Horizon Scanning in Oncology

Ofatumumab (Arzerra®) as maintenance therapy in patients with relapsed chronic lymphocytic leukaemia (CLL)

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1 Research questions

EUnetHTA HTA Core Model®

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 pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

Element ID	Research question
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C0005	What are the susceptible patient groups that are more likely to be harmed through the use of ofatumumab?
A0021	What is the reimbursement status of ofatumumab?

2 Drug description

Generic/Brand name/ATC code:

Ofatumumab/Arzerra®/L01XC10

B0001: What is ofatumumab?

anti-CD20 antibody

Ofatumumab (Arzerra®) is a human monoclonal antibody, which is produced in recombinant murine cell lines (NS0) [2]. It binds specifically to CD20 on the surfaces of B cells. Thereby, ofatumumab triggers complement-dependent cell lysis (CDCL) and antibody-dependent cell-mediated cytotoxicity (ADCC) of CD20 overexpressing B cells. CD20 is a non-glycosylated cell surface phosphoprotein that acts as a calcium ion channel. It is only expressed on B cells during most stages of B-cell development [3].

Ofatumumab is available in single-use vials either containing 100 mg/5 mL or 1,000 mg/50 mL [4].

Ofatumumab should be administered as an intravenous infusion. Depending on the indication, different treatment regimens of ofatumumab are used in chronic lymphocytic leukaemia (CLL).

300 mg (D1)
1,000 mg (D8)
7 weeks later 1,000 mg
every 8 weeks 1,000 mg

The recommended dosage for extended treatment in CLL is 300 mg on day 1, followed by 1,000 mg on day 8 one week later and subsequently 1,000 mg 7 weeks later. Thereafter, 1,000 mg every 8 weeks for up to a maximum of two years [4].

A0022: Who manufactures ofatumumab?

Novartis Pharma GmbH

3 Indication

A0007: What is the target population in this assessment?

indicated as maintenance therapy of relapsed CLL

Ofatumumab maintenance therapy is indicated for the treatment of adult patients with relapsed chronic lymphocytic leukaemia (CLL).

4 Current regulatory status

A0020: For which indications has ofatumumab received marketing authorisation?

orphan designation by the EMA 2008

approved by the EMA since 2010

On 7th November 2008, orphan designation (EU/3/08/581) was granted by the European Medicine Agency (EMA) to Glaxo Group Limited, United Kingdom, for ofatumumab for the treatment of CLL. In May 2015, the sponsorship was transferred to Novartis Europharm Limited, United Kingdom [5]. Ofatumumab (Arzerra®) was approved by the European Medicines Agency (EMA):

- for the treatment of CLL in patients refractory to fludarabine and alemtuzumab (2010).
- in combination with chlorambucil or bendamustine, indicated for the first-line treatment of patients with CLL and for patients who are not eligible for fludarabine-based therapy (2014) [2].

Ofatumumab (Arzerra®) was approved by the United States Food and Drug Administration (FDA):

FDA approval since 2009

- for the treatment of patients with CLL refractory to fludarabine and alemtuzumab (2009).
- in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukaemia (CLL) for whom fludarabine-based therapy is considered inappropriate (2014).

FDA approval for maintenance treatment in CLL since 2016

- for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL (January 2016).

5 Burden of disease

A0002: What is CLL?

A0004: What is the natural course of CLL?

indolent B-cell non-Hodgkin lymphoma

CLL pertains to the group of indolent B-cell non-Hodgkin lymphomas (NHL). It is a disorder of morphologically mature but immunologically less mature lymphocytes (white blood cells) and is manifested by advanced accumulation of these cells mainly in the blood, bone marrow, and lymphatic tissues [6]. In case of CLL lymphocyte counts in the blood are typically greater than or equal to 5,000/mm^3 with a characteristic immunophenotype (CD5- and CD23-positive B cells) [7].

CLL progresses from an indolent lymphocytosis → generalised lymphatic enlargement

The course of CLL progresses from an indolent lymphocytosis devoid of other evident disease to one of generalised lymphatic enlargement with accompanying pancytopenia (reduction of red and white blood cells, as well as platelets). The major cause of death in CLL patients are complications of pancytopenia, including haemorrhage and infection [8].

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

A0023: How many people belong to the target population?

most common form of leukaemia in Western countries; affects mostly men aged about 70 years

Leukaemia in general affects around 8 in 100,000 of the Austrian population, with more than 1,000 people being diagnosed with leukaemia each year. It is estimated that 700 people die of the disease per year [9]. CLL is one of the most common form of leukaemia in adults in Western countries, accounting for approximately 25% to 30% of all leukaemias [10]. The median age of diagnosis is at about 70 years, and it occurs more often in males than in females (2:1 ratio) [11].

A0005: What are the symptoms of CLL?

only 5–10% of all CLL patients show typical symptoms

Discernible signs during physical examination indicating CLL may include lymphadenopathy, splenomegaly, hepatomegaly or skin lesions. If symptoms occur, they range from painless swelling of lymph nodes to symptoms corresponding to acquired immunodeficiency disorders such as infections or autoimmune complications. In the majority of CLL cases any signs or symptoms are detectable; only 5–10% of affected patients show the so called „B symptoms" [12]:

- unintentional weight loss ≥ 10% of body weight within the previous 6 months,
- fevers of > 38°C for ≥ 2 weeks without evidence of infection,
- night sweats without evidence of infection,
- extreme fatigue.

A0003: What are the known risk factors for CLL?

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

Risk factors for CLL are a family history of CLL or other lymph-related cancers, older age, gender (men are more often affected than women), ethnicity (CLL is more common in North America and Europe than in Asia) and certain chemical exposures (i.e. Agent Orange) [13].

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

most patients are asymptomatic at diagnosis and are diagnosed incidentally

In most instances, CLL is discovered incidentally in the scope of routine blood tests, because patients are asymptomatic at the time of diagnosis. The diagnosis is established by blood counts, blood smears, and immunophenotyping of circulating B-lymphocytes, which identify a clonal B-cell population carrying the CD5 antigen as well as B-cell markers [14].

two staging systems for CLL: Rai & Binet staging systems

There are two existing prognostic staging systems, the Rai and Binet staging systems, which are established by physical examination and blood counts. The Rai staging system distinguishes three major prognostic groups with distinct clinical outcomes [14, 15]:

- Stage 0: lymphocytosis
- Stages I to II: lymphadenopathy, organomegaly
- Stages III to IV: anaemia, thrombocytopenia.

The Binet staging system is subdivided into three different stages with patients being classified according to the number of involved sites plus the occurrence of anaemia (haemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/μL) [15, 16]:

- Stage A: fewer than three involved lymphoid sites
- Stage B: three or more involved lymphoid sites
- Stage C: presence of anaemia and/or thrombocytopenia.

additional prognostic factors

However, there are patients who are classified as having early-stage disease and still show rapid progress in their disease. Therefore, the following additional prognostic factors have been investigated: presence of certain serum markers (thymidine-kinase, beta-2 microglobulin), genetic markers (including IGHV mutational status), cytogenetic abnormalities (deletion of 11q, 13q and 17p, CD38 expression and ZAP-70 expression) and other genetic lesions (including mutations in NOTCH1, SF3B1 and/or BIRK3 genes) [15, 16].

6 Current treatment

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

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

There are several treatment options for CLL dependent on disease stage, patient's age and presence of cytogenetic lesions or concomitant disease (Table 1). Patients diagnosed in an early stage only should be observed [17].

Patients with advanced Binet or Rai stages or with active, symptomatic disease need therapy. The present standard of therapy for physically fit patients is chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab. Patients in impaired physical conditions should be treated with an anti-CD20 antibody (obinutuzumab or rituximab or ofatumumab) in combination with a milder chemotherapy (chlorambucil) may be applied [14].

treatment options for relapsed CLL

If the disease progresses after a period of six months or after either complete or partial remission, it is defined as a relapse [18]. At relapse, the initial treatment may be repeated if the treatment-free interval exceeds two to three years. If relapse occurs earlier, the therapy should be adjusted using alternative agents like bendamustine (plus rituximab), alemtuzumab, lenalidomide, ofatumumab, ibrutinib or idelalisib. Patients with a del(17p) or TP53 mutation may be treated with ibrutinib or a combination of idelalisib and rituximab. Allogeneic stem cell transplantation (SCT) can be considered in relapsing patients with TP53 mutations or del(17p) or patients that are refractory (no response to therapy) to repeated chemo- or immunotherapies [14].

Table 1: Treatment algorithm for CLL patients in first- and second-line indications [14]

CLL 1st line treatment			
Stage	**Fitness**	**Del(17p) p35mut**	**Therapy**
Binet A–B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III–IV	Go go[1]	No	Fludarabine + cyclophosphamide + rituximab (FCR) (bendamustine + rituximab above 65 years?)
		Yes	Ibrutinib, idelalisib + rituximab (Allogeneic SCT)
	Slow go[2]	No	Chlorambucil + obinutuzumab or + rituximab or + ofatumumab
		Yes	Ibrutinib, alemtuzumab, HD of rituximab or ofatumumab
CLL 2nd line treatment			
Response to 1st line therapy	**Fitness**	**Therapy**	
		Standard	**Alternatives (trials)**
Refractory or progression within 2 years	Go go[1]	Ibrutinib, A-Dex, fludarabine + alemtuzumab, FCR → allogeneic SCT (?)	Lenalidomide, bendamustine + rituximab, (other kinase inhibitors, ABT-199)
	Slow go[2]	Change therapy (include in trial)	Ibrutinib, idelalisib + rituximab, alemtuzumab for del(17p), ABT-199, FCR-lite, bendamustine + rituximab, lenalidomide, ofatumumab, HD of rituximab
Progression after 2 years	All	Repeat 1st-line therapy	

Abbreviations: C = cyclophosphamide, CLL = chronic lymphocytic leukaemia, DEX = dexamethasone, F = fludarabine, HD = high dose, R = rituximab, SCT = stem cell transplantation

7 Evidence

systematic search in 5 databases: 180 hits

included: 1 phase III trial

A literature search was conducted on 29 January 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were „Ofatumumab", „Arzerra", „HuMax-CD20", „chronic lymphocytic leukaemia", „CLL", „relapsed" and „maintenance". Overall, 180 references were identified through systematic literature search. Also, the manufacturer was contacted and submitted one article and further information, which had already been identified through the 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 like 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. Additionally, 26 references were identified through hand search.

[1] Go go = good physical condition of patients, defined by a normal creatinine clearance and a low score at the "cumulative illness rating scale" (CIRS)

[2] Slow go = impaired physical condition of patients

7.1 Clinical efficacy and safety – phase III studies

PROLONG: a randomised phase III study in 474 patients

PROLONG [19] is an open-label, multicentre, randomised phase III study comparing ofatumumab maintenance treatment to observation of patients in remission after reinduction treatment for relapsed chronic lymphocytic leukaemia. Reported are the results of a prespecified interim analysis, where two thirds of the planned study events (disease progression or death) had occurred.

comparison of ofatumumab vs. observation

A total of 474 patients were randomly assigned in a 1:1 ratio to receive either ofatumumab at a dose of 300 mg followed by 1,000 mg 1 week later and every 8 weeks for up to 2 years or to undergo observation. The randomisation was stratified, in a block size of four, due to clinical response at entry (complete remission or partial remission), number of previous induction treatments (two or three) and type of latest prior treatment (chemoimmunotherapy, alkylating monotherapy only or other treatment).

median follow-up duration at the time of data cut-off → 19.1 months

The median duration of follow-up at the time of data cut-off (June 2014) was 19.1 months, ranging from 10.3 to 28.8. From 238 patients of the ofatumumab group, 59 (25%) had received all 13 cycles of ofatumumab were as 205 (86%) patients had received all assigned treatment doses. 78 events were recorded in the ofatumumab group (74 progression and four deaths), while 120 events were recorded in the observation group (116 progressions and four deaths).

patients aged ≥ 18 years, second or third complete or partial remission, WHO: 0–2

Enrolled patients were at least 18 years or older (ranging from 33 to 87 years) with a diagnosis of CLL in complete or partial remission after second- or third-line therapy on the basis of the International Workshop on Chronic Lymphocytic Leukaemia's (IWCLL) updated National Cancer Institute-sponsored working group (NCI-WG) criteria and a WHO performance status between 0 and 2. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 4.

primary outcome: PFS

The primary outcome of PROLONG was investigator-assessed progression-free survival (PFS); secondary outcomes were overall survival (OS), time to next treatment (TTNT), progression-free survival after next-line therapy, safety outcomes including adverse events (measured using the National Cancer Institute's (NCI) common terminology criteria for adverse events, version 4.0). β-2 microglobulin (β2M), serum immunoglobulin concentrations and IGHV mutation status were measured by standard techniques within 14 days before treatment started. Quality-of-life (QoL) was assessed via EORTC core and quality-of-life questionnaires: QLQ-C30 and QLQ-CLL16.

7.1.1 Clinical efficacy

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

no evidence for a difference in OS between the two groups

Compared with the observation group the hazard ratio (HR) of death was 0.85 (95% CI 0.52–1.37, p = 0.4877 by a log-rank test) in the ofatumumab group with no evidence for a difference between the two groups. Median OS data for the two groups were not available, neither in the results of the interim analyses nor in the supplementary appendix to the study.

D0006: How does ofatumumab affect progression (or recurrence) of CLL?

significantly improved PFS in the ofatumumab group across all subgroups

The primary endpoint, by physical examination investigator-assessed PFS, was significantly improved ($p < 0.0001$) in the ofatumumab group compared to the observation group. The median investigator-assessed PFS by physical examination (palpatory measurement of lymph nodes and organs) was 29.4 months (95% CI 26.2–34.2) in the ofatumumab group and 15.2 months (95% CI 11.8–18.8) in the observation group. The HR for disease progression for ofatumumab compared to observation was 0.50 (95% CI 0.38–0.66). Overall PFS results were consistent across all subgroups irrelevant of baseline characteristics (age, sex, remission status at study start, previous treatments, baseline minimal residual disease, cytogenetic abnormalities, beta-2M concentration or mutational status).

PFS results by an independent review committee

Similar estimates of median PFS (30.4 months (95% CI 25.3–35.6) in the ofatumumab group vs. 14.8 months (95% CI 11.3–21.2) in the observation group; HR 0.55 (95% CI 0·42–0.72); $p < 0.0001$) had been found by an independent review committee (Parexel International, Waltham, MA, USA).

investigator assessed PFS by CT scan

In both groups, slightly shorter PFS could be observed in the investigator-assessed PFS by computer tomography (CT) scan compared to assessment by physical examination. Median PFS was 23.7 months (95% CI 22.8–28.9) in the ofatumumab group and 13.5 months (95% CI 11.4–21.2) in the observation group. The HR for disease progression for ofatumumab compared to observation was 0.66 (95% CI 0.50–0.87; $p = 0.002$).

D0005: How does ofatumumab affect symptoms and findings (severity, frequency) of CLL?

There were no response rate data available.

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

No evidence was found to answer this research question.

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

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

no clinically relevant difference in HRQoL

Between the two groups no clinically relevant differences regarding health-related quality of life (HRQoL) could be found at any time point during treatment. Using the EORTC QLQ-C30 (global health status domain), a mean reduction of 0.2 points (standard deviation (SD) 38.5) in the ofatumumab group and a mean reduction of 1.9 points (SD 38.5) in the observation group were detected. Concerning the B-symptoms index, a repeated measures analysis of all time points demonstrated that patients in the ofatumumab group had no change in symptoms from baseline to the end of 2 years of treatment (mean points change 0.01 (SD 27.7), whilst patients in the observation group reported a worsening of symptoms (mean points change 2.8 (SD 26.2); $p = 0.002$). In the QLQ-CLL16 questionnaire patients were asked about worry for future health. Concerning this question, patients who had been treated with ofatumumab were less worried than patients in the observation group (four points difference, $p = 0.06$); being in an open-label study the patients were not blinded to their treatments.

Table 2: Efficacy results of the PROLONG trial

Descriptive statistics and estimate variability	Treatment group	Ofatumumab	Observation
	Number of subjects	238	236
	PFS[3] median (95% CI), months	29.4 (26.2–34.2)	15.2 (11.8–18.8)
	PFS – IRC[4] median (95% CI), months	30.4 (25.3–35.6)	14.8 (11.3–21.2)
	PFS – CTS[5] median (95% CI), months	23.7 (22.8–28.9)	13.5 (11.4–21.2)
	TTNT median (95% CI), months	38.0 (28.3–NR)	31.1 (21.6–NR)
Effect estimate per comparison	*Comparison group*		*Ofatumumab vs. Observation*
	PFS[3]	HR	0.50
		95% CI	0.38–0.66
		Log-rank test p value	< 0.0001
	OS	HR	0.85
		95% CI	0.52–1.37
		Log-rank test p value	0.4877
	TTNT	HR	0.66
		95% CI	0.47–0.92
		Log-rank test p value	0.011
	PFS after next treatment	HR	1.00
		95% CI	0.48–2.07
		Log-rank test p value	0.9977

Abbreviations: CI = confidence interval, HR = hazard ratio, NR = not reached, OS = overall survival, PFS = progression-free survival, TTNT = time to next treatment

7.1.2 Safety

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

more grade ≥ 3 AEs in the ofatumumab group

higher incidence of grade ≥ 3 neutropenia & infection in the ofatumumab arm

The ofatumumab group showed a higher total number of adverse events (AEs) as well as a higher number of grade 3 or higher adverse events than the observation group. The most frequent grade ≥ 3 AEs (up to 60 days after the last treatment) were neutropenia and infections. In post-hoc analyses the ofatumumab group showed an increased incidence of grade 3 or higher neutropenia compared to the observation group (p = 0.0001). Prolonged and severe neutropenia[6] occurred more frequently in the ofatumumab group than the observation group (5%, n = 13/237 vs. 2%, n = 5/237). Additionally, the incidence of grade 3 or higher infections increased and was more prevalent in the ofatumumab group (31 (13%) of 237 patients) than in the observation group (20 (8%) of 237 patients) (p = 0.11). 42 patients (18%) of the ofatumumab group needed growth factor support (G-CSF) compared to 17 patients (7%) of the observation group.

[3] Investigator-assessed PFS by physical examination

[4] PFS – IRC = assessed by an independent review committee

[5] PFS – CTS = investigator-assessed PFS by CT scans

[6] Prolonged and severe neutropenia = grade 3 or 4 neutropenia experienced during the treatment phase and not resolving within 42 days of the last dose

peripheral blood B cells started to recover after ofatumumab maintenance treatment

At study entry, serum immunoglobulin concentrations were lower than normal in both study groups. The ofatumumab group showed no change in these concentrations during treatment, however, serum concentrations of Immunoglobulin M (IgM) increased during follow-up. 3 months after the end of ofatumumab treatment peripheral blood B cells began to recover; however, they had not yet reached normal levels at the end of follow-up.

a total of 66 patients died; no deaths were attributed to the study drug

In 8% of patients in the ofatumumab group and in 1% of patients in the observation group, AEs led to permanent discontinuation of treatment. Between the first dose and 60 days afterwards, two patients in the ofatumumab and five patients in the observation group died because of AEs. A total of 66/474 (14%) patients died, 31 of these deaths were due to progressive disease. None of these deaths could be ascribed to the study drug. No Richter transformation[7] could be detected in the ofatumumab group compared to two in the observation group.

36 patients of the ofatumumab arm showed grade 1/2 infusion-related reactions

Infusion-related reactions were rarely detected, 36 patients in the ofatumumab arm showed grade 1 or 2 reactions, whereas grade 3 reactions were reported in three patients treated with ofatumumab, and there were no reports of infusion related reactions in the observation group. No grade 4 or 5 infusion-related reactions were reported. All treatment-related AEs can be found in Table 3.

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

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 ofatumumab?

Anti-CD20 monoclonal antibodies carry a risk of hepatitis B reactivation among patients positive for HBsAg or anti-HBc. Prior to treatment all patients should be screened for hepatitis B. Patients with verification of prior hepatitis B infection should be monitored for clinical and laboratory signs of reactivation during therapy and after completion of therapy. Immunotherapy should be discontinued in patients with reactivated hepatitis [19].

[7] Richter transformation = transformation of CLL to a highly aggressive non-Hodgkin lymphoma

Table 3: Treatment-related adverse events reported by investigator[8]

Adverse Event (according to CTCAE version 4.0)	**Ofatumumab** (n = 237)			**Observation** (n = 237)		
Any grade 5, n (%)	1 (< 1)			6 (< 4)		
	Grade ½ n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade ½ n (%)	Grade 3 n (%)	Grade 4 n (%)
Neutropenia	10 (4)	33 (14)	23 (10)	4 (2)	13 (5)	10 (4)
Cough	48 (20)	2 (1)	0	22 (9)	0 (0)	0
Upper respiratory tract infection	42 (18)	3 (1)	0	22 (9)	1 (<1)	0
Pyrexia	33 (14)	4 (2)	0	22 (9)	2 (1)	0
Pneumonia	9 (4)	11 (5)	5 (2)	5 (2)	9 (4)	1 (< 1)
Fatigue	27 (11)	0 (0)	0	16 (7)	0	0
Diarrhoea	32 (14)	1 (<1)	0	9 (4)	0	0
Infusion-related reaction[9]	36 (15)	3 (1)	0	0	0	0
Bronchitis	19 (8)	2 (1)	0	15 (6)	(< 1)	0
Thrombocytopenia	15 (6)	2 (1)	2 (1)	7 (3)	5 (2)	5 (2)
Rash	22 (9)	1 (< 1)	0	10 (4)	0	0
Sinusitis	17 (7)	2 (1)	0	11 (5)	0	0
Arthralgia	16 (7)	1 (< 1)	0	11 (5)	1 (< 1)	0
Pruritus	20 (8)	1 (< 1)	0	7 (3)	0	0
Respiratory tract infection	11 (5)	1 (< 1)	0	13 (5)	0	1 (< 1)
Headache	20 (8)	1 (< 1)	0	5 (2)	0 (0)	0
Herpes zoster	10 (4)	3 (1)	0	7 (3)	1 (< 1)	0
Back pain	11 (5)	1 (< 1)	0	8 (3)	0 (0)	0
Urinary tract infection	8 (3)	1 (< 1)	0	7 (3)	1 (< 1)	1 (< 1)
Insomnia	12 (5)	1 (< 1)	0	5 (2)	0	0
Dyspnoea	9 (4)	1 (< 1)	0	5 (2)	0	0
Asthenia	6 (3)	1 (< 1)	0	9 (4)	0	0
Hypertension	7 (3)	3 (1)	0	5 (2)	0	0
Febrile neutropenia	2 (1)	5 (2)	3 (1)	0	3 (1)	1 (< 1)
Hypogammaglobulinaemia	9 (4)	2 (1)	0	0	2 (1)	0
ALT increased	7 (3)	1 (< 1)	0	2 (1)	0	0
Decreased appetite	7 (3)	1 (< 1)	0	1 (< 1)	0	0
Weight decreased	2 (1)	1 (< 1)	0	5 (2)	0	0

Abbreviations: ALT = alanine aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events

7.2 Clinical effectiveness and safety – further studies

No further study results on ofatumumab from phase II/III trials in the reviewed indication (ofatumumab maintenance treatment with relapsed chronic lymphocytic leukaemia) are available yet.

no further studies in reviewed indication

[8] occurring in at least 2% of patients, any grade

[9] Infusion-related reactions = events occurring during infusion or within 24 hours after completion of infusion, includes chills, dyspnoea, flushing, hypotension, nausea, pain, pruritus, pyrexia, rash, and urticaria

8 Estimated costs

A0021: What is the reimbursement status of ofatumumab?

300 mg: € 673.80
1,000 mg: € 2,172.05

In Austria, ofatumumab (Arzerra®) is available in vials of 5 mL (100 mg) in a package with 3 vials at € 673.80 and vials of 50 mL (1,000 mg) at € 2,172.05 [20].

In patients with relapsed CLL in remission after re-induction treatment, the recommended and FDA approved dosage for maintenance treatment is a dose of 300 mg on day 1 followed by 1,000 mg one week later (day 8) and every 8 weeks for up to a maximum of two years [4, 21]. According to this treatment regimen, costs for the first cycle (day 1: 3 x 100 mg vials, day 8: 1 x 1,000 mg vial) of ofatumumab are € 2,845.85; for additional 23 months of ofatumumab maintenance treatment, costs of € 24,978.58 would incur. A treatment of two years with ofatumumab including cycle 1 and 8-week intervals would cost € 27,824.43.

2 years' treatment:
€ 27,824.43

Additional costs would incur due to premedication (acetaminophen, 1,000 mg, oral, antihistamine – diphenhydramine, 50 mg, intravenous or oral, and a glucocorticoid – prednisolone, 50 mg, intravenous) prior to each infusion of ofatumumab [21].

9 Ongoing research

1 ongoing phase III study in patients with relapsed CLL

In February 2016, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted; one ongoing phase III trial investigating ofatumumab in patients with relapsed CLL could be identified and two which use ofatumumab as a control:

- **NCT00824265:** An open-label, randomised trial evaluating the safety and efficacy of ofatumumab added to fludarabine-cyclophosphamide in patients with relapsed CLL. The estimated study completion date is October 2017.
- **NCT01578707:** A randomised, multicentre, open-label, phase III study of the bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory CLL/small lymphocytic lymphoma (SLL). The estimated study completion date is December 2017.
- **NCT02004522:** A phase III study of duvelisib versus ofatumumab in patients with relapsed or refractory CLL/SLL (DUO). The estimated study completion date is June 2021.

ofatumumab is investigated in various studies

Several phase I and phase II studies are currently conducted (NCT01465334, NCT01532700, NCT01809847, NCT01497496, and NCT01294579).

10 Discussion

indication approved by the FDA, but not by the EMA

Ofatumumab (Arzerra®) was approved by the FDA (based on the PROLONG trial) in January 2016 for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL [4]; the EMA has not granted marketing authorisation for this indication yet.

PROLONG: improvement in PFS & TTNT, but not in OS, in patients receiving ofatumumab

The FDA approval was based on the results of the PROLONG [21] trial, a randomised, open-label phase III study. 474 previously treated patients were randomised to either observation or ofatumumab intravenously. Results showed a significant increase in PFS (investigator-assessed PFS by physical examination) in patients who received ofatumumab; patients receiving ofatumumab gained 14.2 months in median compared to the observation arm. Median TTNT was also improved among patients who received ofatumumab: it was 38.0 months in the ofatumumab group compared to 31.1 months in the observation group. Nevertheless, no statistically significant difference between the two study arms could be detected in OS (HR 0.85, p = 0.4877).

efficacy & safety results are based on interim analysis

However, it must be noted that efficacy and toxicity results of the PROLONG trial are based on a prespecified interim analysis. It provides results on two thirds of the planned study events after 66 patients died (14%) and disease progression could be observed in 190 patients. In this respect, a complete data set will be of interest to see whether the difference in PFS will increase further or decreases between the treatment groups.

QoL results showed no difference between the two treatment groups at any time point. But as the provided results are interim analyses, the full dataset will be necessary to definitively exclude negative effects on QoL.

efficacy in subgroups

Although overall PFS outcomes were consistent across all subgroups irrelevant of baseline characteristics, the results of the cytogenetic subgroups (high-risk patients: del(17p) and del(11q)) and of the patients who showed a complete response at study entrance should be interpreted with caution due to the low number of investigated patients. To identify any advantages or disadvantages, these subgroups should be examined further.

total rates & grades ≥ 3 treatment-related AEs are more frequent in the ofatumumab arm

The total rates of treatment-related AEs and those with grades 3–5 were more frequent in patients of the ofatumumab group compared to patients in the observation group. The most common grade ≥ 3 AEs were neutropenia and infections. Post-hoc analysis showed an increase in frequency of grade ≥3 neutropenia as well as a higher frequency of prolonged and severe neutropenia in the ofatumumab arm. Furthermore, the percentage of discontinuation (8%) in the ofatumumab group and the fact that only 25% of patients received all 13 cycles of ofatumumab should be taken into consideration. Therefore, the long-term side effect profile of ofatumumab will have to be analysed further since side effects can compromise QoL in the long term if ofatumumab is continuously used.

significant PFS results, without a survival impact

It should be noted that the primary outcome of the study (PFS) is a surrogate parameter for OS. However, in contrast to the PFS outcomes, OS results showed no significant difference between the two study arms. This could be due to the fact that unlike with OS, in which the date of death is precise, the date of progression is subject to measurement error and other kinds of bias (i.e. attrition bias) [22]. Another possible explanation, which has not been

properly investigated yet, could be that following initial delay of progression the agent caused evolutionary changes in tumours, resulting in the emergence of a more aggressive phenotype after treatment [23-25].

Furthermore, an extended follow-up should be considered to investigate whether this could be a reason why ofatumumab maintenance treatment has no impact on OS.

open-label study design led to a higher risk of assessment bias

Additionally, if the primary outcome of a study is PFS, patients and investigators should preferably be blinded to avoid assessment bias. Since this was not the case in PROLONG, there is an increased risk of assessment bias in this study [26].

effects of censoring on PFS results

In the PROLONG trial [21], PFS was censored at the time of last follow-up for patients who neither had disease progression nor died. Furthermore, PFS was also censored for patients who received new anticancer treatment before disease progression and for patients who missed two or more visits. As censoring is incrementally recognised as a potential risk of bias, affecting estimates of PFS in randomised trials, the number of censored patients at each time interval should be reported for a better understanding of its possible effects [27].

two other phase III trials investigating anti-CD20 antibody maintenance treatment

Two other phase III trials of anti-CD20 antibody maintenance treatment in CLL were reported [28, 29]. Both compared rituximab maintenance treatment to observation; both showed an improvement in PFS, with high-risk patients (del(11q) and del(17p)) in one study also exhibiting an improvement in OS. Thus, it would be interesting to directly compare ofatumumab with rituximab to determine from which drug patients benefit the most. Another consideration might be the addition of chlorambucil or other agents to anti-CD20 monoclonal antibodies for treatment of young or middle-aged patients, as this is assumed to result in higher response rates [19].

prevention of resistance

Besides the potential for improved clinical outcomes, the rationale for combination therapies is to avoid the development of resistance. This mechanism has not been well documented yet. A study from Baig et al. [30] showed that the optimal efficacy of CD20-targeted therapy for CLL requires the determination of a dose size and frequency that optimises the killing of CLL cells, without exceeding the capacity of the cytotoxic mechanisms and thereby reducing the loss of CD20 expression in the surviving CLL cells. Therefore, long-term data would be necessary to exclude the risk of developing a resistance with the currently used dosage of ofatumumab.

higher costs than standard of care

Another concern to be addressed are the costs for ofatumumab treatment. Compared to the standard of care, i.e. observation until disease progression, costs are much higher (2 years of treatment: € 27,824.43) for ofatumumab maintenance treatment. It will also be of interest to compare costs associated with various therapeutic strategies as well as with new agents. Depending on the treatment duration and the costs associated with the required premedication, the costs for ofatumumab may be considerably higher.

significant improvement of PFS but no benefit in OS, and higher rates of AEs

long-term data required

Although the costs are high for ofatumumab compared to observation treatment, the significant improvement of PFS due to ofatumumab maintenance treatment should not be neglected. However, the lack of a prolonged gain in OS in addition to the increased rate of AEs highlight the requirement of long-term data on efficacy and safety as well as on the potential risk of developing resistance needs to be stressed. Furthermore, differences in clinical benefit for specific cytogenetic subgroups, especially del(17p) and del(11q), should be further examined.

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12 Appendix

Table 4: Characteristics of the PROLONG trial

Title: Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase III study [21, 31]			
Study identifier	NCT01039376, EudraCT number 2009-012518-39, PROLONG		
Design	Phase III, randomised, international, multicentre, open-label trial, cross-over was not allowed as well as dose reductions		
	Duration		Enrolment: 2010-05-6 to 2014-06-19 *Median follow-up (at the time of data cut-off):* 19.1 months (IQR 10.3 to 28.8) *Cut-off date for analyses:* 2014-06-16 (prespecified interim analysis)
Hypothesis	Superiority This study was designed and powered to detect differences in PFS between the two investigated groups. The planned sample size of the study was 478 patients to detect at least a 40% improvement in PFS (HR 0.71), with 80% power and a two-sided α error of 0.05.		
Funding	Novartis Pharma GmbH		
Treatments groups	Intervention (n = 238)		Ofatumumab administered intravenously at a dose of 300 mg at Day, 1,000 mg on Day 8 and every 8 weeks for up to a maximum of two years
	Control (n = 236)		observation
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from randomisation to the earliest date of disease progression or death due to any cause
	Overall survival	OS	Time from randomisation until date of death due to any cause
	Time to next treatment	TTNT	Time from end of primary treatment to institution of next therapy [32]
	Progression-free survival after next-line therapy	PFS after next-line therapy	Time from randomisation until progression or death after next-line therapy
Database lock	NR		
Results and Analysis			
Analysis description	**Primary Analysis** All efficacy analyses were done in the intention-to-treat population. Safety analyses included all patients who were randomly assigned to treatment, grouped based on the actual treatment received (per protocol). Log-rank tests (adjusted for the stratification factors) were used to analyse PFS, OS, TTNT and PFS after next-line therapy. All p values are two-sided. Kaplan-Meier curves were generated to graphically show the differences between the survival distributions of the treatment groups.		
Analysis population	Inclusion		❁ Age ≥ 18 years ❁ Diagnosis of CLL in second or third complete or partial remission (based on IWCLL updated NCI-WG criteria) ❁ WHO performance status of 0–2 ❁ response assessment within the previous 3 months
	Exclusion		❁ have refractory disease ❁ autoimmune haemolytic anaemia requiring treatment ❁ chronic or active infection requiring treatment ❁ previously received maintenance treatment or autologous or allogeneic stem-cell transplant ❁ neutrophil count less than 1.0×10^9 cells per L ❁ platelet count less than 50×10^9 platelets per L ❁ creatinine more than 1.5 times the upper limit of normal (ULN) ❁ total bilirubin, alanine aminotransferase, and aspartate aminotransferase more than 2.5 times the ULN

Title: Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase III study [21, 31]				
Study identifier	NCT01039376, EudraCT number 2009-012518-39, PROLONG			
Analysis population *(continuation)*	Characteristics		Intervention	Control
		Median age[10] (range), years	64.0 (33–86)	65.0 (39–87)
		Gender: n (%)	♂: 161 (68) ♀: 77 (32)	♂: 159 (67) ♀: 77 (33)
		Median time since diagnosis (range), years	6.0 (1-22)	5.0 (1-22)
		Response to last CLL treatment, n (%): CR PR Missing	 45 (19) 193 (81) 0 (0)	 46 (19) 189 (80) 1 (<1)
		Baseline minimal residual disease, n (%): Negative Positive Missing	 31 (13) 137 (58) 70 (29)	 41 (17) 107 (45) 88 (37)
		Number of previous treatments, n (%): 2 3 Other	 168 (71) 66 (28) 4 (2)	 166 (70) 62 (26) 8 (3)
		Type of last previous treatment, n (%): Chemoimmunotherapy BR FCR FR Other RCVP Alkylating monotherapy Other	 191 (80) 46 (24) 100 (52) 4 (2) 28(15) 13 (7) 14 (6) 33 (14)	 189 (80) 47 (25) 103 (54) 5 (3) 23 (12) 11 (6) 9 (4) 38 (16)
		Baseline cytogenetics[11], n (%): Deletion 11q Deletion 17p Deletion 6q or 12q trisomy or deletion 13q No aberration Missing	 15 (6) 7 (3) 44 (18) 150 (63) 22 (9)	 12 (5) 4 (2) 16 (7) 171 (72) 33 (14)
		IgHV mutational status, n (%): Mutated Not mutated Not available or missing	 47 (20) 129 (54) 62 (26)	 66 (28) 108 (46) 62 (26)

Abbreviations: CLL = chronic lymphocytic leukaemia, BR = bendamustine plus rituximab, FCR = fludarabine, cyclophosphamide, plus rituximab, FR = fludarabine plus rituximab, OS = overall survival, PFS = progression-free survival, RCVP = rituximab, cyclophosphamide, vincristine, and prednisolone, IgHV = immunoglobulin heavy chain variable region genes, TTNT = time to next treatment.

[10] Age was calculated from birth date to screening date in years

[11] 12% cut-off (i.e., at least 12% of chromosome interphases should have the specific chromosomal abnormality for the patient to be scored as having deletion 11q, deletion 17p, etc.)