab?

No evidence was found to answer this research question.

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of obinutuzumab?

HBV reactivation and fetal B-cell depletion

Obinutuzumab can cause fetal B-cell depletion in pregnant women. Furthermore, it can lead to a Hepatitis B virus (HBV) reactivation that may result in fulminant hepatitis, hepatic failure and death. Reactivations have been reported in hepatitis B surface antigen (HBsAg)-positive as well as in hepatitis B core antibody (anti-HBc)-positive patients [2].

Table 2: Most frequent treatment-related adverse events in the whole study population

Adverse event/Laboratory abnormalities (according to CTCAE)	**Obinutuzumab-bendamustine** (n = 194)		**Bendamustine** (n = 198)	
	Any grade (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Adverse reactions reported in ≥ 5% of patients with indolent NHL, which are at least 2% greater in the obinutuzumab-bendamustine group				
Infusion-related reactions[11]	69	11	63	6
Neutropenia	35	33	28	26
Constipation	19	0	16	0
Dyspepsia	5	0	3	0
Pyrexia	18	1	14	0
Asthenia	11	1	8	0
Upper respiratory tract infection	13	2	8	1
Sinusitis	12	1	5	0
Urinary tract infection	10	3	6	0
Nasopharyngitis	9	0	4	0
Arthralgia	12	0	5	0
Pain in extremity	9	1	4	0
Cough	26	0	17	0
Nasal congestion	7	0	2	0
Pruritus	9	0	6	0
Post-baseline laboratory abnormalities in ≥ 5% of patients with indolent NHL, which are at least 2% greater in the obinutuzumab-bendamustine group				
Neutropenia	75	52	77	42
Leukopenia	86	47	88	34
Lymphopenia	99	93	99	85
Hypocalcaemia	38	2	26	2
Hypophosphataemia	41	7	38	7
ALT/SGPT increased	35	1	31	4
Elevated creatinine	87	4	92	2
Creatinine clearance (decreased)	58	6	61	4

Abbreviations: ALT = alanine aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, SGPT = Serum glutamic pyruvic transaminase

[11] Defined as any related adverse reaction that occurred during or within 24 hours of infusion

7.2 Clinical efficacy and safety – further studies

GAUGIN: efficacy of obinutuzumab in relapsed/refractory indolent NHL

The GAUGUIN study was an open-label, multicentre, non-randomised, dose-escalating phase I/II trial assessing the safety and efficacy of two different doses of obinutuzumab in relapsed/refractory indolent NHL [25]. 40 patients were enrolled, of which 34 patients had FL and 22 were rituximab refractory. Patients either received 8 cycles of obinutuzumab as a flat dose of 400 mg on days 1 and 8 of cycle 1 and also on day 1 of cycles 2–8 (400/400 mg) or 1,600 mg on days 1 and 8 of cycle 1 and 800 mg on day 1 of cycles 2 to 8 (1,600/800 mg).

ORR 1,600/800 mg: 55%
ORR 400/400 mg: 17%

The overall response rate (ORR) at the end of treatment was 55% (95% CI 32%–76%, CR: 9%) in the 1,600/800 mg group compared to 17% (95% CI 4%–41%, no complete responders) in the 400/400 mg group. The median PFS was 6.0 months (range: 1.0–33.9 months) in the 400/400 mg arm and 11.9 months (range: 1.8–33.9 months) in the 1,600/800 mg arm. Most frequent AEs were infusion-related reactions (IRRs), which occurred in 73% of patients, of which two patients, both from the 1,600/800 mg arm, had grade 3–4 IRRs.

8 Estimated costs

A0021: What is the reimbursement status of obinutuzumab?

estimated costs for 6 treatment cycles and 2 years of obinutuzumab monotherapy: € 73,364

In Austria, obinutuzumab is available as a 1,000 mg concentrate for solution for infusion at € 3,668.20 [26].

In patients with relapsed/refractory FL, the recommended and FDA-approved dose is 1,000 mg administered as an intravenous infusion on days 1, 8, and 15 of a cycle 1 (28 days). In the following cycles 2–6 1,000 mg are recommended on each respective day 1. After cycle 6, 1,000 mg should be administered every 2 months for 2 years [2]. According to this treatment regimen, costs of € 73,364 would incur for 6 cycles and 2 years of obinutuzumab monotherapy.

Additional costs incur due to the combination therapy with bendamustine, which is administered at a dose of 90 mg/m² on days 1 and 2 of cycles 1–6 [2]. Assuming a body surface of 1.70 m², total costs of about € 35,207.58 would incur for 6 treatment cycles of combination therapy.

9 Ongoing research

1 phase III study is investigating obinutuzumab in indolent NHL patients

In June 2016, a search in databases www.clinicaltirals.gov and www.clinicaltrialsregister.eu was conducted. The following ongoing phase III trial is investigating obinutuzumab in patients with indolent NHL:

- NCT01332968: A multicentre, phase III, open-label randomised study in previously untreated patients with advanced indolent non-Hodgkin's lymphoma evaluating the benefit of GA101 (RO5072759) + chemotherapy compared to rituximab + chemotherapy followed by GA101 or rituximab maintenance therapy in responders. Estimated study completion date is March 2017.

numerous ongoing phase I and phase II trials in different treatment lines

Various phase I and II studies are currently ongoing in different treatment lines in patients with indolent NHL, either using obinutuzumab monotherapy or in combination (e.g. NCT01995669, NCT02393157, NCT01889797 and NCT00825149).

10 Discussion

positive opinion by the CHMP: obinutuzumab for relapsed/refractory FL

In April 2016, the CHMP adopted a positive opinion for the extension of indication of obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance treatment for patients with relapsed/refractory FL. Obinutuzumab has been approved in combination with chlorambucil for the first-line treatment of CLL since July 2014 [3, 4].

approved by the FDA in 2016

In the US, obinutuzumab was approved by the FDA in 2013 as a combination therapy for the treatment of previously untreated CLL patients. Obinutuzumab in combination with bendamustine, followed by obinutuzumab monotherapy, has been approved for the treatment of patients with relapsed/refractory FL since February 2016 [2].

GADOLIN: PFS improvement, no difference in OR, and OS was not reached

The FDA approval was based on the pre-planned interim analysis of the GADOLIN trial, which is currently only available in abstract form [5]. This open-label, multicentre, randomised phase III study enrolled 392 indolent NHL patients (81% with FL), who either received obinutuzumab plus bendamustine and subsequent obinutuzumab maintenance treatment or bendamustine alone. PFS-IRF and PFS-IA were significantly improved (PFS-IRF: $p < 0.0001$, PFS-IA: $p < 0.0001$) in the obinutuzumab-bendamustine group compared to the bendamustine arm, though PFS-IRF was not reached and correspondent data is not available. The study endpoint, OS, was reached in neither treatment group. OR rates indicated no difference between the two treatment regimens (obinutuzumab-bendamustine: 78.7%, bendamustine: 74.7%).

PFS improvement: maintenance vs combination treatment

There was no difference in OR and an initial overlap of the Kaplan-Meier curves for PFS (FL patients) at around six months. The two curves separated approximately after the induction time was finished. Therefore, it would be of great interest to determine to which extent PFS improvement was conferred to obinutuzumab maintenance treatment in contrast to obinutuzumab-bendamustine combination therapy.

In terms of safety outcomes, the most common grade 3–4 AEs in the obinutuzumab-bendamustine as well as in the bendamustine group were neutropenia (33% vs 26.3%), thrombocytopenia (10.8% vs 16.2%) and infusion-related reactions (10.8% vs 5.6%). Pneumonia and neutropenia were the most frequent reported serious AEs in both treatment groups. Regarding health-related quality of life (HRQoL), no notable differences in the average scores between the two treatment groups in any of the FACT-Lym[5] subscales, either over time during the treatment period or during follow-up, could be identified.

most common grade 3–4 AEs: neutropenia, thrombocytopenia and infusion-related reactions

The trial was discontinued early at the pre-planned interim analysis due to significantly improved PFS results, though PFS-IRF was not reached. The early termination caused a lack of long-term OS data. Therefore, the current OS results are immature and should be reconsidered when long-term data is available. Further follow-up will be necessary to exclude any risks of late side effects as well as negative effects on QoL.

trial was stopped early; immature OS data; missing data on long-term side effects/QoL

As obinutuzumab has been approved for refractory/relapsed FL based on interim analysis only, available solely in abstract form, no detailed information exists about the study. Thus, data on subgroup analysis are missing. It is therefore impossible to exclude any disadvantages for specific patient groups. For instance, since the number of prior therapies was ranging from 1 to 10, it would be of interest if patients who were heavily pretreated showed the same PFS benefit as patients who received 1–2 lines of prior therapy. In addition, the early termination of the trial may negatively influence the probability that a nominally statistical finding actually represents a true effect [27].

data for subgroup analysis are missing

In general, NHL is more frequently diagnosed in people aged 65–74, of which the majority of patients are diagnosed at an advanced stage of disease [9, 15]. Since patients were on average 63 years old and had an ECOG score between 0 and 1 in about 95% of cases, the study population did not reflect the affected FL patients in clinical practice.

patient group in practice vs study population

A kinase inhibitor called idelalisib has been approved by the EMA and the FDA since 2014. Idelalisib received marketing authorisation for the treatment of patients with relapsed FL who received at least two prior systemic therapies [28, 29]. It is currently under close monitoring due to severe complications that led to death in some cases [22]. Dependent on the safety profile resulting from this monitoring process, idelalisib could be used as a future comparator to yield information as to which drug the patients benefit from most. It may also be considered to add idelalisib to obinutuzumab to offer an alternative treatment option for relapsed/refractory FL.

idelalisib as another comparator or for combination therapy

Total costs of about € 73,364 would incur for 6 treatment cycles of combination therapy and 2 years of obinutuzumab monotherapy, not including the treatment of side effects. Even though the treatment with obinutuzumab-bendamustine is costly, the associated improvement in PFS with this therapy should not be neglected. However, the lack of mature OS data, in addition to the fact that there was no difference in OR, highlight the need for long-term data. Further, a long-term safety profile as well as further QoL data will be necessary to exclude any risks of late side effects. In addition, the original article presenting the study will be necessary to identify potential advantages and disadvantages for specific subgroups. Finally, idelalisib, which is currently under close monitoring due to severe AEs, could be used as another comparator or as a combination treatment option with obinutuzumab in the future, if it shows manageable AEs.

high treatment costs

PFS improvement

long-term/mature data on efficacy and safety will be necessary to make a more confident statement

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12 Appendix

Table 3: Characteristics of the GADOLIN trial

Title: A study to investigate the efficacy and safety of bendamustine compared with bendamustine + obinutuzumab (GA101) in patients with rituximab-refractory, indolent non-Hodgkin's lymphoma (GADOLIN) [2, 23]			
Study identifier	NCT01059630, EudraCT Number 2009-015504-25, GAO47539, GADOLIN		
Design	Open-label, multicentre, randomised phase III study		
	Duration		Data analysis cut-off: 2014-09-01 Median follow-up: 21 months; number of patients who were still participating in the study at median follow-up: obinutuzumab + bendamustine: n = 149 bendamustine: n = 141
Funding	Roche Registration Ltd		
Hypothesis	Superiority The study was designed to show a prolonged PFS in patients treated with obinutuzumab plus bendamustine compared to those who received bendamustine alone. The primary endpoint (PFS) was assessed by an independent radiology facility (IRF), with 80% power to detect 43% improvement in median PFS.		
Treatments groups	Intervention		Obinutuzumab was administered as follows: cycle 1: 1,000 mg on days 1, 8 and 15; cycles 2–6: 1,000 mg on day 1; followed by 1,000 mg every 2 months for up to 2 years) plus bendamustine (cycles 1–6: 90 mg/m²/day on days 1 and 2). After CR, PR or SD, patients received obinutuzumab maintenance therapy: 1,000 mg every two months for two years or until progression.
	Control		Bendamustine was administered in cycles 1–6: 120 mg/m²/day on days 1 and 2.
Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	Defined as the time from randomisation to first occurrence of progression or relapse, or death
	Overall survival	OS	Defined as the time from randomisation to death
	Best overall response	OR	Best response of CR/PR within 12 months of study start
Results and analysis			
Analysis description	**Primary analysis** No information is available on the included patient population regarding efficacy and safety. Patient-reported HRQoL analyses included all randomised patients in the intent-to-treat population who had a non-missing baseline and at least one post-baseline patient-reported outcome assessment (PRO). Descriptive statistics for recorded values at each visit and changes from baseline were presented with the use of the PRO analysis set, for each PRO endpoint. PFS was analysed by a stratified log-rank test.		
Analysis population	Inclusion		❁ Age ≥ 18 years ❁ History of histologically documented CD20+, indolent NHL ❁ Refractory to any previous regimen containing rituximab ❁ Previously treated with a maximum of four unique chemotherapy-containing treatment regimens ❁ All patients must have at least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan)

<table>
<tr><td rowspan="2">Analysis population
(continuation)</td><td>Exclusion</td><td colspan="3">❁ Prior use of any monoclonal antibody (other than anti-CD20) within 3 months
❁ Chemotherapy or other investigational therapy within 28 days
❁ Prior treatment with bendamustine (within 2 years of the start of study treatment)
❁ Prior allogeneic stem cell transplant
❁ History of severe allergic or anaphylactic reactions to monoclonal antibody therapies
❁ History of sensitivity to mannitol
❁ Central nervous system lymphoma or histological evidence of transformation to high-grade or diffuse large B-cell lymphoma
❁ History of other malignancy that could affect compliance with the protocol or interpretation of results
❁ Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results
❁ Known active bacterial, viral, fungal, mycobacterial, parasitic or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with intravenous antibiotics or hospitalisation within 4 weeks
❁ Vaccination with a live vaccine a minimum of 28 days prior to randomisation
❁ Recent major surgery (within 4 weeks), other than for diagnosis
❁ Presence of positive test results for hepatitis B or hepatitis C
❁ Known history of HIV seropositive status
❁ Positive test results for human T-lymphotropic virus type I (HTLV 1) virus in endemic countries
❁ Women who are pregnant or lactating
❁ Agreement to use an effective form of contraception for the duration of the study
❁ Ongoing corticosteroid use > 30 mg/day prednisone or equivalent</td></tr>
<tr><td>Characteristics[12]</td><td></td><td>Obinutuzumab-bendamustine</td><td>Bendamustine</td></tr>
<tr><td></td><td>Median age, years (range)</td><td colspan="2">63 (34–87)</td></tr>
<tr><td></td><td>Gender:%</td><td>♂: 56.7
♀: 43.4</td><td>♂: 58.4
♀: 41.6</td></tr>
<tr><td></td><td>Number of prior treatments, median (range)</td><td colspan="2">2 (1–10)</td></tr>
<tr><td></td><td>Median time since initial diagnosis, years</td><td colspan="2">3</td></tr>
<tr><td></td><td>ECOG 0–1</td><td>95.4</td><td>95.5</td></tr>
<tr><td></td><td>Ann Arbor stage IV disease</td><td>60.3</td><td>52.7</td></tr>
<tr><td></td><td>Prior rituximab + chemotherapy treatment,%</td><td>80.4</td><td>77.7</td></tr>
<tr><td></td><td>Prior treatment with rituximab monotherapy,%</td><td>19.6</td><td>22.3</td></tr>
<tr><td></td><td>Follicular lymphoma,%</td><td>79.9</td><td>82.2</td></tr>
<tr><td></td><td>Marginal zone lymphoma,%</td><td>13.9</td><td>9.4</td></tr>
<tr><td></td><td>Small lymphocytic lymphoma,%</td><td>6.2</td><td>7.9</td></tr>
</table>

Abbreviations: CR = complete response, CT = Computer tomography, ECOG = Eastern Cooperative Oncology Group, HRQoL = health-related quality of life, PR = partial response

[12] Data based on the whole study population (indolent NHL patients) of the GADOLIN study