Horizon Scanning in Oncology

Obinutuzumab (Gazyva®) for previously untreated patients with chronic lymphocytic leukaemia (CLL)

Ludwig Boltzmann Institut
Health Technology Assessment

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Institute for Health Technology Assessment (LBI-HTA)
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1 Drug description

Generic/Brand name/ATC code:

Obinutuzumab/Gazyva®/L01XC15

Developer/Company:

Hoffmann-La Roche Inc.

Description:

Obinutuzumab (afutuzumab, GA101, RO5072759) is a type II, glycoengineered, humanised anti-CD20 monoclonal antibody with potential antineoplastic activity. It selectively binds to the extracellular domain of the human CD20 antigen on malignant human B cells and promotes antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity [1, 2].

a glycoengineered, humanised antibody binding to the CD20 antigen

Obinutuzumab is available in single-use vials containing 1,000 mg/40 ml (25 mg/ml). The recommended dose regimen for six cycles (28-day cycles) is:

- 100 mg on day 1 cycle 1
- 900 mg on day 2 cycle 1
- 1000 mg on day 8 and 15 of cycle 1
- 1000 mg on day 1 of cycles 2–6 [3].

available in single-use vials

Gazyva® should be administered as intravenous infusion, not as an intravenous push or bolus. Furthermore, premedication with glucocorticoid, acetaminophen and anti-histamine is recommended. Warnings in terms of hepatitis B virus reactivation causing hepatic failure or death, development of progressive multifocal leukoencephalopathy, Tumour Lysis Syndrome, neutropenia and thrombocytopenia have been formulated and are incorporated in the U.S. Food and Drug Administration (FDA) drug label information [3].

given intravenously after recommended premedication

2 Indication

Obinutuzumab is indicated for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) patients.

indicated for untreated CLL patients

3 Current regulatory status

On 10 October 2012, orphan designation (EU/3/12/1054) was granted by the European Commission for obinutuzumab for the treatment of CLL [4], but obinutuzumab is not yet licensed in Europe.

EMA granted orphan designation in October 2012

FDA licensed obinutuzumab in November 2013

The FDA approved obinutuzumab for use in combination with chlorambucil for the treatment of patients with previously untreated CLL on 1 November 2013 [5].

4 Burden of disease

CLL most common form of leukaemia in industrialised countries affecting mostly patients ≥65 years

CLL belongs to the group of indolent B-cell non-Hodgkin lymphomas (NHL) and is the most common type of adult leukaemia in Western countries, accounting for approximately 25% to 30% of all leukaemias [6]. The median age at diagnosis is 72 years [7], and 70% of patients are older than 65 years at diagnosis. CLL is rarely seen in younger persons. Fewer than 2% of patients are younger than 45 years at the time of diagnosis. The male to female ratio is 2:1 [6, 8].

risk factors: age, sex, ethnicity, family history, other cancers

Risk factors for developing CLL include older age, male sex, white ethnicity, family history of CLL or other blood and bone marrow cancers and exposure to certain chemicals, such as herbicides and insecticides [9].

most patients are asymptomatic at diagnosis and are diagnosed incidentally

In the majority of cases CLL is diagnosed incidentally by routine complete blood count examination, because most patients are asymptomatic at the time of diagnosis. Diagnosis is established by blood counts, blood smears and immunophenotyping of circulating B-lymphocytes [10]. The most common symptom is lymphadenopathy, followed by so-called "B" symptoms, including fever, night sweats and weight loss. The life expectancy of patients with early-stage disease at diagnosis is greater than ten years but decreases with advanced disease at diagnosis [11, 12].

two classification systems for CLL: Rai classification, Binet staging system

There are two classification systems for the clinical staging of CLL, depending on standard laboratory tests and physical examination, including the Rai classification and the Binet staging system. The Rai classification distinguishes low (formerly Rai stage 0), intermediate (formerly Rai stage I or II) and high (formerly Rai stage IV and V) risk disease, whereas the Binet staging is subdivided into stages A, B and C [13].

Table 1: Binet staging system for CLL (from [14])

Stage	Description
A	Two or less lymphoid-bearing areas enlarged*
B	Three or more lymphoid-bearing areas enlarged*
C	Presence of anaemia (Hgb <10.0 g/dl) or thrombocytopenia (platelet count <100,000/µl)

* Five lymphoid bearing areas are possible: cervical, axillary, inguinofemoral, spleen and liver.

watch and wait in early stage of disease

The initiation of treatment is not recommended for asymptomatic early-stage disease (Rai 0, Binet A). In these patients a watch-and-wait strategy with controls of blood cell counts and clinical examination every three to six months is recommended until there is evidence of disease progression. In patients with intermediate and high-risk disease, according to the Rai classification as well as patients with Binet stage B or C disease, the initiation of treatment is recommended, whereas some patients with intermediate disease or Binet stage B may also be monitored until disease progresses [15].

Cytogenetic abnormalities are present in about 80% of patients with previously untreated CLL. These cytogenetic abnormalities also influence prognosis. The most common abnormalities include:

80% of patients show cytogenetic abnormalities

- Del (13q) (55%)
- Del (11q) (18%)
- Trisomy 12 (16%)
- Del (17p) (7%)
- Del (6q) (7%) [16].

5 Current treatment

There are various treatment options for CLL depending on disease stage, patient's age, presence of cytogenetic lesions or concomitant diseases. Patients diagnosed with CLL at an early stage should be observed only [15]. Currently, fludarabine, cyclophosphamide, and rituximab (FCR) immunochemotherapy is the standard of care for previously untreated patients with CLL. However, this regimen is in general neither appropriate for patients with impaired renal function nor for patients above the age of 65 years nor for patients with a comorbidity burden (CIRS >6) [17].

treatment options depending on stage, age, cytogenetic lesions, other diseases

The regimen in first-line therapy varies along with patient characteristics such as age, genetic mutations or comorbidity [15]. Therapy options include:

treatment options for CLL

- Alkylating agents: chlorambucil, bendamustine, cyclophosphamide
- Anthracyclines (e.g. adriamycine), anthrachinolones (e.g. mitoxantrone)
- Purine/pyrimidine nucleoside analogues: fludarabine, cladribine, pentostatin
- Monoclonal antibodies: rituximab, alemtuzumab
- Immunomodulation drugs: lenalidomide
- Corticosteroid drugs: prednisone [15, 17-19].

Combination or single-agent therapy is indicated depending on patient characteristics. In the past few years, antibody monotherapy and the addition of monoclonal antibodies to chemotherapy have moved into the focus of interest. For example, rituximab in addition to chemotherapy is an effective treatment option for CLL patients [20].

antibody monotherapy or a combination with chemotherapy is common

Treatment options especially for older patients with CLL who have comorbidities include:

therapy options for older patients with CLL with comorbidities

- Chlorambucil plus rituximab
- Bendamustine plus rituximab
- Pulsed intermittent single-agent chlorambucil (e.g. a single oral dose of 0.8 mg/kg every four weeks, adjusted as needed)
- Lower-dose fludarabine (25 mg/m^2 IV for three consecutive days every month)
- FR (Fludarabine plus rituximab)
- Tyrosine kinase inhibitors (e.g. ibrutinib), PI3K inhibitors (e.g. idelalisib), bcl-2 inhibitors (already licensed or expected to be licensed soon in the U.S.) [21].

6 Evidence

literature search in four databases: 254 hits

included: one phase III trial

A literature search was conducted on the 16th of April 2014 in four databases (Medline, Embase, CRD, Cochrane Central). Search terms were "chronic lymphocytic leukaemia", "obinutuzumab", "gazyva" and "afutuzumab". Overall, 254 references were identified through literature search. The manufacturer additionally submitted five articles, which had already been identified through literature search. Eligible for inclusion were phase III trials (full text, abstracts) and phase II studies published as full text but also other study designs such as results from compassionate-use programmes or meta-analyses. After applying these inclusion criteria, one phase III trial and no phase II trial were included in this report.

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions [22-24]			
Study identifier	NCT01010061		
Design	Open-label, three-group study, randomisation in a 1:2:2 ratio, stratification according to geographic region and Binet stage, multinational (26 countries, 189 centres), patients who progress during or within six months of end of Chlorambucil treatment have the opportunity to cross over		
	Duration	*Enrolment:* April 2010–July 2012 *Median follow-up:* 14.2 months as of July 2012 [17] *Cut-off dates for analyses:* July/August 2012 (stage 1 primary analysis), May 2013 (stage 1 updated analysis, stage 2 interim analysis)	
Hypothesis	❖ Stage 1a: obinutuzumab in combination with chlorambucil vs. chlorambucil alone (O-Clb vs. Clb): superiority of O-Clb over Clb for initial application ❖ Stage 1b: rituximab in combination with chlorambucil vs. chlorambucil alone (R-Clb vs. Clb): superiority of R-Clb over Clb ❖ Stage 2: obinutuzumab in combination with chlorambucil vs. rituximab in combination with chlorambucil (O-Clb vs. R-Clb): superiority of O-Clb over R-Clb		
Funding	Hoffmann-La Roche Inc.		
Treatment groups	Stage 1a: O-Clb vs. Clb (obinutuzumab in combination with chlorambucil vs. chlorambucil alone) Stage 1b: R-Clb vs. Clb (rituximab in combination with chlorambucil vs. chlorambucil alone) Stage 2: O-Clb vs. R-Clb (obinutuzumab in combination with chlorambucil vs. rituximab in combination with chlorambucil)		
	Obinutuzumab + chlorambucil (stage 1a n=238 stage 2 n=333)	Obinutuzumab administered intravenously at a dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6 + chlorambucil administered orally at a dose of 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle	
	Rituximab+ chlorambucil (stage 1b n=233 stage 2 n=330)	Rituximab administered intravenously at a dose of 375 mg/m² of body-surface area on day 1 of cycle 1 and 500 mg/m² on day 1 of cycles 2 through 6 + chlorambucil administered orally at a dose of 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle	
	Chlorambucil (stage 1a/1b n=118)	Chlorambucil administered orally at a dose of 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle	
Endpoints and definitions	Progression free survival (primary outcome)	PFS	Time from randomisation to the first occurrence of progression, relapse or death due to any cause
	Overall survival	OS	Time between the date of randomisation and the date of death due to any cause
	Event-free survival	EFS	Time between the date of randomisation and the date of disease progression/relapse, death or start of new anti-leukaemia treatment
	End of treatment response	-	Response occurring at the end of treatment before start of new anti-leukaemia treatment
	Complete response	CR	Date of first recorded complete response to the date of

			disease progression or death due to any cause
	Partial response	PR	Date of first recorded partial response to the date of disease progression or death due to any cause
	Disease-free survival	-	For all patients with complete response at any time from 56 days after end of treatment onward
	Time to new anti-leukaemic therapy	-	Time between the date of randomisation and the date of first intake of re-treatment or new leukaemic therapy
	Quality of life	QoL	Assessed with the EORTC QLQC30
Results and analysis			
Analysis description	ITT Primary analysis included treatment comparison using a two-sided stratified (by Binet stage) log-rank test and estimation of median times with 95% CI; secondary end points were analysed with a two-sided test at a 5% alpha level		
Analysis population	Inclusion		✵ Documented CD20 + B-CLL ✵ Previously untreated CLL requiring treatment ✵ Total CIRS score >6 and/or creatinine clearance <70 ml/min ✵ Life expectancy >6 months
	Exclusion		✵ Previous CLL therapy ✵ Transformation of CLL to aggressive NHL ✵ One or more individual organ/system impairment score(s) of 4 as assessed by the CIRS definition ✵ Inadequate renal function: creatinine clearance <30 ml/min ✵ Inadequate liver function ✵ Active bacterial, viral or fungal infection requiring systemic treatment
	Characteristics [22]		✵ Age – median (range): O-Clb vs. Clb: 74 (39-88) vs. 72 (43-87) R-Clb vs. Clb: 73 (40-90) vs. 72 (43-87) O-Clb vs. R-Clb: 74 (39-89) vs. 73 (40-90) ✵ CIRS Score – median (range): O-Clb vs. Clb: 8 (1-20) vs. 8 (0-18) R-Clb vs. Clb: 8 (0-18) vs. 8 (0-18) O-Clb vs. R-Clb: 8 (0-22) vs. 8 (0-18) ✵ Median calculated creatinine clearance (ml/min): O-Clb vs. Clb: 61.4 vs. 63.8 R-Clb vs. Clb: 61.8 vs. 63.8 O-Clb vs. R-Clb: 62.5 vs. 62.6 ✵ Binet stage A, n (%): O-Clb vs. Clb: 55 (23) vs. 24 (20) R-Clb vs. Clb: 49 (21) vs. 24 (20) O-Clb vs. R-Clb: 74 (22) vs. 74 (22) ✵ Binet stage B, n (%): O-Clb vs. Clb: 98 (41) vs. 50 (42) R-Clb vs. Clb: 100 (43) vs. 50 (42) O-Clb vs. R-Clb: 142 (43) vs. 135 (41) ✵ Binet stage C, n (%): O-Clb vs. Clb: 85 (36) vs. 44 (37) R-Clb vs. Clb: 84 (36) vs. 44 (37) O-Clb vs. R-Clb: 117 (35) vs. 121 (37) ✵ Unmutated IGHV, n/total n (%):

		O-Clb vs. Clb: 129/210 (61) vs. 58/99 (59) R-Clb vs. Clb: 126/204 (62) vs. 58/100 (58) O-Clb vs. R-Clb: 188/305 (62) vs. 182/298 (61) ❁ Del (17p) on FISH, n/total n (%): O-Clb vs. Clb: 16/203 (8) vs. 10/96 (10) R-Clb vs. Clb: 9/196 (5) vs. 10/97 (10) O-Clb vs. R-Clb: 22/295 (7) vs. 20/287 (7)

Descriptive statistics and estimated variability **May 2013 [22, 24]**	Treatment group	Stage 1a		Stage 1b		Stage 2	
		O-Clb	Clb	R-Clb	Clb	O-Clb	R-Clb
	Number of subjects	N=238	N=118	N=233	N=118	N=333	N=330
	Median PFS, months (SI-assessed) [22]	26.7	11.1	16.3	11.1	26.7	15.2
	Median PFS, months (IRC-assessed, secondary endpoint) [24]	27.2	11.2	16.1	11.2	26.7	14.9
	Patients with a complete response (%) [22]	22.3	0	7.3	0	20.7	7.0
	Patients with a partial response (%) [22]	55.0	31.4	58.4	31.4	57.7	58.1
	Event-free survival, median in months (IRC-assessed) [24]	26.1	10.8	15.4	10.8	26.1	14.3
	Time to new anti-leukaemic therapy, median in months (IRC-assessed) [24]	NR	14.8	30.8	14.8	NR	30.8
July 2012 [23]	Event-free survival, median in months	23.0	10.6	NR		NR	
	End of treatment response, % 95% CI	75.5 69.1-81.1	30.2 21.7-39.9	NR		NR	
	Time to new anti-leukaemic therapy, median in months	NR	14.8	NR		NR	
Effect estimate per comparison	***Comparison groups***		***O-Clb vs Clb***	***R-Clb vs Clb***		***O-Clb vs R-Clb***	
	Median PFS [22]	HR	0.18	0.44		0.39	
		95% CI	0.13-0.24	0.34-0.57		0.31-0.49	
		P value	<0.001	<0.001		<0.001	
	Probability of OS [22]	HR	0.41	0.66		0.66	

		95% CI	0.23-0.74	0.39-1.11	0.41-1.06
		P value	0.002	0.11	0.08
	Event-free survival [24]	HR	0.19	0.39	0.43
		95% CI	0.14-0.25	0.30-0.51	0.34-0.54
		P value	<0.0001	<0.0001	<0.0001
	Time to next anti-leukaemic therapy [24]	HR	0.24	0.34	0.59
		95% CI	0.16-0.35	0.24-0.48	0.42-0.82
		P value	<0.0001	<0.0001	0.0018

Abbreviations: CI = confidence interval, CIRS = Cumulative Illness Rating Scale, Clb = chlorambucil, CLL = chronic lymphocytic leukaemia, EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer QLQ-C30 Questionnaire, FISH = fluorescence in situ hybridisation, HR = hazard ratio, IGHV = immunoglobulin heavy-chain variable region gene, IRC = Independent Radiologic Assessment Committee, ml/min = millilitre per minute, n = number, NHL = Non-Hodgkin Lymphoma, NR = not reported, O-Clb = obinutuzumab-chlorambucil, OS = overall survival, PFS = progression free survival, R-Clb = rituximab-chlorambucil, SI = site investigator

Table 2: Adverse events

NCT01010061						
	Stage 1a		Stage 1b		Stage 2	
AEs of Grade 3 or higher [22][1]	O-Clb (n=241)	Clb (n=116)	R-Clb (n=225)	Clb (n=116)	O-Clb (n=336)	R-Clb (n=321)
Any event, n (%)	175 (73)	58 (50)	125 (56)	58 (50)	235 (70)	177 (55)
Infusion-related reactions, n (%)	51 (21)	-	9 (4)	-	67 (20)	12 (4)
Neutropenia, n (%)	84 (35)	18 (16)	60 (27)	18 (16)	111 (33)	91 (28)
Anaemia, n (%)	11 (5)	5 (4)	10 (4)	5 (4)	14 (4)	12 (4)
Thrombocytopenia, n (%)	27 (11)	5 (4)	8 (4)	5 (4)	35 (10)	10 (3)
Leukopenia, n (%)	13 (5)	0	3 (1)	0	15 (4)	3 (1)
Infections, n (%)	27 (11)	16 (14)	30 (13)	16 (14)	40 (12)	44 (14)
Pneumonia, n (%)	8 (3)	4 (3)	11 (5)	4 (3)	13 (4)	17 (5)
Febrile neutropenia, n (%)	4 (2)	5 (4)	4 (2)	5 (4)	8 (2)	4 (1)
Other serious AEs [24][2]						
Neoplasm, n (%)	17 (7)	5 (4)	16 (7)	5 (4)	19 (6)	18 (6)
Respiratory tract infection, n (%)	2 (<1)	3 (3)	2 (<1)	3 (3)	3 (<1)	2 (<1)
Sepsis, n (%)	0	3 (3)	0	3 (3)	1 (<1)	1 (<1)
Cardiac failure, n (%)	3 (1)	2 (2)	0	2 (2)	4 (1)	1 (<1)
Urinary tract infection, n (%)	3 (1)	1 (<1)	0	1 (<1)	3 (<1)	1 (<1)
Cerebrovascular accident, n (%)	3 (1)	0	1 (<1)	0	3 (<1)	1 (<1)

Abbreviations: AE = adverse event, Clb = chlorambucil, n = number, O-Clb = obinutuzumab-chlorambucil, R-Clb = rituximab-chlorambucil

[1] Data for the incidence rate of 3% or higher in any treatment group [22]

[2] Data for the incidence rate of ≥1% in any treatment arm [24]

A three arm, open-label, multicentre phase III study [22] examined the efficacy and safety of obinutuzumab in combination with chlorambucil and chlorambucil alone, rituximab in combination with chlorambucil and chlorambucil alone as well as obinutuzumab in combination with chlorambucil and rituximab in combination with chlorambucil in patients with CLL. 781 patients were randomly assigned.

phase III study compared obinutuzumab-chlorambucil, rituximab-chlorambucil and chlorambucil monotherapy in 781 patients

The study included 2 stages: stage 1 randomised patients into three study arms on a 1:2:2 basis (randomisation to the chlorambucil alone arm, the obinutuzumab-chlorambucil or the rituximab-chlorambucil arm) and stage 2 randomised additional patients at a 1:1 ratio (randomisation continued only to the obinutuzumab-chlorambucil or the rituximab-chlorambucil arm and was stopped to the chlorambucil alone arm). Randomisation for both stages was stratified by Binet stage at baseline and geographic region. The primary analysis of stage 1 was performed in July/August 2012, whereas an updated analysis of stage 1 and the interim analysis of stage 2 were done in May 2013. Patients had to be previously untreated but requiring treatment and had to had a total CIRS score[3] of > 6 and/or a creatinine clearance <70 ml/min. Included patients had a median age of 73 years, a creatinine clearance of 62 ml/min and a CIRS score of 8. 21% of the patients were in Binet stage A, 42% in Binet stage B and 36% in Binet stage C.

randomisation stratified by Binet stage and geographic region

included patients: median age of 73 years, creatinine clearance of 62 ml/min and a CIRS score of 8

Treatment with obinutuzumab–chlorambucil or rituximab–chlorambucil provided a significant improvement concerning median PFS, the primary outcome, as compared with chlorambucil monotherapy (26.7 months with obinutuzumab–chlorambucil vs. 11.1 months with chlorambucil alone, HR 0.18, 95% CI 0.13-0.24, p<0.001 and 16.3 months with rituximab–chlorambucil vs. 11.1 months with chlorambucil alone, HR 0.44, 95% CI 0.34-0.57, p<0.001). Treatment with obinutuzumab–chlorambucil compared with rituximab–chlorambucil showed also a PFS benefit for the obinutuzumab–chlorambucil group (median PFS 26.7 vs. 15.2 months, HR 0.39, 95% CI 0.31-0.49, p<0.001). Subgroup analyses showed that this benefit was consistent across most patient subgroups (age, sex, Binet stage, circulating lymphocyte count, total CIRS score) with the only exception of patients with del (17p) mutations [24].

PFS improved significantly in patients treated with obinutuzumab–chlorambucil or rituximab–chlorambucil compared with chlorambucil alone, benefit consistent across subgroups (except patients with del (17p) mutation

Concerning OS, obinutuzumab–chlorambucil was associated with better results compared with chlorambucil monotherapy (HR 0.41, 95% CI 0.23-0.74, p=0.002). No significant benefit was seen for rituximab–chlorambucil over chlorambucil alone (HR 0.66, 95% CI 0.39-1.11, p=0.11). No benefit was noted for obinutuzumab–chlorambucil compared with rituximab–chlorambucil (HR 0.66, 95% CI 0.41-1.06, p=0.08). The overall survival analysis included 22 patients from the chlorambucil monotherapy arm who crossed over to receive obinutuzumab–chlorambucil upon disease progression. At the time of data cut-off, none of these patients had died [23].

results on OS favoured treatment with obinutuzumab–chlorambucil compared with chlorambucil alone, but no benefit was shown for obinutuzumab–chlorambucil compared with rituximab–chlorambucil

[3] The CIRS index uses a scoring system that includes 14 body system domains and a severity scale (0–4) for each domain. It is used to quantify the number and the severity of coexisting medical conditions [17]

AEs were most frequent in patients treated with obinutuzumab-chlorambucil

Adverse events were most frequent in treatment with obinutuzumab-chlorambucil. Any adverse event of grade 3 or higher occurred in 73% and 70% of all patients receiving obinutuzumab–chlorambucil in stages 1a and 2, respectively compared with 50% and 55% in stage 1a chlorambucil monotherapy in patients and with stage 2 rituximab–chlorambucil patients, respectively. In patients with rituximab–chlorambucil compared with chlorambucil alone, 56% vs. 50% had any adverse events of grade 3 or higher. Neutropenia, infusion-related reactions, infections and thrombocytopenia occurred also more frequently in the obinutuzumab–chlorambucil group.

no findings on QoL were available

Findings on quality of life were not available in the study or the supplementary appendix documents, but the authors mentioned that quality of life did not deteriorate due to antibody therapy in comparison to chlorambucil alone.

6.2 Efficacy and safety – further studies

no phase II study found

No phase II studies were found for obinutuzumab in patients with previously untreated CLL.

7 Estimated costs

no cost estimates available for Austria

No cost estimates are available yet for Austria.

In the US, cost estimates for obinutuzumab are $6,192 for one vial (1,000 mg). Costs for 28 days are estimated at $18,576 (cycle 1) and $6,192 (cycles 2-6) [16].

8 Ongoing research

one ongoing phase III study in patients with CLL

At http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/ one ongoing phase III study investigating obinutuzumab in patients with CLL was found.

- NCT01905943: A multicentre, open-label, single-arm study evaluating the safety of obinutuzumab alone or in combination with chemotherapy in patients with previously untreated or relapsed/refractory CLL. The estimated study completion date is June 2018.

obinutuzumab is investigated in different studies

Several other phase I and phase II studies are currently conducted (NCT01414205, NCT01889797, NCT01287741).

9 Commentary

orphan designation in Europe, licensed in the USA

On 10 October 2012, the European Commission granted orphan designation for obinutuzumab for the treatment of CLL, but obinutuzumab is not yet licensed in Europe [4]. The FDA approved obinutuzumab for use in combination with chlorambucil for the treatment of patients with previously untreated CLL on 1 November 2013 [5].

obinutuzumab approved with breakthrough therapy designation by FDA

Obinutuzumab is the first drug approved with breakthrough therapy designation in the U.S. Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence demonstrating that the drug may show substantial improvement on at least one clinically significant endpoint over available therapy [25]. Breakthrough therapy designation covers all features of the fast track programme and involves more intensive FDA guidance on an efficient drug development programme [21, 23, 26].

phase III study on efficacy and safety in patients with untreated CLL

A phase III study (trial divided into three stages: Stage 1a NCT01010061; Stage 1b NCT01998880; Stage 2 NCT02053610) examined the efficacy and safety of obinutuzumab in combination with chlorambucil and chlorambucil monotherapy, rituximab in combination with chlorambucil and chlorambucil monotherapy as well as obinutuzumab combined with chlorambucil and rituximab in combination with chlorambucil in overall 781 previously untreated patients with CLL. Since patients were on average about 74 years old, had to have a creatine clearance of 30–69 ml/minute and a CIRS score of ≥6, the study population reflected older and co-morbid patients, the group mostly affected by CLL in clinical practice.

PFS improved significantly in patients treated with obinutuzumab–chlorambucil or rituximab–chlorambucil compared with chlorambucil alone

For patients treated with obinutuzumab–chlorambucil or rituximab–chlorambucil, median PFS (primary outcome) improved significantly compared with chlorambucil monotherapy by 15.6 months and 5.2 months, respectively. Treatment with obinutuzumab–chlorambucil compared with rituximab–chlorambucil also showed a PFS benefit for the obinutuzumab–chlorambucil group by 11.5 months (median PFS 26.7 vs. 15.2 months, HR 0.39, 95% CI 0.31-0.49, $p<0.001$). These results were consistent among investigators and independent radiologic assessors (IRC). Better results were also shown for obinutuzumab–chlorambucil than for rituximab–chlorambucil in terms of complete and partial responses, but preliminary OS results indicated no difference between these two regimens.

most frequent AEs: neutropenia, infusion-related reactions, infections, thrombocytopenia

results on quality of life are not available

In terms of safety, the most frequent AEs grade 3 or higher were neutropenia (33% in the obinutuzumab-chlorambucil arm vs 28% in the rituximab-chlorambucil arm), infusion-related reactions (20% in the obinutuzumab-chlorambucil arm vs 4% in the rituximab-chlorambucil arm), infections (12% in the obinutuzumab-chlorambucil arm vs 14% in the rituximab-chlorambucil arm) and thrombocytopenia (10% in the obinutuzumab-chlorambucil arm vs 3% in the rituximab-chlorambucil arm) [22]. Results on quality of life are lacking, but authors say that no deterioration during or after antibody therapy happened compared to treatment with chlorambucil alone [22].

phase III study dealing with untreated elderly patients and comparing treatment strategies for CLL

Even though the phase III study [22] is the first to deal with untreated, elderly patients with coexisting conditions, the drug was licensed in the U.S. for previously untreated patients without any restrictions in terms of patients' populations. Rituximab in combination with fludarabine and cyclophosphamide can be considered standard therapy for physically fit patients, but first-line treatment options for comorbid CLL patients are limited and mainly consisted of chlorambucil alone [7, 19, 27]. However, since anti-CD20 monoclonal antibodies such as rituximab emerged as targeted therapy, a combination with chlorambucil also became a viable treatment option [28, 29]. The phase III study directly compared both regimens with obinutuzumab-chlorambucil and found improved efficacy results for this treatment strategy but at the expense of more AEs.

price considerations may influence choice of treatment

no cost estimates are available for Austria

Whether obinutuzumab offers advantages over rituximab (both drugs are manufactured by Roche) also for younger patients who can tolerate combination therapies with more toxic chemotherapies still needs to be determined. In addition, price considerations may influence the choice of monoclonal antibodies. No cost estimates are yet available for Austria, but because the patent of rituximab expired in Europe at the end of 2013 and will expire in the U.S. in 2015 [30, 31], new biosimilars may become available at potentially lower costs soon.

selection of eligible patients for treatment with obinutuzumab concerning comorbidity, functional status, etc.

Thus, assessing the CLL patients' tolerability of aggressive chemotherapy will be an important driver for selecting eligible patients for obinutuzumab therapy. Age alone with a clear cut-off at e.g. 65–70 years will not suffice to determine the best course of action. There is consensus that comorbidity and functional status should be assessed for each patient prior to treatment initiation. However, views differ as to how pre-existing comorbidities may be evaluated. Since the European Society for Medical Oncology mentioned CIRS "as a helpful tool" for assessing comorbidity [19], this instrument was also used in the phase III trial, but the FDA noted that it has not been validated for use in CLL or in other cancer settings [16].

biomarkers and cytogenetic abnormalities as important factors for future research

Another consideration concerns the presence of cytogenetic abnormalities. Since most patients with previously untreated CLL show cytogenetic abnormalities and subgroup analysis indicated less benefit on PFS in patients with del (17p), the incorporation of biomarkers might be an important factor to be considered in future research [27]. Also, possible early or late toxicities of long-term obinutuzumab therapy need to be assessed and monitored [32].

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