London, 22 May 2014
EMA/475698/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Arzerra

International non-proprietary name: OFATUMUMAB

Procedure No. EMEA/H/C/001131/II/0023

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE: Adverse event

AIHA Autoimmune hemolytic anemia

ALK: Alkylators

AUC: Area under the concentration-time curve

B: Bendamustine

β2M: Beta 2-microglobulin

BSA: Body surface area

CL: Clearance

CLL: Chronic lymphocytic leukemia

CHL: Chlorambucil

C_{max}: Maximum observed concentration

CR: Complete response

Cri: Complete response, incomplete bone marrow recovery

CrCL: Creatinine Clearance

CT: Computed tomography

C_{trough}: Minimum observed drug concentration prior to next dose

DLBCL: Diffuse large B-cell lymphoma

ECOG: Eastern Cooperative Oncology Group

EMA: European Medicines Agency

ESMO: European Society for Medical Oncology

EU: European Union

F: Fludarabine

FC: Fludarabine plus cyclophosphamide

FCR: Fludarabine, cyclophosphamide, rituximab combination

FDA: Food and Drug Administration

GSK: GlaxoSmithKline

HAHA: Human Anti-Human Antibodies

HBV: Hepatitis B Virus

HR: Hazard ratio

IgG: Immunoglobulin G

IgVH: Immunoglobulin Heavy Chain Variable Region

IRC: Independent Review Committee

ITT: Intent-to-treat

IWCLL: International Workshop for Chronic Lymphocytic Leukaemia

mAb: Monoclonal antibody

mPFS: Median progression-free survival

MRD: Minimal residual disease

O+ALK: Combination treatment with ofatumumab and chlorambucil or bendamustine (O+CHL and O+B)

O+B: Combination treatment with ofatumumab and bendamustine

O+CHL: Combination treatment with ofatumumab and chlorambucil

O+FC: Combination treatment with ofatumumab, fludarabine and cyclophosphamide

nPR: nodal partial response

OR: Overall response

ORR: Overall response rate

OS: Overall survival

PML: Progressive Multifocal Leukoencephalopathy

PD: Progressive disease

PFS: Progression-free survival

PR: Partial response

PS: Performance status

QTcF: QT interval duration corrected for heart rate by Fridericia's formula

R: Rituximab

RA: Rheumatoid Arthritis

RMP: Risk management plan

SAE: Serious Adverse Event

t½ Terminal phase half-life

TLS Tumor lysis syndrome

Vss Volume of distribution at steady state

ZAP-70 Zeta-chain associated protein kinase 70

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Glaxo Group Ltd submitted to the European Medicines Agency on 4 October 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Arzerra	ofatumumab	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 (a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of indication to the first line treatment of CLL in combination with alkylator-based regimens in patients not eligible for fludarabine-based therapy. As a result, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC were proposed to be updated. The Package Leaflet was proposed to be updated accordingly. Editorial changes to sections 4.7 and 6.3 of the SmPC were also proposed.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The variation proposed amendments to the SmPC and Package Leaflet.

Arzerra was designated as an orphan medicinal product EU/3/08/581 on 7 November 2008. Arzerra was designated as an orphan medicinal product in the following indication: Treatment of chronic lymphocytic leukaemia. The calculated prevalence of this condition was 3.5 per 10,000 EU population.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jens Ersboll Co-Rapporteur: Ingunn Hagen Westgaard

Submission date:	04/10/2013
Start of procedure:	25/10/2013
Rapporteur's preliminary assessment report circulated on:	17/01/2014
Co-Rapporteur's preliminary assessment report circulated on:	16/12/2013
PRAC RMP Advice and assessment overview adopted by PRAC:	09/01/2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	23/01/2014
MAH's responses submitted to the CHMP on:	21/03/2014
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22/04/2014
PRAC RMP Advice and assessment overview adopted by PRAC :	08/05/2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	14/05/2014
CHMP opinion:	22/05/2014
The CHMP adopted a report on the significant clinical benefit for Arzerra in comparison with existing therapies on (see appendix):	22/05/2014

2. Scientific discussion

2.1. Introduction

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in the Western world. It is a neoplasm characterised by a progressive accumulation of functionally incompetent B-lymphocytes. According to the 2008 International Workshop on CLL (IWCLL) guidelines, the diagnosis of CLL requires «a circulating B-lymphocyte count greater than or equal to 5 x 109 /L in the peripheral blood, for the duration of at least 3 months».

CLL patients are often asymptomatic at diagnosis, but fatigue, autoimmune haemolytic anaemia, infections, splenomegaly, hepatomegaly, lymphadenopathy, or extra-nodal infiltrates may be present. Two widely accepted staging methods are used: the Rai and the Binet classification system. In both systems, patients are classified into low, intermediate and high-risk groups based on the degree of

lymphocytosis, presence of lymphadenopathy, hepato- or splenomegaly, anaemia and thrombocytopenia. In general, it is recommended to start treatment with active, symptomatic disease, at late stage CLL (Rai III/IV or Binet C) or with high risk cytogenetics. The aim of therapy is to control disease, improve symptoms, and prolong survival, while minimising toxicity with regimens which are well tolerated and acceptable to patients who are predominantly older than 65 years of age.

Drugs currently used for the initial treatment of CLL include alkylating agents (such as chlorambucil and bendamustine), purine analogues (such as fludarabine, cladribine, and pentostatin) alone or in combination, and rituximab in combination with chemotherapy [National Comprehensive Cancer Network guidelines, 2013; ESMO guidelines, 2011]. For previously untreated CLL patients who are young and physically fit with normal renal function, the addition of rituximab to a chemotherapeutic backbone (fludarabine, cyclophosphamide, and rituximab (FCR) regimen) has been shown to improve overall survival compared to FC alone. Therefore, in this patient group FCR is the standard first-line therapy.

Older, less physically active patients with comorbidities and/or decreased renal function are often not considered eligible for the FCR regimen. However, no universal criteria exist for determining when fludarabine (F) based therapy regimens are inappropriate. Since almost 70% of CLL patients are 65 years or older and over 40% of patients have major comorbidities, a substantial proportion of CLL patients is considered F-inappropriate at diagnosis.

Chlorambucil was the standard therapy for these patients at the time of study start for this application. However, nowadays there exists a different standard of care for some of these patients. Patients with few comorbidities or not very high age have several more aggressive treatment options than chlorambucil, such as FCR lite, FC, PCR (pentostatin, cyclophosphamide and rituximab), FR, chlorambucil-R, or bendamustine(-R). However, treatment options are guided by several co-existing recommendations not always in agreement, making therapeutic management of patients inappropriate for the FCR regimen complex.

Arzerra (ofatumumab) is a human(ised) monoclonal antibody, IgG1κ, targeting the CD20 molecule expressed on B-lymphocytes. The CD20 molecule is not shed from the cell surface and is not internalised following antibody binding. The binding of ofatumumab to CD20 induces cell death, primarily through complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC) in CLL patients. Ofatumumab was able to induce complement mediated lysis of isolated B-CLL cells and in cell lines expressing low levels of CD20 and high levels of CD55/CD59, which diminish the lytic effect of complement.

Arzerra is currently indicated for the treatment of CLL patients who are refractory to fludarabine and alemtuzumab (mAb targeting CD52). The recommended dose is 300 mg ofatumumab for the first infusion and 2,000 mg ofatumumab for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4-5 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions.

With this variation application, the MAH proposed to extend the Arzerra indication to the treatment of previously untreated CLL patients who are inappropriate for fludarabine-based therapy. The recommended dosing regimen for previously untreated CLL is two doses in the first cycle (300 mg on Day 1, 1000 mg on Day 8), with a single 1000 mg dose on Day 1 of subsequent four-week cycles for a maximum or 12 cycles or best response.

Further to the review of the application, the CHMP agreed to the following indication in:

Previously untreated chronic lymphocytic leukaemia (CLL):

Arzerra in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.

See section 5.1 for further information.

2.2. Non-clinical aspects

2.2.1. Introduction

Since the Arzerra marketing authorisation, two new investigative pharmacodynamic studies with specific relevance to this indication have been conducted and were submitted in support of this variation application.

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro study (Report 2012N148613)

Ofatumumab in combination with fludarabine (a purine analogue/alkylating agent) was compared to treatment with ofatumumab alone, or to rituximab (a chimeric anti-CD20 mAb) in the presence or absence of fludarabine in a CLL-cell-viability assay. CLL cells were obtained from patients and defined as either low- or intermediate- (patients without a 17p-deletion, without TP53 mutation, and not refractory to purine analogues) or high-risk (non-functional DNA damage/p53 pathway).

In one assay, ofatumumab (2.5 µg/mL) was incubated in combination with fludarabine (1 µM) in a CLL-cell-viability assay for 48 hours and compared to treatment with ofatumumab alone (2.5 or 10 µg/mL) or rituximab (10 µg/mL) in the presence or absence of fludarabine.

In high-risk cases, ofatumumab (mean viability: 47.99%, n=25) in combination with 1 µM fludarabine showed equal activity as the rituximab-fludarabine combination (mean: 46.4%, n=25). As expected, fludarabine showed almost no activity in high-risk CLL cases and potentially additive or synergistic activity with either ofatumumab or rituximab was therefore absent.

Regarding low-risk CLL cases only, 1 µM fludarabine led to a considerable reduction of CLL cells (mean viability: 36.1%, n=15). Ofatumumab in combination with fludarabine showed comparable activity to rituximab in combination with fludarabine (mean viability ofatumumab+fludarabine: 29.42%, and rituximab+fludarabine: 29.26%, n=15).

In vivo study (Haskova, 2012)

Ofatumumab alone or in combination with bendamustine (a purine analogue/alkylating agent) was evaluated with special regard to the CD20-dependent tumour growth inhibition in mouse models of chronic lymphocytic leukaemia (CLL).

C.B-17 severe combined immunodeficiency female mice were subcutaneously injected with Ramos human CLL (CD-20+, high expression), JVM-3 human CLL (CD-20+, low expression) or BC-1 human lymphoma (CD20-) cells and the developing tumour volumes were permitted to reach a volume of 80-120 mm^3. Animals were then treated for 4 weeks with ofatumumab at doses ranging from 0.2 to 4 mg/kg/dose given twice weekly intraperitoneally (IP). The combination of ofatumumab (2 mg/kg) and bendamustine (given at 50 mg/kg IP once only on Day 15) was also tested.

As expected, ofatumumab had no effect on BC-1 tumour growth, since these cells do not express CD20. Ofatumumab significantly reduced Ramos CLL tumour growth at all doses, and completely arrested tumour growth at 2 mg/kg. Ofatumumab significantly reduced JVM-3 CLL tumour growth at ≥2 mg/kg. Since ofatumumab at ≥2 mg/kg fully arrested tumour growth or had no effect on Ramos and BC-1 CLL cells, respectively, no combination studies were conducted using these models.

Ofatumumab (2 mg/kg) and bendamustine (given at 50 mg/kg IP once only on Day 15) in combination resulted in a complete arrest of JVM-3 CLL tumour growth compared to control and ofatumumab or bendamustine alone as shown in Figure 1 below.

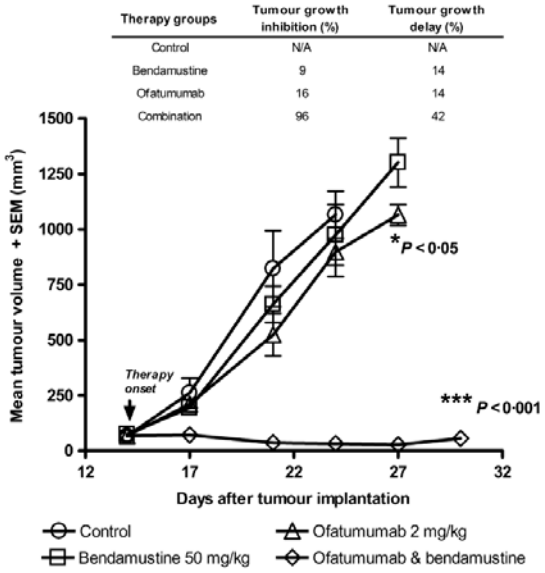


Figure 1: Tumour growth inhibition in CLL xenografts

2.2.3. Discussion on non-clinical aspects

The effect of ofatumumab (2.5 μg/mL) alone or in combination with fludarabine (1 μM) on CLL cell-viability was investigated in an *in vitro* study. Rituximab (10 μg/mL) alone or in combination with fludarabine (1 μM) was also included in the assay.

In this study, ofatumumab in combination with fludarabine was shown to be comparable to rituximab in combination with fludarabine, measured by mean cell viability in CLL cells from patients, without a 17p-deletion or p53 mutation which were not refractory to purine analogues. These data indicated that ofatumumab was at least as suitable as rituximab for combined use in a therapy-regimen with fludarabine.

Ofatumumab alone or in combination with bendamustine (a purine analogue/alkylating agent) was evaluated with special regard to the CD20-dependent tumour growth inhibition in mouse models of chronic lymphocytic leukaemia (CLL).

Dose dependent effects on tumour growth inhibition were observed, with 2 mg/kg being less effective than 4 mg/kg ofatumumab treatment, however, both dose levels were statistically significantly different from the control group. Ofatumumab (2 mg/kg) in combination with bendamustine resulted in a complete arrest of JVM-3 CLL (low CD20+ expression) tumour growth compared to control and ofatumumab or bendamustine alone

Overall, the findings suggest that ofatumumab efficacy in this model is related to CD20 expression, and that a combination of suboptimal doses ofatumumab and bendamustine had synergistic activity on tumour growth inhibition.

The lack of any pharmacokinetic evaluations of the combination of ofatumumab and any alkylating agent is acceptable, as no pharmacokinetic drug interactions are expected with this combination.

A review of the available information revealed no nonclinical findings that might indicate the potential for additive or synergistic toxicity between ofatumumab and alkylating therapies. Therefore, the MAH considered that co-administration toxicology studies were not considered necessary to support the safety of ofatumumab when administered with these alkylator regimens. The CHMP considered the lack of any toxicological evaluations of the combination of ofatumumab and an alkylating agent acceptable, as the expected additive or synergistic toxicity (depletion of circulating B-cell population) can be monitored clinically. The principal toxicity following ofatumumab treatment is CD20-positive B-cell depletion which may be exacerbated following treatment with an alkylating agent, which reduce the peripheral blood cell populations.

No environmental risk assessment report was submitted as ofatumumab is a fully humanised monoclonal antibody. According to the guideline on environmental risk assessment (EMEA/EHMP/SWP/4447/00 corr 1*), no environmental risk assessment is required for proteins, as they are unlikely to result in any significant risk to the environment.

2.2.4. Conclusion on the non-clinical aspects

There are no concerns with this variation application from the non-clinical point of view.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier(s)/ EudraCT No/ NCT no/ (Study Report ID)/ Indication	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	No. of Subjects Entered/Planned - By group	Study Reporting Status (Type of Report)
OMB110911 2008-004932-19 NCT00748189 (2013N163579) CLL	**Pivotal Efficacy and Safety Study** **Primary Objective:** Efficacy (PFS) **Secondary Objectives:** Secondary efficacy, safety, tolerability, PK, PRO	OL, R; PG; AC	Subjects with previously untreated CLL	1:1 randomization into: **Arm A (O+CHL):** ofatumumab as monthly IV infusions (Cycle 1 300 mg day 1 and 1000 mg day 8, subsequent cycles: 1000 mg at day 1 every 28 days) in combination with chlorambucil (10 mg/m² PO at days 1-7 every 28 days) for 3-12 cycles* **Arm B (CHL):** chlorambucil monotherapy (10 mg/m² PO at days 1-7 every 28 days) for 3-12 cycles* **minimum 3 cycles, maximum of 12 cycles or until best response*	Total: 447/444 O+CHL: 221 CHL:226	Completed (Full CSR)

OMB115991 2011-005178-43 NCT01520922 (2013N163233) CLL	**Supportive Efficacy and Safety Study** **Primary Objective:** Efficacy (ORR) **Secondary Objectives**: Secondary efficacy, safety, tolerability, PK	UC	Previously untreated and relapsed patients with CLL	**Subjects with Untreated CLL:** Up to 6 monthly IV infusions of ofatumumab (Cycle 1: 300 mg Day 1 and 1000 mg Day 8; subsequent Cycles: 1000 mg at Day 1 every 28 days) in combination with up to 6 Cycles of IV infusions of bendamustine (90 mg/m2, Days 1 and 2; every 28 days). **Subjects with Relapsed CLL:** Up to 6 monthly IV infusions of ofatumumab (Cycle 1: 300 mg Day 1 and 1000 mg Day 8; subsequent Cycles: 1000 mg at Day 1 every 28 days) in combination with up to 6 Cycles of IV infusions of bendamustine (70 mg/m2, Days 1 and 2; every 28 days)	Total: 80/99 Untreated: 44 Relapsed: 53	Completed (Full CSR)
OMB111774 Hx-CD20-407 2007-000243-10 NCT00410163 (2011N125669) CLL	**Supporting Safety Study** **Primary Objective:** Efficacy (CR) **Secondary Objectives**: Safety and PK	UC, R, 2-dose, PG	Subjects with previously untreated CLL	One infusion with 300 mg ofatumumab followed by one infusion of 500 mg or 1000 mg ofatumumab in combination with fludarabine 25 mg/m2 IV days 1-3 and cyclophosphamide 250 mg/m2 IV days 1-3 monthly for 5 months	Total: 61/56 500 mg group :31 1000 mg group: 30	Completed (Full CSR)
OMB112855 EudraCT not available NCT01110031 (2012N135458) CLL	**Primary Objective**: Effect of ofatumumab on QTcF **Secondary Objectives**: PK/PD; safety and tolerability; anti-tumor activity; effect of ofatumumab on novel circulating biomarkers	UC	Subjects with CLL and refractory to at least one fludarabine-containing treatment regimen (a minimum of at least two cycles).	12 total IV doses of ofatumumab over a 25-week treatment period. Initial (Week 1) dose of 300 mg; Week 2 and all subsequent infusions (i.e., Weeks 3-8, 13, 17, 21, and 25), 2000 mg.	Total: 14/12	Completed (full CPSR)

In addition, the MAH submitted the final study report of study OMB111773/Hx-CD20-406 (pivotal study of the initial marketing authorisation application), an abbreviated study report of study OMB111827 (GEN416) in fludarabine and alemtuzumab refractory CLL patients with disease progression following response or stable disease after previous ofatumumab treatment, as well as safety data from studies is non-CLL indications. These studies contributed safety data and study 406 was also included in the updated population pharmacokinetic analysis (see below).

2.3.2. Pharmacokinetics

For the purpose of this application for previously untreated CLL, additional PK data has been supplied from the following studies:

- Study OMB110911 was an open-label, parallel-arm, randomized, Phase III study to evaluate the safety, efficacy, and pharmacokinetic profile of ofatumumab added to chlorambucil compared with chlorambucil monotherapy in subjects with previously untreated CLL. Ofatumumab was administered as a two-dose first cycle (Day 1 300 mg, Day 8 1000 mg), followed by 1000 mg on Day 1 of subsequent four-week cycles for up to 12 cycles.
- Study OMB111774/Hx-CD20-407 evaluated the safety, efficacy, and pharmacokinetic profile of ofatumumab at two dose levels (300 mg + 5 x 500 mg or 300 mg + 5 x 1000 mg) in combination with fludarabine and cyclophosphamide for six four-week cycles in subjects with previously untreated CLL.
- Additionally, an updated PoP-PK analysis has been performed comprising previous and new PK data.

Absorption

After an infusion of 300 mg (i.e. applied posology of first infusion) of ofatumumab, the geometric mean Cmax values were 42-94 µg/mL and geometric mean AUC(0-∞) values were 1135-5116 µg.h/mL in different studies. After day 8 and cycle 4 with the applied posology the geometric mean Cmax values were 241 and 285 µg/mL, respectively, and geometric mean AUC(0-τ) values were 25369 and 65100 µg.h/mL, respectively. Mean Cmax and AUC(0-∞) values after the sixth infusion of 1000 mg were 427 µg/mL and 397577 µg.h/mL, respectively. From predose concentrations determined in study

OMB110911, steady state seems to be established after 9-12 cycles. Cmax and AUC at steady state are not presented.

Distribution

The geometric mean volume of distribution (Vss) values of ofatumumab ranged from 1.2 – 8.1 L across studies, dose levels, and infusion number. The inter-individual variability (%CV) on central volume of distribution of ofatumumab was estimated to be 0.076 (26.7%).

Elimination

With the applied posology and in patients with previously untreated CLL, the geometric mean values for clearance (CL) and half-life (t½) of ofatumumab were 15.4 mL/h and 445 h (18.5 days) at cycle 4. At the sixth infusion, geometric mean values for CL and t½ were 6.7 mL/h and 746 h (31.1 days). The inter-individual variability (%CV) on clearance of ofatumumab was estimated to be 0.276 (52.5%).

Dose proportionality and time dependencies

Due to insufficient data it is not possible to draw a conclusion about dose proportionality. Modelling and simulation of the proposed dosing regimen based on early pharmacokinetic data in subjects with CLL indicated that the dosing regimen was expected to achieve prolonged maintenance of plasma concentrations above the target level of 5-10 µg/mL in a high proportion of patients with CLL. The target level was based on preclinical studies. However, during the first three cycles in the only study using the applied posology, median predose ofatumumab concentrations were lower than 5-10 µg/ml, indicating that a large proportion of patients experienced predose concentrations lower than the target level.

Special populations

No specific studies in special populations were submitted. An update to the combined population pharmacokinetic analysis was performed on data from 252 CLL subjects, 38 FL subjects, and 187 RA subjects who received multiple infusions of ofatumumab as a single agent at doses ranging from 100 to 2000 mg in studies Hx-CD20-001, Hx-CD20-402, Hx-CD20-403 and OMB111773/Hx-CD20-406. The earlier population analysis had included an interim dataset from study OMB111773/Hx-CD20-406.

Estimated creatinine clearance was not found to be a covariate in the population PK model. Liver function and race were not evaluated as covariates. Body surface area and IgG concentration were found to be covariates for systemic clearance. Body surface area was also found to be a covariate for central and peripheral volumes of distribution, and gender was found to be a covariate affecting central volume of distribution. None of these effects were considered clinically relevant. Ofatumumab has not been tested in children.

Pharmacokinetic interaction studies

No specific DDI studies were submitted. An estimation of the effect of ofatumumab on the pharmacokinetics of chlorambucil and phenylacetic acid mustard were made from a subset dataset of dose-normalized chlorambucil and phenylacetic acid mustard pharmacokinetic parameter values in Study OMB110911 (with ofatumumab) and Study LEUA1001 (monotherapy). These indirect data did not suggest a clinically relevant effect of ofatumuzumab on the PK of chlorambucil or phenylacetic mustard (data not shown).

2.3.3. Pharmacodynamics

Primary pharmacology

In study OMB110911, in combination with chlorambucil in patients with previously untreated CLL, the median reductions in B-cell ($CD5^+CD19^+$) counts were 93%, 94%, and >99% in the ofatumumab + chlorambucil arm and 65%, 73%, and 97% in the chlorambucil arm at Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 6, respectively. At 6 months after the last dose, the median reductions in B-cell counts were >99% in the ofatumumab + chlorambucil arm and 94% in the chlorambucil arm. In study OMB111774/Hx-CD20-407 in combination with fludarabine and cyclophosphamide (FC) in subjects with previously untreated CLL, ofatumumab at either the 500 mg or 1000 mg dose led to rapid reductions in median $CD5^+CD19^+$ B cells after 2 courses that was sustained through treatment and follow-up (18 months after last infusion).

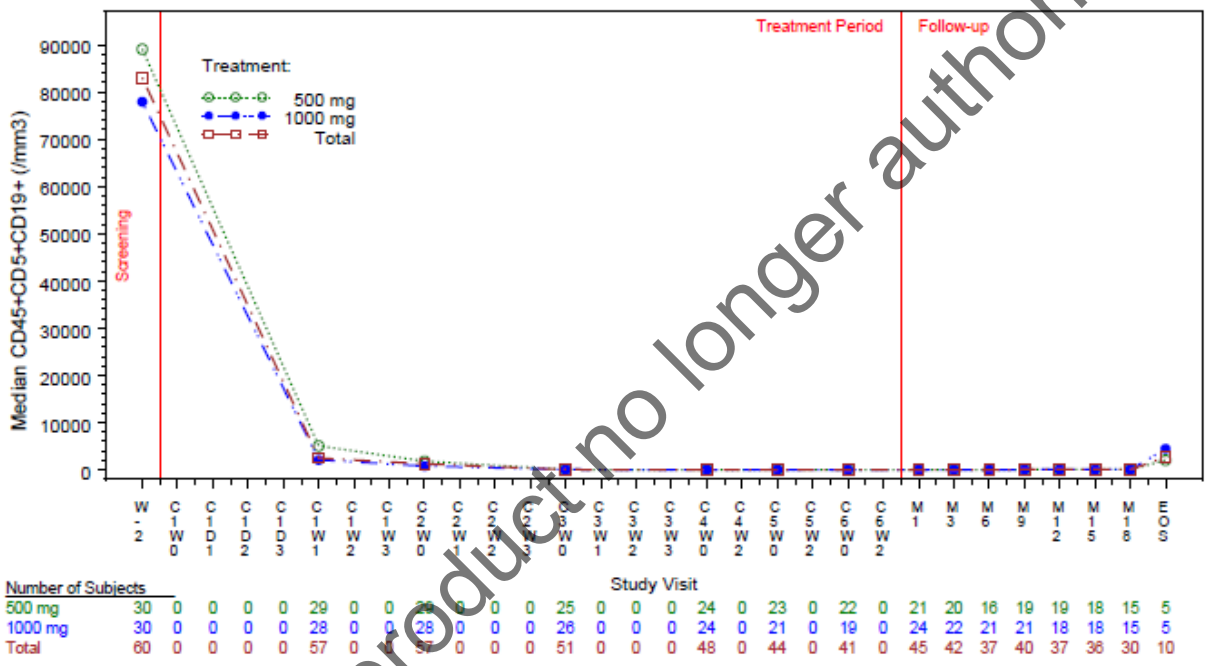


Figure 2: B-cell count progression at two doses of ofatumumab, study Hx-CD20-407

In Study OMB111774/Hx-CD20-407, higher Cmax and Ctrough values at Cycle 3 and higher Cmax and Ctrough AUC values at Cycle 6 were associated with an increased likelihood of CR based on univariate analyses. No ofatumumab exposure values were associated with an increased likelihood of overall response.

Secondary pharmacology

The effect of multiple doses of Arzerra on the QTc interval was evaluated in a pooled analysis of three open-label studies in patients with CLL (N = 85) including study OMB112855, a Phase I study to evaluate the effect of ofatumumab on cardiac repolarisation (QTc duration) in patients with fludarabine-refractory B-cell chronic lymphocytic leukaemia. In Study OMB112855, subjects received an initial dose of ofatumumab (300 mg) infused at Week 1. At Week 2 and all subsequent infusions (i.e., Weeks 3-8, 13, 17, 21, and 25), a full dose (2000 mg) of ofatumumab was administered.

Table 1: Summary of change from baseline in QTcF interval values (msec) over time (study OMB112855, study OMB110911 and study OMB110913)

Timepoint	n	Mean Change	SD	Median Change	Minimum Change	Maximum Change	Median Conc. of O (µg/mL)
OMB112855 Ofatumumab 2000 mg							
Dose 1/Week 1	14	2.6	7.3	3.7	-12	11	74.0
Dose 2/Week 2	14	3.1	12.5	6.3	-21	20	649
Dose 8/Week 8	13	4.0	16.5	4.8	-32	31	1386
Dose 9/Week 13	12	5.0	13.4	5.0	-20	29	859
Dose 12/Week 25	8	11.9	8.8	10.2	-2	24	780
OMB110911/OMB110913 Active[a]							
Cycle 1/Day 1	29	7.0	10.8	6.7	-15	26	617
Cycle 6/Day 1	19	11.9	16.1	13.0	-18	49	308
OMB110911/OMB110913 Control[a]							
Cycle 1/Day 1	31	5.6	10.0	5.8	-11	37	0
Cycle 6/Day 1	20	0.4	14.9	1.0	-23	29	0

Active = 1000 mg ofatumumab regimen + chemotherapy; Control = chemotherapy alone; O = ofatumumab

a. Only matching data at Cycle 1 and Cycle 6 are shown for Study OMB110911/OMB110913.
Data source: eCTD #0055, m5.3.5.3, QTc report

In clinical studies across the ofatumumab development programme, anti-ofatumumab antibody (HAHA) data are available from a total of 1421 patients who have been exposed to ofatumumab (214 FL, 645 CLL, 142 DLBCL, 382 RA, 38 MS); in all but 27 patients with RA, ofatumumab was administered by IV infusion. Post-ofatumumab samples for the detection of HAHA are available from 1242 patients. When the drug tolerance of the ELISA and the ECL ofatumumab binding antibody clinical assays was taken into account, there were 1030 subjects with evaluable post-ofatumumab samples. To date, anti-ofatumumab antibodies have been observed in 3 of 1003 patients after intravenous administration and 0 of 27 subjects after subcutaneous administration (total 3/1030). No anti-ofatumumab antibodies have been detected in patients with CLL.

Of the 1030 patients with evaluable post-ofatumumab immunogenicity data, 361 patients received ofatumumab in the acetate formulation. Twenty-seven (27) of these patients received single subcutaneous injections of 0.3 to 100 mg, while the remaining patients received multiple intravenous infusions of 300 to 2000 mg. None of these patients developed HAHA (0/361).

2.3.4. Discussion on clinical pharmacology

Additional PK data from two new studies in patients with CLL confirmed previous PK characteristics of ofatumumab. The updated PoP-model appeared well documented and validated. The pharmacokinetics of ofatumumab were reasonably described by a two-compartment model with a linear clearance component representing non-specific CL of IgG antibodies and a nonlinear clearance component representing CL mediated by an estimated dynamic target level. Clearance and volume of distribution values were low and half-life values were long for ofatumumab, as seen with other monoclonal antibodies. BSA was found to be a covariate for clearance and for central and peripheral volumes of distribution (<20% difference at the 5th and 95th percentile of BSA compared to the median). Gender was found to be a covariate affecting central volume of distribution (-11.5% for female subjects). These differences are unlikely to be of clinical relevance. Age and renal function were not identified as statistically significant covariates.

The approved posology of Arzerra entails a much higher exposure than the one proposed in the current variation application. Modelling and simulation of the current applied dosing regimen based on early pharmacokinetic data in subjects with CLL indicated that the dosing regimen was expected to achieve prolonged maintenance of plasma concentrations above the target level of 5-10 µg/mL in a high proportion of patients with CLL. The target level was based on preclinical studies. However, during the first three cycles in the only study using the applied posology, median predose ofatumumab concentrations were lower than 5-10 µg/ml, indicating that a large proportion of patients experienced predose concentrations lower than the target level. The concern is whether the applied posology ensures sufficient exposure of ofatumumab for all patients during the whole dosing intervals (see also Clinical efficacy section).

Indirect PK data does not suggest a clinically relevant effect of ofatumumab on the PK of chlorambucil or phenylacetic mustard.

The provided pharmacodynamic results of the pivotal efficacy trial OMB110911 and supportive study OMB111774 indicate benefit of ofatumumab treatment in previously untreated CLL patients.

From the studies available, a meaningful association between exposure and response is not apparent. Data from the pivotal study show that there was no exposure-response relationship for ofatumumab early in dosing, indicating that higher doses are not needed in this population and this combination. The fact that the target upon which ofatumumab exerts its therapeutic effect, B cells, is also a clearance mechanism for the drug, implying that higher exposure after several doses may occur as a result of response rather than cause the response, makes it difficult to explore and conclude whether a more severe disease would gain from higher exposures after several doses.

The MAH has provided reasonable data on QTc prolongation from one dedicated trial and substudy data. Changes in mean QTc values (maximum of 11.9 ms at the 12th cycle of 2000 mg) were apparently unrelated to changes in plasma concentrations, which do not support a causal relationship. A number of inherent design related issues (lack of positive control; no crossover; duration of therapy sample-size; quality controls of measurement) compromise the conclusions that can be made from the data obtained.

Exploration of clinical safety databases revealed three cases of reported QTc prolongation, that all could plausibly be explained by factors other than ofatumumab. A statement was therefore included in section 4.4 and 4.8 of the SmPC to recommend that patients have electrolytes such as potassium and magnesium measured prior to and during the administration of ofatumumab. Electrolyte abnormalities should be corrected.

The risk of immunogenicity appears low, and the conclusion of the MAH is endorsed.

2.3.5. Conclusions on clinical pharmacology

There are no outstanding concerns with this variation application from a clinical PK/PD point of view.

2.4. Clinical efficacy

2.4.1. Dose response studies

No new dose-finding studies were submitted by the MAH (see discussion on Clinical efficacy).

2.4.2. Main study

OMB110911

This was an open label, multicentre, randomised, phase III study in which the combination of ofatumumab with chlorambucil (O+CHL) was compared with chlorambucil alone (CHL) in patients with previously untreated CLL who were considered inappropriate for fludarabine-based therapy.

Methods

Study Participants

Key inclusion criteria were the following:

- Diagnosis of CLL defined by circulating lymphocytes ≥5,000/microL and flow cytometry confirmation of immunophenotype with CD5, CD19, CD20, CD23, CD79b, and surface Ig.
- Considered inappropriate for fludarabine-based therapy, for reasons that include, but not limited to, advanced age or presence of co-morbidities.
- Active disease and indication for treatment based on IWCLL updated NCI-WG guidelines.
- Not previously treated for CLL (including autologous or allogeneic stem cell transplantation).

Key exclusion criteria were the foloowing:

- Chronic or current active infectious disease requiring systemic treatment, positive serology for hepatitis B (HBsAg-positive), or known human immunodeficiency virus (HIV)-positive.
- Clinically significant conditions including cardiac disease, cerebrovascular disease, other past or current malignancy or abnormal laboratory values indicating significantly compromised renal or liver function.
- Glucocorticoid use was prohibited unless given in doses ≤100 mg/day hydrocortisone or equivalent dose of other glucocorticoid for <7 days for exacerbations other than CLL (e.g., asthma).
- Considering the immune system compromising mechanism of action of the study drug, significant infections were excluded; other conditions that could impact the primary endpoint were also excluded.
- Use of high-dose steroids for any condition was prohibited because steroids have known anti-CLL properties and would compromise the efficacy assessment.

Treatments

Ofatumumab was administered as follows:

Cycle 1/Day 1: 300 mg IV

Cycle 1/Day 8: 1000 mg IV

Cycles 2 to 12: 1000 mg IV, 1 dose at day 1 every 28 days

Pre-medication requirements prior to ofatumumab infusions included acetaminophen, antihistamine and glucocorticoid (prednisolone 50 mg IV, or lower dose before the 3th to 13th infusion in absence of grade 3AEs with the first 2 cycles).

Chlorambucil (CHL) was administered in cycles 1-12 as follows: 10 mg/m^2 po, 1 dose days 1-7 every 28 days. No pre-medications were required.

In both arms, treatment was given for a minimum of 3 cycles, up to a maximum of 12 cycles or until best response (i.e. after 3 additional cycles of treatment). Disease status assessments were performed monthly and included physical examination and peripheral blood sample evaluation. At cycles 4, 7 and 10, pre-dose assessed treatment response determined continuation or termination of treatment as per decision guide. A summary of the study design is shown in Figure 3 below.

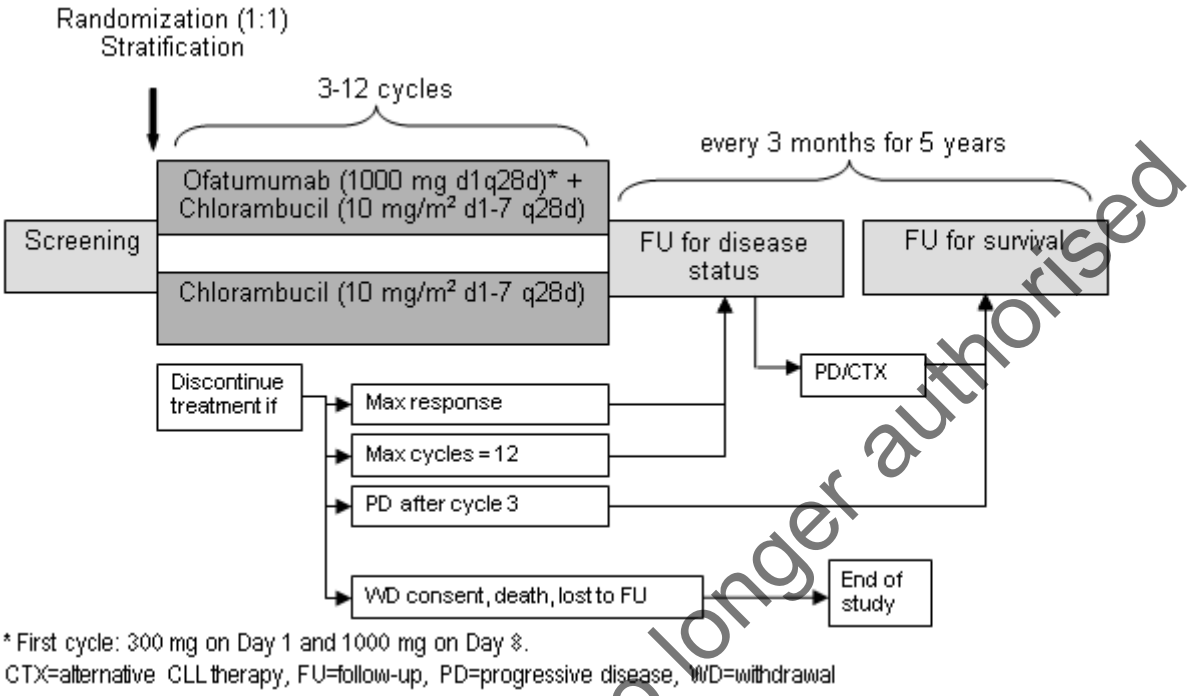


Figure 3: OMB110911 study design

Objectives

The primary objective of the study was to compare the efficacy of the combination of ofatumumab with chlorambucil vs. chlorambucil alone in the intended study population. Comparative safety as well as pharmacokinetics, transcriptomic/pharmacogenomic biomarkers information constituted secondary objectives.

Outcomes / endpoints

Primary endpoint

- The primary endpoint of the pivotal study was *PFS*, defined as the first occurrence of any criteria of progression or death. The length of the PFS interval was calculated from the date of randomisation to the date of death or progression, whichever occurred first, or censoring.

Secondary enpoints

- *Overall and Complete Responses*, where ORR was defined as the percentage of patients who had a best overall response of CR, CRi (complete response with incomplete bone marrow recovery), nodal partial response (nPR), or PR using the IWCLL updated NCI-WG guidelines. (CRi is defined as patients who fulfilled all criteria for CR but had persistent anemia, thrombocytopenia, or neutropenia that was unrelated to CLL but related to drug toxicity.)
- *OS*, defined as the interval between randomisation date and date of death due to any cause.

- *Time to response (TTR)*, defined as time from randomisation to the first response (CR, CRi, nPR, PR)
- *Duration of response (DoR)*, defined as the time from the initial response (CR, CRi, nPR, PR) to first documented sign of disease progression or death due to any cause (non-inferential secondary endpoint).
- *Time to progression (TTP)*, defined as the time from randomisation until disease progression.
- *Time to next treatment (TTNT)*, defined as the time from randomisation until next-line treatment.
- *Event Free Survival (EFS)*, defined as the interval of time between the date of randomisation and the earlier of the date of disease progression, beginning of new CLL treatment, or death due to any cause.
- Correlation clinical response with *prognostic and biological markers*, and by pre-treatment Cumulative Illness Rating Scale (*CIRS*) scores
- Tumour response
    - *Minimal residual disease (MRD)*, for patients that achieved an investigator-assessed best response of CR.
    - *B cell response*
    - *Changes in tumor size*
- Complement activity
- Quality of life related secondary (non-inferential) endpoints:
    - *Changes in B-symptoms/constitutional symptoms/fatigue*
    - *Changes in functionality and symptom scales (Patient Reported Outcomes)*
    - *Changes in ECOG performance status,* as defined by a decrease from baseline by at least one step on the ECOG performance status scale (yes/no).

Other/Exploratory endpoints

- Type of and response to *second line treatment*

Response evaluations and disease progression were determined according to the IWCLL updated NCI-WG guidelines. For this study, overall response rate (ORR) refers to the best overall response. Blinded review of response for each subject was conducted by an Independent Review Committee (IRC).

Sample size

A total of 444 subjects were planned for enrollment, randomised (1:1) into the 2 treatment arms. Assuming an accrual rate of 12 patients per month, a drop-out rate of 10%, and a screening failure rate of 15%, the total number of patients screened was planned to be about 522. The assumption was that subjects treated with CHL would achieve 18 months median PFS based on previously reported results, taking into account the patient populations in these studies. The study was powered to detect at least a 50% improvement in mPFS (hazard ratio [HR] of 0.66), corresponding to an increase from 18 to 27 months in median PFS. A minimum of 259 PFS events was required to detect the targeted difference with 90% power and a 5% two-sided alpha level.

Randomisation

Patients were randomised 1:1 between ofatumumab+chlorambucil vs chlorambucil alone.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary efficacy analysis in the pivotal study was performed in the intent-to-treat (ITT) population including all patients who were randomised to the study drugs. A Per Protocol (PP) analysis excluded patients with major protocol deviation that would impact the efficacy outcome and was used to check robustness of the ITT analysis.

PFS analysis was planned to be conducted after 259 events, using stratified log-rank test, with a significance level of 0.05. The null and alternative hypotheses were designed with the goal of demonstrating the superiority of O+CHL over CHL alone. Superiority was determined using the following hypotheses:

H0: Survival curves for O+CHL and for CHL are the same

H1: Survival curves for O+CHL and for CHL are not the same

Two sensitivity analyses of PFS were planned to confirm the robustness of the primary PFS analysis:

- The assignments of progression and date of censoring for sensitivity analysis of PFS are the same as those of the primary PFS, with the following difference: if a clinical progression is proclaimed by the investigator, the outcome is 'Progressed', and the date of the progression is the date of the claim or the next scheduled visit (if between visits).

- The worst comparison case treating lost-to-follow-ups (missing at least one tumor assessment before data cut-off) as events in the experimental arm and as censored in the control arm will be conducted to assess the robustness of the result of the primary analysis PFS.

The inferential secondary endpoints were overall response rate (ORR) and overall survival (OS). These endpoints would be tested only if the primary endpoint, PFS, was significant. To control for multiplicity across the 'inferential secondary endpoints', tests of H0 would be performed in a sequential manner to control the type I error rate at 0.05 as follows:

- Overall response rate
- Overall survival

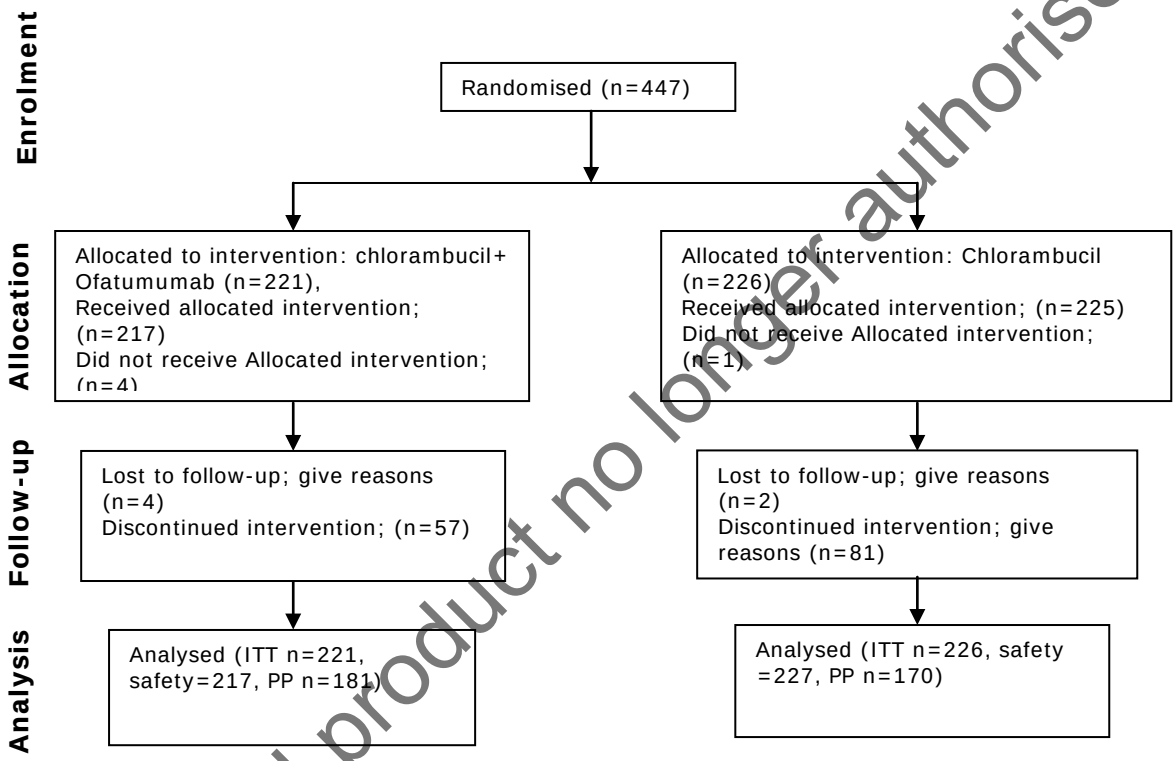
For the primary efficacy endpoint and the inferential secondary endpoints (ORR and overall survival), any p-values for the comparison of O+CHL vs. CHL that achieved statistical significance under multiplicity adjustment would be identified in the CSR as inferentially significant for confirmatory purpose.

Since no multiplicity would be considered in the analysis of the other secondary endpoints it was noted that any p-value that is <0.05 was considered only nominally significant.

Results

Participant flow

A total of 447 patients were randomised 1:1 at 109 centers in 16 countries (EU, USA, Brazil, India and Russia) to receive either O+CHL or CHL alone. The majority of patients (n=357, 80%) were enrolled in Europe. At the time of data cut-off (20 March 2013), with a median follow up of approximately 29 months, one-third of patients (138, 31%) had discontinued the treatment phase per protocol. Adverse events (AEs) were the main reason for early treatment discontinuation (66, 15%). Fewer than 20% of patients had died (74, 17%) and fewer than 15% had withdrawn from the study (55, 12%).



Recruitment

The study was initiated on 22 December 2008. Data cut-off for the analysis submitted in this variation application was 20 March 2013. 100 of the 447 randomised patients were still in follow-up at the time of the data cut-off. No patient was on treatment at the time of the data cut-off.

Conduct of the study

The original study protocol, dated 10 July 2008, was amended 3 times. None of the amendments were implemented for safety concerns. No patient was enrolled under the original protocol.

Key changes for each amendment were as follows:

Amendment 1: 11 August 2008

- The steroid pre-infusion schedule was modified to allow dose reduction for patients where steroid administration was not medically indicated (U.S. FDA request).
- DoR and PROs were removed as inferential secondary endpoints because a formal comparison of these endpoints was not considered feasible with the proposed study design. Instead, OS was added as an inferential secondary endpoint (U.S. FDA/EMA request).

Amendment 2: 10 August 2009

- Addition of inclusion criterion, 'considered inappropriate for fludarabine-based therapy, for reasons that include, but not limited to, advanced age or presence of comorbidities' to further define patient population (U.S. FDA request).
- Addition of a CT scan at time of progression to provide the IRC a means of objective assessment of disease progression by lymphadenopathy, for sensitivity analysis (U.S. FDA request).
- Update of CLL diagnosis definition and response assessment criteria in alignment with the IWCLL updated NCI-WG guidelines (U.S. FDA/EMA request).

Amendment 3: 25 November 2009

- Addition of a drug-drug interaction and electrocardiogram (ECG) substudy to evaluate potential ofatumumab/chlorambucil interaction and any effect of ofatumumab on QTc intervals (FDA request).

Most patients (88%) had at least one protocol deviation, with the majority (66%) being visit window deviations. Patients with protocol deviations that could potentially compromise the efficacy outcome were recorded in 25% of CHL patients, vs. 18% of O+CHL patients. These patients were excluded in the PP analysis of the primary endpoint.

Baseline data

Baseline demographic and disease characteristics, as well as baseline prognostic markers and comorbidities are summarised in the following Tables 1-4.

Table 2: Baseline demographic characteristics, study OMB110911

		CHL (N=226)	O+CHL (N=221)	Total (N=447)
Age, years	Median (min-max)	70 (36-91)	69 (35-92)	69 (35-92)
	<65, n (%)	71 (31)	69 (31)	140 (31)
	≥65, n (%)	155 (69)	152 (69)	307 (69)
	≥70, n (%)	117 (52)	104 (47)	221 (49)
	≥75, n (%)	63 (28)	56 (25)	119 (27)
Sex, n (%)	Male	140 (62)	142 (64)	282 (63)
	Female	86 (38)	79 (36)	165 (37)
Ethnicity, n (%)	Not Hispanic/Latino	218 (96)	211 (95)	429 (96)
	Hispanic/Latino	8 (4)	10 (5)	18 (4)
Race, n (%)	White	201 (89)	196 (89)	397 (89)
	Asian	22 (10)	21 (10)	43 (10)
	Central/South Asian	22 (10)	19 (9)	41 (9)
	Mixed Asian	0	2 (<1)	2 (<1)
	African American/African	2 (<1)	4 (2)	6 (1)
	American Indian or Alaskan Native[a]	1 (<1)	0	1 (<1)

Table 3: Baseline prognostic markers, study OMB110911

	CHL (N=226)	O+CHL (N=221)	Total (N=447)
IgV_H Mutational Status, N	203	201	404
Sequence homology >98%, n (%)	113 (56)	114 (57)	227 (56)
Sequence homology ≤98%, n (%)	90 (44)	87 (43)	177 (44)
V_H3-21 Usage, n (%)	208	207	415
Yes, n (%)	10 (5)	11 (5)	21 (5)
Chromosomal Aberration, N	216	209	425
6q deletion, n (%)	4 (2)	2 (<1)	6 (1)
11q deletion, n (%)	24 (11)	40 (19)	64 (15)
12q trisomy, n (%)	34 (16)	35 (17)	69 (16)
17p deletion, n (%)	17 (8)	10 (5)	27 (6)
13q deletion, n (%)	105 (49)	122 (58)	227 (53)
No Aberration, n (%)	64 (37)	41 (26)	105 (31)
CH_{50}, N	216	210	426
<LLN, n (%)	19 (9)	24 (11)	43 (10)
LLN-ULN, n (%)	85 (39)	81 (39)	166 (39)
>ULN, n (%)	112 (52)	105 (50)	217 (51)
CD20 Expression (MFI), N	221	215	436
<LLN, n (%)	211 (95)	209 (97)	420 (96)
β2m, N	217	214	431
Median, µg/L	4850	4540	4690
≤3500 µg/L, n (%)	48 (22)	61 (29)	109 (25)
>3500 µg/L, n (%)	169 (78)	153 (71)	322 (75)
ZAP-70 , N	213	208	421
Positive, n (%)	80 (38)	81 (39)	161 (38)
Negative, n (%)	48 (23)	52 (25)	100 (24)
Intermediate, n (%)	85 (40)	75 (36)	160 (38)
Combined IgV_H and ZAP-70 , N	117	127	244
IgV_H mutated & ZAP-70 positive, n (%)	23 (20)	12 (9)	35 (14)
IgV_H unmutated & ZAP-70 negative, n (%)	10 (9)	17 (13)	27 (11)
IgV_H unmutated & ZAP-70 postiive, n (%)	54 (46)	68 (54)	122 (50)
IgV_H mutated & ZAP-70 negative, n (%)	30 (26)	30 (24)	60 (25)

LLN=lower limit of normal, MFI=mean fluorescence intensity, ULN=upper limit of normal

Table 4: Baseline disease characteristics, study OMB110911

		CHL (N=226)	O+CHL (N=221)	Total (N=447)
Rai Stage, n (%)	Low risk (0)	21 (9)	16 (7)	37 (8)
	Intermediate (I, II)	116 (51)	113 (51)	229 (51)
	High risk (III,IV)	89 (39)	92 (42)	181 (40)
Binet Stage, n (%)	A	70 (31)	77 (35)	147 (33)
	B	87 (38)	74 (33)	161 (36)
	C	69 (31)	70 (32)	139 (31)
ECOG Status, n (%)	0,1	205 (91)	204 (92)	409 (91)
	2	19 (8)	17(8)	36 (8)
	3-5	0	0	0
Lymphocytes, Gi/L	Median (min-max)	69.9 (1-608)	69.3 (1-488)	69.7 (1-608)
Lymphadenopathy[a], n (%)		70 (31)	51 (23)	121 (27)
B-Symptoms[b], n (%)		120 (53)	118 (53)	238 (53)

[a]Defined as massive nodal clusters (≥10 cm longest diameter), symptomatic or progressive lymphadenopathy
[b]At least 1 B-symptom (fever, night sweats)

Table 5: Baseline comorbidities, study OMB110911

	CHL (N=226)	O+CHL (N=221)	Total (N=447)
Presence of Comorbidities, median (min-max)	3 (0-10)	3 (0-10)	3 (0-10)
0, n (%)	27 (12)	29 (13)	56 (13)
1, n (%)	40 (18)	30 (14)	70 (16)
≥2, n (%)	159 (70)	162 (73)	321 (72)
Creatinine, µmol/L, median (min-max)	89 (45-199)	87 (51-194)	88 (45-199)
CrCl, median (min-max) mL/min	69 (21-209)	72 (26-172)	70 (21-209)
CrCl <70 mL/min, n (%)	115 (51)	99 (45)	214 (48)
Combined Age and Comorbidity Assessment[a], n (%)			
Age ≥65 yrs and ≥2 comorbidities	129 (57)	131 (59)	260 (58)
Age ≥65 yrs or ≥2 comorbidities	185 (82)	183 (83)	368 (82)
Age ≥65 yrs or ≥2 comorbidities or CrCl <70 ml/min	197 (87)	192 (87)	389 (87)
Considered Inappropriate for Fludarabine[b], n (%)	211 (93)	200 (90)	411 (92)
Advanced age	121 (54)	117 (53)	238 (53)
Presence of comorbidity	78 (35)	71 (32)	149 (33)
Advanced age and presence of comorbidity	34 (15)	30 (14)	64 (14)
Advanced age or presence of comorbidity	165 (73)	158 (71)	323 (72)
Other	58 (26)	49 (22)	107 (24)
Patient's choice	25 (11)	23 (10)	48 (11)
Medical decision	18 (8)	17 (8)	35 (8)
Financial constraint	13 (6)	7 (3)	20 (4)
Fludarabine availability/standard of care	25 (11)	16 (7)	41 (9)
Not applicable	15 (7)	21 (10)	36 (8)
CIRS-G, median (min-max)	8 (4-19)	9 (4-21)	9 (4-21)
>10, n (%)	56 (25)	81 (37)	137 (31)

CIRS-G=Cumulative Illness Rating Scale-Geriatric

a. Data from CRF.

b. Assessed by investigator; the eligibility criterion 'considered inappropriate for fludarabine' was added as protocol amendment and the reason was collected. CRF choices were 'advanced age', 'presence of comorbidity,' and 'other' (free text). More than 1 reason could be selected.'Not applicable' are subjects enrolled prior to the amendment but for whom the investigator retrospectively could not provide a reason.

Table 6: Baseline characteristics: combined age & comorbidity and investigator-assessed fludarabine-inappropriateness

	CHL (N=226)	O+CHL (N=221)	Total (N=447)
Combined Age and Comorbidity Assessment based on eCRF data, n (%)			
Age <65 yrs and <2 comorbidities	41 (18)	38 (17)	79 (18)
Age <65 yrs and ≥2 comorbidities	30 (13)	31 (14)	61 (14)
Age ≥65 yrs and <2 comorbidities	26 (12)	21 (10)	47 (11)
Age ≥65 yrs and ≥2 comorbidities	129 (57)	131 (59)	260 (58)
Considered Inappropriate for Fludarabine based on investigator assessment, n (%)			
Advanced age	87 (38)	87 (39)	174 (39)
Presence of comorbidity	44 (19)	41 (19)	85 (19)
Advanced age and presence of comorbidity	34 (15)	30 (14)	64 (14)
Other reason (includes Patient's choice, Medical decision, Financial constraint, Fludarabine availability/standard of care)	46 (20)	42 (19)	88 (20)
Not applicable	*15 (7)*	*21 (10)*	*36 (8)*

Data Source: m1 Response to Questions_Additional: Table 367.0101, Table 367.0401
Subjects counted under 'other' had 'other' as sole reason. Subjects where 'other' reason was provided in addition to 'advanced age', 'presence of comorbidities' or 'advanced age and presence of comorbidities' are not listed under 'other' but under the respective category.

Numbers analysed

Efficacy and PRO analyses were conducted on the ITT population, which comprised all 447 randomised patients (CHL n= 226, O+CHL n=221). The PP population comprised 351 patients (CHL n=170, O+CHL n=181) who did not have protocol deviations. This population was used for sensitivity analysis of the primary endpoint.

Outcomes and estimation

Primary endpoint

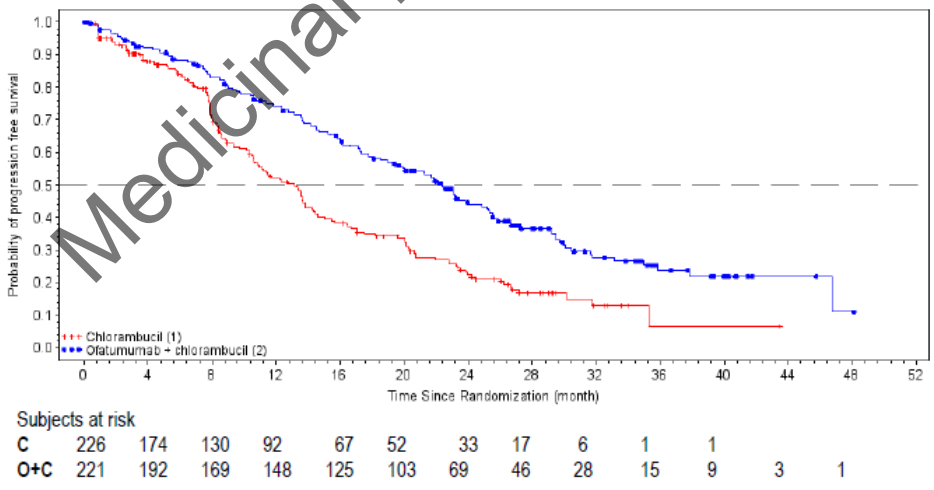
Results with regard to the primary efficacy endpoint of Progression-Free Survival (PFS) are summarised in the following Table 5 and Figure 4.

Table 7: IRC-assessed PFS results, study OMB110911

	CHL (N=226)	O+CHL (N=221)
Subject Classification, n (%)		
Progressed or died (event)	151 (67)	136 (62)
Death	10 (4)	12 (5)
Progression	141 (62)	124 (56)
Censored, last adequate assessment (LAA)[a]	40 (18)	72 (33)
Censored, LAA on or before anti-cancer therapy[b]	33 (15)	7 (3)
Censored, randomization[c]	2 (<1)	5 (2)
Censored, LAA before death[d]	0	1 (<1)
Kaplan-Meier Estimate for PFS (Months)[e]		
1st Quartile (95% CI)	7.9 (6.8, 8.2)	11.4 (8.8, 13.7)
Median (95% CI)	**13.1 (10.6, 13.8)**	**22.4 (19.0, 25.2)**
3rd Quartile (95% CI)	23.3 (20.1, 26.7)	35.9 (30.0, n/a)
Hazard Ratio Estimate[f] (95% CI)	**0.57 (0.45, 0.72)**	
Stratified Log-Rank p-value	**<.001**	

LAA=last adequate assessment, defined as a visit where all components (blood, lymph nodes, organ and constitutional symptoms) for response assessment are available; n/a = not available

a. Subjects alive and progression-free, censored at LAA.
b. Subjects took alternative therapy prior to documented progression, censored at LAA.
c. No disease assessment after randomization.
d. Event occurred after 2 or more missed visits, censored at LAA.
e. Confidence intervals were obtained using the Brookmeyer-Crowley method.
f. Hazard ratios were obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with O+CHL compared with CHL. The hazard ratio and p-value from the stratified log-rank test are adjusted for age, ECOG performance status, and Binet stage.



Subjects at risk

C	226	174	130	92	67	52	33	17	6	1	1		
O+C	221	192	169	148	125	103	69	46	28	15	9	3	1

Figure 4: Kaplan-Meier estimates of IRC-assessed PFS, study OMB110911

Secondary endpoints

Results in terms of response rate are summarised in the following Table 6.

Table 8: Best response by IRC, investigator and IRC with CT scan, study OMB110911

	IRC		Investigator		IRC with CT scan	
	CHL (N=226)	O+CHL (N=221)	CHL (N=226)	O+CHL (N=221)	CHL (N=226)	O+CHL (N=221)
Best Response, n(%)						
CR	**3 (1)**	**27 (12)**	44 (19)	96 (43)	0	14 (6)
CRi	**0**	**5 (2)**	4 (2)	12 (5)	0	2 (<1)
PR	**152 (67)**	**149 (67)**	126 (56)	77 (35)	63 (28)	94 (43)
nPR	**0**	**1 (<1)**	8 (4)	10 (5)	0	0
SD	**53 (23)**	**26 (12)**	30 (13)	13 (6)	58 (26)	48 (22)
PD	**10 (4)**	**5 (2)**	7 (3)	4 (2)	33 (15)	14 (6)
NE	**7 (3)**	**6 (3)**	0	0	9 (4)	10 (5)
Missing	**1 (<1)**	**2 (<1)**	7 (3)	9 (4)	63 (28)	39 (18)
Response Rate[a], n(%)	**155 (69)**	**182 (82)**	182 (81)	195 (88)	63 (28)	110 (50)
95% CI	**62.1,74.6**	**76.7,87.1**	74.8,85.5	83.2,92.2	22.1,34.2	43.0,56.6
p-value[b]	**.001**		.044		<.001	
Response Odds Ratio	**2.16**		1.81		2.53	
95% CI for Odds Ratio	**1.36,3.42**		(1.06, 3.11)		(1.70, 3.75)	
p-value[c]	**.001**		.031		<.001	

CR=complete response, CRi=CR in incomplete bone marrow recovery, PR=partial response, nPR=nodular PR, SD=stable disease, PD=progressive disease, NE=not evaluable

a. Responders include CR, CRi, nPR, and PR.
b. Cochran-Mantel-Haenzel test, adjusting for stratification factors: age, Binet stage, and ECOG performance status.
c. P-value for the test of odds ratio being 1.

OS results are presented in the following Table 7 and Figure 8.

Table 9: Overall survival results, study OMB110911

	CHL (N=226)	O+CHL (N=221)
Median OS (95% CI), months[a]	n/a	n/a (46.06, n/a)
Events (death), n (%)	40 (18)	34 (15)
Hazard Ratio[b] Estimate (95% CI)	0.91 (0.57, 1.43)	
Stratified Log-Rank P-Value	.666	
Survival rate, %		
2-year	86	88
3-year	78	82

n/a= not available

a. Kaplan-Meier estimate; confidence intervals were obtained using the Brookmeyer-Crowley method.
b. Hazard ratios were obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with this treatment compared with chlorambucil.

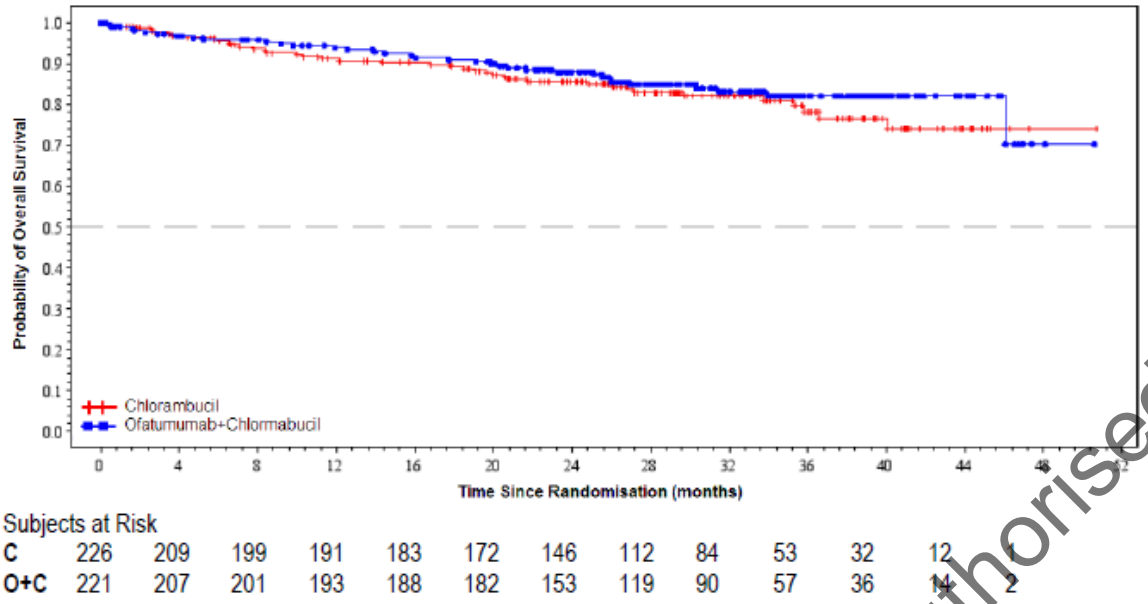


Figure 5: Kaplan-Meier curves for OS, study OMB110911

Results regarding the secondary endpoints time to response, duration of response, time to progression, time to next therapy, event free survival (EFS) and minimal residual disease analysis are shown in Table 8.

Table 10: Summary of other secondary endpoints, study OMB110911

	CHL (N=226)	**O+CHL (N=221)**
Time to Response, median (95% CI)[a] [mos] Events (Response), n (%) HR[e] (95% CI), stratified, log-rank p-value	2.8 (1.9, 3.1) 154 (68)	1.9 (1.2, 1.9) 182 (82) 1.13 (0.91, 1.40), 0.204
Duration of Response, median (95% CI)[a] [mos] Events (progression or death after response), n (%) HR[e] (95% CI), stratified, log-rank p-value	13.2 (10.8, 16.4) 107 (47)	22.1 (19.1, 24.6) 109 (49) 0.56 (0.43, 0.74), <0.001
Time to Progression, median (95% CI)[a] [mos] Events, n (%) HR[e] (95% CI), stratified, log-rank p-value	13.6 (11.2, 14.6) 141 (62)	23.1 (21.2, 25.8) 124 (56) 0.54 (0.42, 0.69), <0.001
Time to Next Therapy, median (95% CI)[a] [mos] Events, n (%) HR[e] (95% CI), stratified, log-rank p-value	24.7 (22.6,29.1) 99 (44)	39.8 (34.7,48.8) 64 (29) 0.49 (0.36, 0.67), <0.001
EFS, IRC-assessed, median PFS (95% CI)[a] [mos] HR[e] (95% CI), stratified, log-rank p-value	10.7 (8.9, 12.8)	21.9 (17.7, 23.8) 0.52 (0.42, 0.65), <0.001
Minimal residual disease absent, all subjects n (%) **Minimal residual disease absent**, subjects with IRC-assessed, CR n (%)	8 (4) 0	26 (12) 10 (37)

a. Confidence intervals were obtained using the Brookmeyer-Crowley method.

e. Hazard ratios were obtained using the Pike estimator.

Over 40% of responders in the O+CHL arm, regardless of whether assessed by the IRC or investigator, showed near complete B cell depletion and >10% showed complete B cell depletion. In contrast, no O+CHL non-responder had complete B cell depletion. B cell depletion (complete or near-complete) in responders in the CHL arm was limited (≤2%) and absent in non-responders.

Decrease in the sum of products of lymph node diameter (SPD) in patients with lymphadenopathy >1.5 cm at baseline was seen for most patients, as assessed by the investigator. The median percent reduction from baseline was 68% for patients in the O+CHL arm compared with 48% for patients in the CHL arm.

There was no median change from Baseline to Day 85 in complement activity (CH50) in both treatment arms and irrespective of response.

The majority of patients in both treatment arms had an ECOG performance status of 0 or 1 throughout the study. Almost no patients experienced a shift in ECOG status during the study.

In both treatment arms, the number of patients without B-symptoms increased over time, and many patients remained B-symptoms free after completion of treatment. The frequency of patients with B symptoms decreased in almost similar rates in the O+CHL arm compared with the CHL arm. After 6 cycles of treatment, 7% of patients in the O+CHL experienced B symptoms, vs. 9% in the CHL arm.

Baseline health related quality of life (HRqOL) values were similar for both treatment arms. No statistically significant differences have been observed between treatment arms after study start.

During period 1 (throughout active therapy), data have been presented for cycle 4 and 7 only, due to limited available data after from cycle 7 onwards. The Global health scale (GHS)/QOL domain from the EORTC QLQ-C30 and Fatigue Scale from the EORTC QLQ-CLL16 were pre-specified as the principal QoL outcomes. Patients had positive changes from baseline in both arms at the cycle 4 as well as cycle 7 assessments (Table 11).

Table 11: Change from Baseline in EORTC QLQ-C30 GHS/QOL Scores for Period 1

EORTC QLQ-C30 Functionality or Symptom Subscale Score	Visit	CHL (N=226)			O+CHL (N=221)		
		n	Mean	SD	n	Mean	SD
GHS/QOL	Cycle 4 Day 1	139	1.92	21.22	159	6.08	21.08
	Cycle 7 Day 1	52	8.01	22.20	55	6.97	17.55

The fatigue scale from the EORTC QLQ-CLL16 analysis during period 1 showed less fatigue compared with baseline in both arms at cycle 4 and 7. The changes at cycle 4 were similar in both arms. At cycle 7, a higher change from baseline was observed in the O+CHL arm.

All other functional domains/symptom scales of EORTC QLQ-C30 and EORTC QLQ-CLL16 showed numerical improvements in both treatment arms other than 'social functioning' and 'constipation' in Cycle 4, 'nausea and vomiting' in Cycles 4 and 7, and 'diarrhoea' in Cycle 7 for the CHL arm; and 'nausea and vomiting' in Cycle 4 and 'constipation' in Cycles 4 and 7 for subjects in the O+CHL arm.

During period 2 (during follow-up), GHS/QOL and fatigue scale assessments have been presented at 1, 6 and 12 months follow-up. For GHS/QOL patients had positive changes from baseline (=last on-treatment visit) in both arms at all time-points. None of these differences exceeded the MID of 5. For Fatigue, subjects had improvements from Baseline (last on-treatment visit) in both treatment arms at all time-points except for Month 12 for the O+CHL arm.

At disease progression, patients did not report any substantive changes for GHS/QOL, fatigue scale or remaining domains compared with the pre-progression visit in either treatment arm.

Ancillary analyses

All PFS sensitivity analyses (including PFS analysis in the PP population, an analysis where CT scan measurements replaced palpated lymph node and organ size, and investigator based analysis) showed a statistically significant prolonged PFS with O+CHL vs. CHL alone (data not shown). Point estimates for HRs ranged from 0.52 to 0.61, and upper 95% CIs were all ≤0.73. Median PFS based on the investigator's assessment of progression was 1 month longer for the O+CHL arm (23.4 months) and 1.7 months longer for the CHL arm (14.8 months) compared with the IRC-assessed analysis of PFS. The HR for this sensitivity analysis (0.58) was comparable with the primary analysis and was

statistically significant. Although the investigator-based PFS analysis still showed comparable results to the primary IRC based analysis, 25% of PDs were diagnosed later by investigator than by the IRC.

PFS subgroup analyses by baseline demographic and disease characteristics are shown in the following Figure 6.

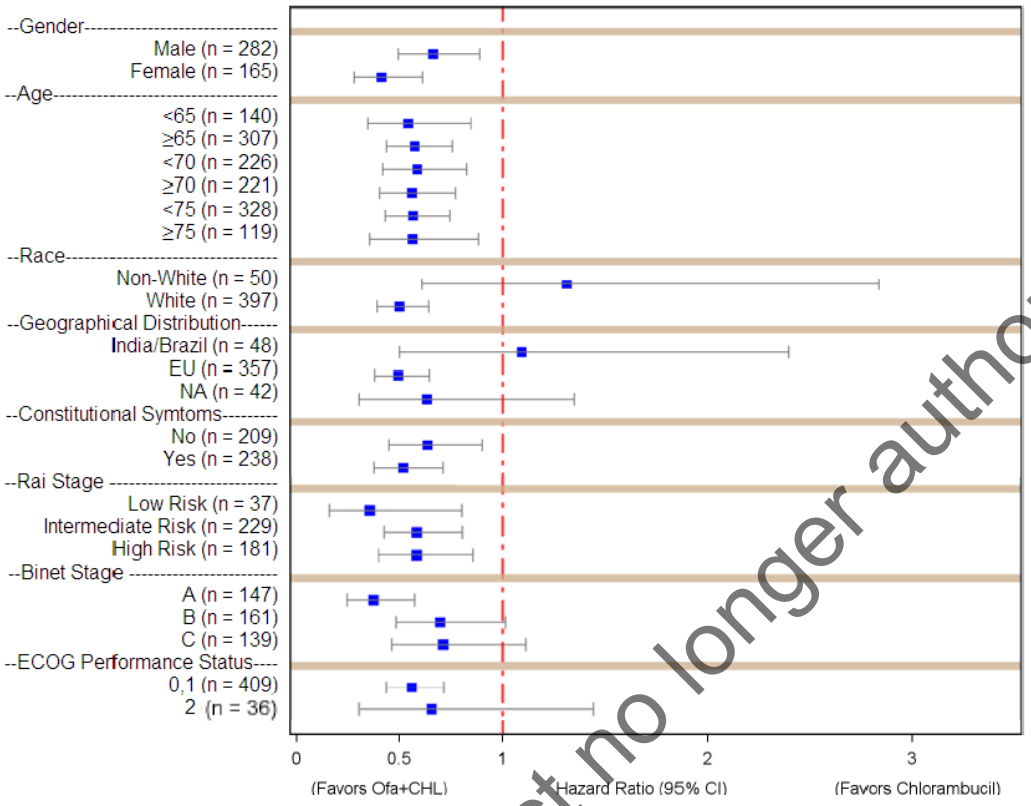


Figure 6: Forest plot of hazard ratios and 95% CIs for PFS by baseline demographic and disease characteristics, study OMB110911

PFS subgroup analyses by baseline fitness and comorbidities are shown in the following Figure **7**.

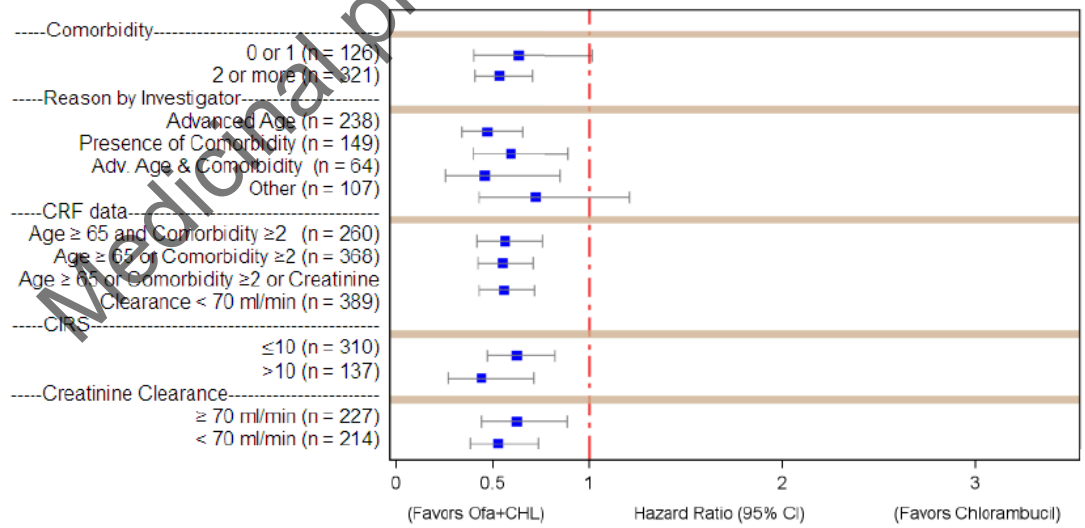


Figure 7: Forest plot of hazard ratios and 95% CIs for FPS by baseline fitness and comorbid condition burden, study OMB110911

PFS subgroup analyses by baseline prognostic markers are summarised in the following Figure 8.

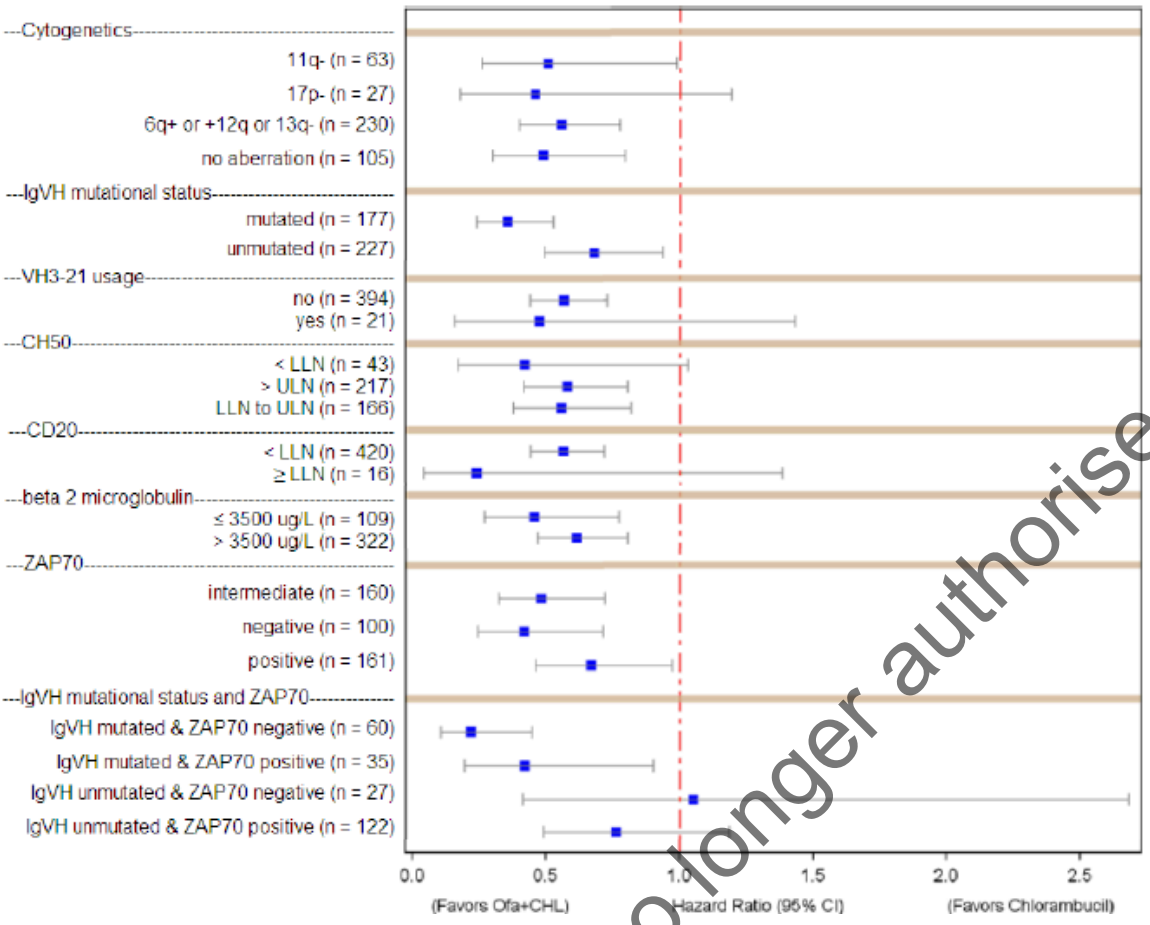


Figure 8: Forest plot of hazard ratios and 95 % CIs for FPS by baseline prognostic markers, study OMB110911

Finally, PFS subgroup analyses by combined baseline age, comorbidity and investigator-assessed fludarabine-inappropriateness are summarised in the following Figure 9.

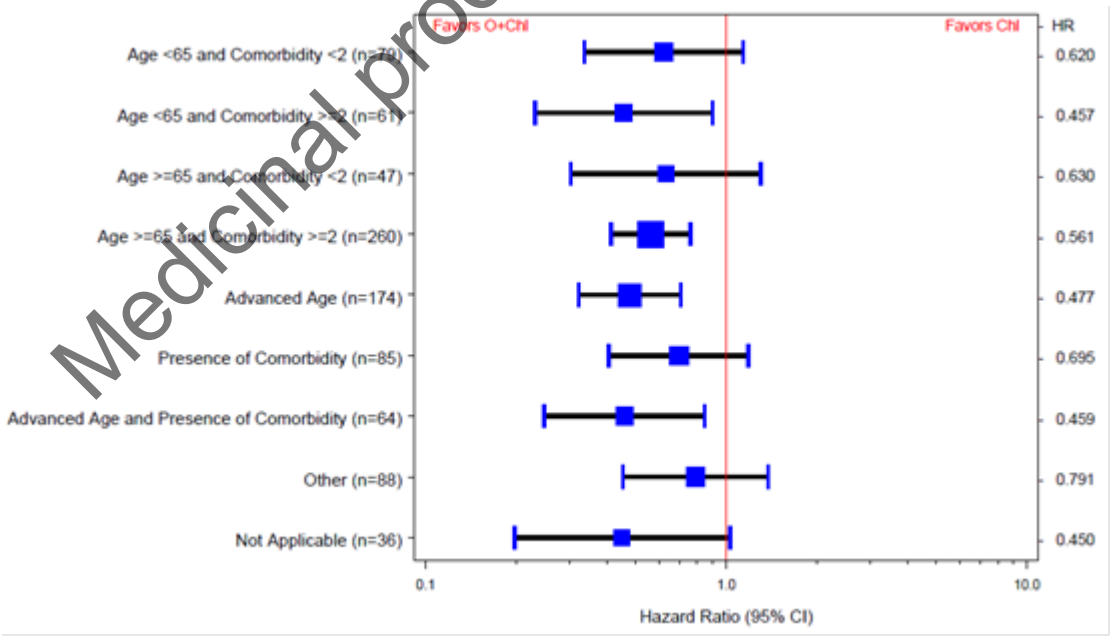


Figure 9: Forest Plot of IRC-assessed Kaplan-Meier PFS by subgroups: combined baseline age & comorbidity and investigator-assessed fludarabine-inappropriateness

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12: Summary of Efficacy for trial OMB110911

Title: A Phase III, open label, randomised, multicentre trial of Ofatumumab added to Chlorambucil vs. Chlorambucil Monotherapy in previously untreated patients with Chronic Lymphocytic Leukaemia			
Study identifier	OMB110911, NCT00748189, EudraCT: 2008-004932-19		
Design	open label, randomised, multicentre		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Superiority		
Treatments groups	ofatumumab+chlorambucil		Ofatumumab 300 mg IV on Day 1/Cycle 1, 1000 mg IV on Day 8/Cycle 1, 1000 mg IV on Day 1/Cycles 2-12, cycle duration 28 days Chlorambucil10 mg/m^2 po, 1 dose on days 1-7 on cycles 1-12 (n=221)
	chlorambucil		Chlorambucil10 mg/m^2 po, 1 dose on days 1-7 on cycles 1-12 (n=226)
Endpoints and definitions	Primary endpoint: progression-free survival	PFS	Time from randomisation to first occurrence of progression or death
	Secondary endpoint: Overall response rate	ORR	percentage of patients who had a best overall response of CR, CRi (complete response with incomplete bone marrow recovery: persistent anemia, thrombocytopenia, or neutropenia that was unrelated to CLL but related to drug toxicity), nodal partial response (nPR), or PR using the IWCLL updated NCI-WG guidelines
	Secondary endpoint: Overall survival	OS	Time from randomisation to death
Database lock	20 March 2013		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat At 259 PFS events		
Descriptive statistics and estimate variability	Treatment group	ofatumumab+ chlorambucil	chlorambucil
	Number of subject	221	226
	PFS (median, months)	22.4	13.1
	95% CI	19.0, 25.2	10.6, 13.8

	ORR (number of patients (%))	182 (82%)	155 (69%)
	95% CI	76.7, 87.1	62.1, 74.6
	OS (median, months)	n/a	<n/a
	95% CI	46.06, n/a	n/a, n/a
Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups	Ofatumumab+chlorambucil vs chlorambucil
		Hazard Ratio (HR)	0.57
		95% CI	0.45, 0.72
		P-value	<0.001
	Secondary endpoint (ORR)	Comparison groups	Ofatumumab+chlorambucil vs chlorambucil
		Response Rate odds ratio	2.16
		95% CI	1.36, 3.42
		P-value	0.001
	Secondary endpoint (OS)	Comparison groups	Ofatumumab+chlorambucil vs chlorambucil
		Hazard Ratio (HR)	0.91
		95% CI	0.57, 1.43
		P-value	0.666

Analysis performed across trials (pooled analyses and meta-analysis)

Integrated analysis of PFS between the pivotal and the supportive study was completed, but only 1 patient progressed in the supportive study (data not shown). Investigator assessed ORR data from the 2 studies were integrated such that patients treated with ofatumumab added to an alkylating agent (chlorambucil or bendamustine) were pooled to form an 'integrated ofatumumab plus 'alkylator'' (O+ALK) group. In O+ALK group, overall and complete response rates supported response rates of the pivotal study. The investigator assessed ORR was 89% in the O+ALK group (88% O+CHL, 95% O+B, 81% CHL), and CR occurred in 43% of patients (43% O+CHL, 43% O+B, 19% CHL).

Clinical studies in special populations

In the pivotal study, study results were mostly based on a patient population of 65 years of age or older (N=307, 69%). A large number of patients (n=119, 27%) was even 75 years or older. The primary efficacy and ORR analysis did not indicate substantial differences in the HR for PFS between patients in the different age categories (><65, ><70, and ≥75 years).

Patients with abnormal laboratory values indicating significantly compromised renal or liver function were excluded from the pivotal trial. A substantial part of patients (n=214, 48%) did have a creatinine clearance <70 mL/min. The primary efficacy and ORR analysis did not indicate substantial differences in the HR for PFS between patients with a creatinine clearance over and under 70 mL/min.

Table 12 shows the distribution of renal impairment categories by treatment arm at baseline.

Table 13: Summary of baseline renal impairment

	CHL (n=226)	O+CHL (n=221)	Total (n=447)
No Impairment (>50 mL/min)	184 (83%)	185 (85%)	369 (84%)
Mild Impairment (20-50 mL/min)	39 (17%)	33 (15%)	72 (16%)
Moderate Impairment (10-<20 mL/min)	0	0	0
Severe Impairment (<10 mL/min)	0	0	0

Source data: m1 Response to Questions_Additional: Table 368.0201

Primary efficacy assessment for the renal impairment subgroups is summarized in the table below.

Table 14: Summary of IRC-assessed Kaplan-Meier estimates of PFS by renal impairment subgroups.

mPFS, months	CHL (N=226)	O+CHL (N=221)	Hazard Ratio
IRC-Assessed PFS	**13.1**	**22.4**	**0.57**
No Impairment (>50 mL/min) (n=369)	13.6	22.4	0.59
Mild Impairment (20-50 mL/min) (n=72)	8.1	23.8	0.48

Data Source: m1 Response to Questions_Additional: Table 368.0301, Table 368.0302

No data is available in children or adolescents under 18 years, and pregnant or lactating woman.

Supportive study

The main supportive study to the variation application of Arzerra was study OMB115911. This study is an open-label, single arm Phase II study investigating the safety and efficacy of ofatumumab (O) plus bendamustine (B) in patients with untreated or relapsed CLL, with ORR as primary endpoint. Efficacy data of 44 previously untreated CLL patients were presented to support this variation application. No prior treatment for CLL was allowed and patients were to be considered inappropriate for fludarabine-based therapy. This study enrolled younger patients (median age 62.5 years) compared with the pivotal study. Median lymphocyte count was slightly lower in the O+B study than the pivotal study, all other baseline disease characteristics were comparable. The frequency of patients having at least 2 comorbidities was higher (82% O+B vs. 72% in the pivotal study). No patients with ECOG performance status of 2 at screening were included, and 25% of patients (n=11) had a CIRS-G over 10. Prognostic markers associated with higher risk CLL were similar with the pivotal study.

Patients received intravenous infusions of ofatumumab (Cycle 1: 300 mg Day 1 and 1000 mg Day 8; subsequent Cycles 2-6: 1000 mg at Day 1 every 28 days) in combination with 6 cycles of bendamustine comprising 12 intravenous infusions (90 mg/m2, Days 1 and 2; every 28 days). All eligible subjects were permitted to receive 3 cycles of study treatment.

The primary efficacy analysis showed an investigator-assessed ORR of 95% (95% CI, 84.53 to 99.44) with a CR rate of 43% following the last dose of O+B treatment. The response rates reported using CT scan results were lower than those reported without CT scan results. The ORR and CR rate decreased to 82% and 27%, respectively, when CT scans were used to assess response. The sponsor sensitivity analysis of response was also lower than the investigator-assessed response (ORR 89%, CR 14%).

The secondary endpoints PFS, OS, duration of response, time to progression and time to next therapy were not yet mature. An additional analysis provided by the applicant reported a median duration on study of approximately 14 months. No deaths were reported and 1 subject (2%) had PD.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The supportive study OMB110991 evaluated ORR of ofatumumab + another alkylating agent: bendamustine (n=44).

The open label, randomised Phase III pivotal study evaluated whether ofatumumab added to chlorambucil (n=226) improved PFS compared with chlorambucil alone (n=221) in fludarabine-inappropriate CLL patients. The approved ofatumumab regimen as monotherapy in the treatment of patients with fludarabine- and alemtuzumab-refractory CLL is eight weekly doses (300 mg initial dose, then seven 2000 mg doses), followed five weeks later by four consecutive monthly 2000 mg doses. A lower dose was used in the pivotal efficacy study and proposed in this variation application. The proposed dosing regimen is two doses in the first cycle (300 mg on Day 1, 1000 mg on Day 8), with a single 1000 mg dose on Day 1 of subsequent four-week cycles. This 1000mg regimen was based on preclinical data and PK modelling, suggesting that this dose could achieve prolonged maintenance of plasma concentrations above the target level (>10 µg/ml) in a high proportion of patients with CLL. Forty three (43) % of responders in the O+CHL arm, did not achieve complete/near-complete B-cell depletion, when depletion is defined as <5 cells/µL. However the decrease in B-cell counts from baseline was rapid in all subjects in the O+CHL arm, when compared to B-cell depletion with chlorambucil. B-cell depletion with 1000 mg O+CHL can be considered as rapid and extensive for the majority of subjects. It is not known whether a faster response could have been achieved with a higher dose, however data are not available and the current dose is considered acceptable.

Treatment was administered for a minimum of 3 cycles up to a maximum of 12 cycles, and was to be stopped 3 cycles after a subject achieved maximum response. The rationale for an additional 3 cycles of treatment after maximal response was that once a subject had received maximal response, it was unlikely that additional benefit would occur beyond 3 further cycles and the risks of therapy may then outweigh the benefit for more therapy. For obvious practical reasons the 4 weekly schedule fits better with the chlorambucil regimen. The treatment duration (maximum 12 cycles) is endorsed. Currently, there are no data showing that longer (maintenance) therapy with anti-CD20 therapy is indicated in CLL.

Overall the study was well designed and conducted and the use of IRC assessed PFS as primary endpoint is endorsed. The MAH has selected a population of elderly and co-morbid patients unfit for FCR or other fludarabine-containing chemotherapy.

Further to the CHMP request, the MAH has performed a thorough analysis of the various reasons behind the “fludarabine-inapproriate” criteria with a forest plot. The various reasons are well balanced between arms. However, there could be within these two groups, patients that could formally be “fludarabine-eligible”. Elimination of subjects in whom fludarabine-appropriateness could not be confirmed from the analysis showed that efficacy assessment was not impacted and consistent with the overall population. The forest plot HRs as described in Figure 9 favoured O+CHL but the 95% CI included the value ‘1’ for several of the smaller sub-groups. However, none of the subgroups seemed particularly unfavourable compared to the rest.

In addition, the fact that 18 % of patients received subsequent fludarabine treatment did not necessarily mean that they were fludarabine eligible when given first-line therapy (as benefit-risk assessment is different for initial and second-line treatment, dose regimen could be reduced and the absence of alternative options).

A protocol deviation in visit schedule and assessment procedures was recorded in a high percentage of patients (66% and 50%, respectively). However the deviation types were similar across both treatment arms with any differences primarily driven by the different assessment requirements in the two treatment arms. Timing of the visit schedule deviations was similar across both arms and timing of the CT scan to confirm response was identical for CHL and O+CHL. Analysis of the time to assessment, irrespective of reported deviations, did show a wider spread of actual visit dates occurring in the follow-up phase. The median time to assessment and the distribution around the median were similar for both treatment arms, specifically for the initial follow-up visits where assessments for confirmation of response (bone marrow analysis and CT scan) were scheduled to be performed.

Efficacy data and additional analyses

A statistically significant 71% improvement in mPFS as assessed by the IRC was observed for O+CHL over CHL, with a median PFS of 22.4 months for O+CHL compared with 13.1 months for CHL (a gain of 9.3 months, HR 0.57, (95% CI: 0.45, 0.72, p<.001). CHL performed somewhat worse than expected (assumption PFS of 18 months for the sample size calculation).

Sensitivity analysis confirmed the robustness of the PFS analysis. Investigator-assessed PFS and IRC-assessed PFS with CT scan were similar to the primary endpoint (investigator: O+CHL: 23.4 months, CHL: 14.8 months; IRC with CT: O+CHL: 23.4 months, CHL: 14.5 months). This study also confirms previous finding that the addition of CT scans is of limited value in patients with CLL.

PFS subgroup analysis was consistent with the overall population analysis and demonstrated a benefit with O+CHL regardless of gender, age, number of co-morbidities, disease stage or reason for fludarabine inappropriateness. PFS benefit with O+CHL was also observed for prognostic factor subgroups, including non-favourable risk groups with 17p or 11q deletion, unmutated IgVH, elevated beta2m and ZAP-70 positivity. Assessment of exploratory markers such as CD20 expression and CH50 activity was inconclusive due to small numbers of subjects.

EFS, which compared with PFS was shorter for CHL but similar to O+CHL. The short EFS in the CHL arm, compared to PFS, is consistent with clinical practice, since a nonresponse to treatment after 3-6 months may be considered a failure and prompt initiation of a new regimen, even in the absence of a true progression as per the IWCLL updated NCI-WG guidelines.

Response, as assessed by the IRC, resulted in higher ORR and CR with O+CHL compared with CHL alone. The ORR was 82% with O+CHL compared with 69% for CHL, which was a statistically significant improvement. Onset of response was rapid and response was consistent across subgroups, irrespective of fitness or risk factors. 12% of subjects achieved a CR in the study with O+CHL, with an additional 2% of subjects achieving CRi,) compared with 1% CR+CRi with CHL.

There was an 85% concordance between the investigator and the IRC for the overall response but there was a high discordance for the assessment of CRs, with a much higher rate of CRs reported by the investigator. Since this difference is balanced between the two treatment groups this is not considered to be a major concern when assessing the overall results.

DoR was significantly improved in O+CHL versus CHL (22.1 vs. 13.2; HR 0.56, p<.001). Thus, the improvement in response duration and PFS in the O+CHL arm resulted in a significant and clinically meaningful treatment-free interval for patients.

MRD negative status was demonstrated by 12 of 32 (38%) subjects who achieved an IRC assessed CR or CRi in the O+CHL arm. In addition, considering that many subjects were diagnosed with CR by the investigator, but bone marrow data were incomplete for IRC confirmation, a further 14 subjects with a best response of nPR or PR achieved a MRD negative status after treatment. Thus, 12% of all subjects

in the O+CHL arms achieved MRD negativity after therapy. For many subjects MRD negative status was maintained for a prolonged duration. This result may not be seen as impressing but the O-CHL regimen may considered to be a very intensive regimen and MRD negativity is very rarely achieved CHL alone.

As of the data-cut off for this CSR, median OS was not reached for O+CHL or CHL, but showed a positive trend for O+CHL after 2 and 3 years post randomization (2 yrs: 88% vs. 86%, 3 yrs: 82% vs.78%). With the limited data, subgroup analysis for OS was not feasible. OS difference is not often seen in a population of elderly and comorbid patients with CLL. The most important finding is that the addition of ofatumumab does not seem to have detrimental effects on OS.

These efficacy measures are supported by a higher degree of tumour size reduction and more subjects in the O+CHL arm were B-symptoms free and at an earlier time point compared with the CHL arm. Moreover, the observed prolonged time to next therapy (+15 months) with ofatumumab treatment is considered an important clinically relevant benefit.

While patient-reported outcomes should be interpreted with caution in an open-label study and acknowledging that it could be difficult to evaluate quality of life data in patients with a median age of 69 years and >70% already having one or more comorbidities prior to study start, subjects receiving either O+CHL or CHL alone experienced improvements in various aspects of HRQoL functionality and several symptoms while receiving active therapy. Comparison of HRQoL between treatment arms showed that most aspects did not significantly differ. Results suggest that the addition of ofatumumab to chlorambucil does not negatively impact HRQoL during therapy and may improve certain aspects of patients' quality of life during and after active treatment. The significant differential improvement in the 'B-symptoms' score favouring the O+CHL arm may suggest that the combination of O+CHL had a positive impact on subjects' constitutional symptoms.

The supportive OMB115991 is a relatively small phase II study. The only efficacy endpoint that can be reliably assessed is ORR. From the data presented, the ORR (and CR rate) for bendamustine + ofatumumab seems quite high. An analysis of additional 5.5 months (total median follow-up of 14 months) confirms that ofatumumab in combination with bendamustine provides durable responses for subjects with previously untreated CLL. No additional subjects have progressed and thus 98% of responding subjects remain progression-free.

2.4.4. Conclusions on the clinical efficacy

Efficacy has convincingly and robustly been demonstrated for the O-CHL regimen intended to be used in elderly co-morbid patients with CLL. Considering the known value of anti-CD20 therapy this result is not surprising. There are no weaknesses in the pivotal study that could challenge the overall results (substantial PFS gain and increased ORR). Although clinical relevance in terms of quality of life related endpoints is not significantly demonstrated, the improved time to next therapy is considered an important benefit to CLL patients.

2.5. Clinical safety

Data from three trials were presented in the safety analysis of ofatumumab treatment in chronic lymphocytic leukaemia (CLL) patients. Only patients with previously untreated CLL were included in the safety analysis (n=518):

- Study OMB110911: 444 patients where 227 received chlorambucil (CHL) and 217 received ofatumumab in combination with chlorambucil (O+CHL). Treatment given up to 12 cycles.

- Study OMB115991: 44 patients received ofatumumab in combination with bendamustine (O+B). Treatment given up to 6 cycles.
- Study OMB111774: 30 patients received ofatumumab in combination with fludarabine and cyclophosphamide (O+FC). Treatment given up to 6 cycles.

In the pivotal trial OMB110911 and supportive study OMB115991, all patients were considered fludarabine inappropriate, in line with the targeted patient population. In trial OMB111774, the patients were not and represented a younger and more fit population. All patients in the safety population received the 1000 mg dose of ofatumumab.

Safety data were provided for each of the three trials separately, as well as in two different integrated analyses: 1) all patients in the three trials who had received ofatumumab in combination with a chemotherapy regimen (O+Chemo, n=291), 2) only fludarabine inappropriate patients from trial OMB110911/OMB115991 (O+ALK, n=261). However, limited data were presented from the O+ALK group, so that the integrated safety population refers to the O+chemo group.

Patient exposure

In the pivotal trial the median dose of ofatumumab was 6300 mg. The mean/median total dose of chlorambucil was slightly higher in the O+CHL arm (806mg/763mg) than in the CHL arm (729mg/728mg). The majority of patients in both arms ended treatment after 6 cycles: 82% in the O+CHL arm (both ofatumumab and chlorambucil treatment) and 70% in the CHL arm.

At cycles C4, C7 and C10, pre-dose assessed treatment response determined continuation or termination of treatment based on response. Overall, less patients discontinued in the O+CHL arm (25%) compared with the CHL arm (35%). The primary reason for discontinuation was adverse events in both arms (13.8% O+CHL vs. 15.8% CHL of all patients). More patients in the CHL arm discontinued due to progressive disease (8.4% vs. 1.8% O+CHL arm).

In the supportive trial OMB115991 89% completed the maximum of 6 cycles (median dose of ofatumumab 6300 mg) and all administered bendamustine infusions were completed in full. In trial OMB111774 63% of the patients completed the maximum of 6 cycles (median dose of ofatumumab 5300 mg) and 70% of subjects received the planned dose of FC.

The frequency of patients discontinuing due to adverse events was higher in these studies compared with the pivotal trial (O+B: 60% and O+FC: 69% of discontinued patients).

Adverse events

An overview of adverse events in the safety population is presented in the following Table 11.

Table 15: Overview of adverse events, safety population

	OMB110911		OMB115991	OMB111774	Integrated
	CHL (N=227)	O+CHL (N=217)	O+B (N=44)	O+FC (N=30)	O+Chemo (N=291)
Any AE, n (%)	**203 (89)**	**206 (95)**	**43 (98)**	**30 (100)**	**279 (96)**
AEs related to study treatment	148 (65)	182 (84)	42 (95)	30 (100)	254 (87)
AEs leading to permanent discontinuation of study treatment	31 (14)	28 (13)	3 (7)	8 (27)	39 (13)
AE leading to dose reduction	38 (17)	36 (17)	13 (30)	0	49 (17)
AE leading to dose interruption	64 (28)	150 (69)	31 (70)	13 (43)	194 (67)
AEs ≥Grade 3	103 (45)	131 (60)	25 (57)	26 (87)	182 (63)
Any SAE, n (%)	**71 (31)**	**84 (39)**	**15 (34)**	**23 (77)**	**122 (42)**
SAEs related to study treatment	30 (13)	32 (15)	14 (32)	20 (67)	66 (23)
Fatal SAEs	14 (6)	23 (11)	0	1 (3)	24 (8)
Fatal SAEs related to study treatment	2 (<1)	3 (1)	0	0	3 (1)

The most common AEs (≥20% of subjects) in the O+Chemo group were neutropenia, nausea, rash, and pyrexia. Overviews of the most common adverse events, grade 3 or greater adverse events and treatment-related adverse events in the O+Chemo group are presented in the following Tables 12-14.

Table 16: Adverse events in ≥5% of patients in the O+Chemo group, safety population

	OMB110911		OMB115991	OMB111774	Integrated
Preferred Term	CHL (N=227)	O+CHL (N=217)	O+B (N=44)	O+FC (N=30)	O+Chemo (N=291)
Any event, n (%)	**203 (89)**	**206 (95)**	**43 (98)**	**30 (100)**	**279 (96)**
Neutropenia	41 (18)	59 (27)	21 (48)	23 (77)	103 (35)
Nausea	57 (25)	46 (21)	19 (43)	13 (43)	78 (27)
Rash	22 (10)	54 (25)	12 (27)	8 (27)	74 (25)
Pyrexia	22 (10)	46 (21)	11 (25)	7 (23)	64 (22)
Thrombocytopenia	59 (26)	30 (14)	8 (18)	12 (40)	50 (17)
Diarrhea	33 (15)	40 (18)	5 (11)	4 (13)	49 (17)
Fatigue	40 (18)	34 (16)	7 (16)	6 (20)	47 (16)
Cough	26 (11)	35 (16)	3 (7)	7 (23)	45 (15)
Vomiting	26 (11)	27 (12)	5 (11)	6 (20)	38 (13)
Pruritus	12 (5)	26 (12)	7 (16)	3 (10)	36 (12)
Dyspnea	12 (5)	25 (12)	5 (11)	4 (13)	34 (12)
Anemia	30 (13)	20 (9)	7 (16)	5 (17)	32 (11)
Leukopenia	4 (2)	14 (6)	2 (5)	16 (53)	32 (11)
Headache	7 (3)	20 (9)	6 (14)	5 (17)	31 (11)
Urticaria	2 (<1)	21 (10)	6 (14)	3 (10)	30 (10)
Chills	2 (<1)	19 (9)	5 (11)	5 (17)	29 (10)
Infusion related reaction	0	20 (9)	4 (9)	0	24 (8)
Asthenia	12 (5)	18 (8)	5 (11)	0	23 (8)
Insomnia	17 (7)	12 (6)	6 (14)	4 (13)	22 (8)
Constipation	13 (6)	10 (5)	6 (14)	5 (17)	21 (7)
Decreased appetite	20 (9)	14 (6)	6 (14)	1 (3)	21 (7)
Arthralgia	7 (3)	11 (5)	4 (9)	5 (17)	20 (7)
Back pain	13 (6)	12 (6)	5 (11)	1 (3)	18 (6)
Edema peripheral	13 (6)	13 (6)	4 (9)	1 (3)	18 (6)
Upper respiratory tract infection	17 (7)	13 (6)	3 (7)	2 (7)	18 (6)
Bronchitis	10 (4)	13 (6)	2 (5)	2 (7)	17 (6)
Nasopharyngitis	19 (8)	11 (5)	2 (5)	4 (13)	17 (6)
Dizziness	16 (7)	11 (5)	5 (11)	0	16 (5)
Erythema	2 (<1)	11 (5)	3 (7)	2 (7)	16 (5)
Pneumonia	16 (7)	14 (6)	0	2 (7)	16 (5)
Abdominal pain upper	6 (3)	10 (5)	5 (11)	0	15 (5)
Hyperhidrosis	4 (2)	12 (6)	2 (5)	1 (3)	15 (5)
Hypotension	2 (<1)	13 (6)	2 (5)	0	15 (5)
Urinary tract infection	10 (4)	12 (6)	2 (5)	0	14 (5)

Table 17: Grade ≥3 adverse events in ≥1% of patients in the O+Chemo group, safety population

	OMB110911		OMB115991	OMB111774	Integrated
Preferred Term	CHL (N=227)	O+CHL (N=217)	O+B (N=44)	O+FC (N=30)	O+Chemo (N=291)
Any event, n (%)	**103 (45)**	**131 (60)**	**25 (57)**	**26 (87)**	**182 (63)**
Neutropenia	33 (15)	57 (26)	16 (36)	22 (73)	95 (33)
Leukopenia	1 (<1)	6 (3)	0	16 (53)	22 (8)
Thrombocytopenia	23 (10)	10 (5)	1 (2)	7 (23)	18 (6)
Anemia	12 (5)	11 (5)	1 (2)	5 (17)	17 (6)
Pneumonia	8 (4)	12 (6)	0	2 (7)	14 (5)
Febrile neutropenia	6 (3)	3 (1)	1 (2)	4 (13)	8 (3)
Rash	2 (<1)	6 (3)	2 (5)	0	8 (3)
Lymphopenia	0	2 (<1)	0	5 (17)	7 (2)
Sepsis	1 (<1)	4 (2)	0	2 (7)	6 (2)
Lower respiratory tract infection	2 (<1)	4 (2)	1 (2)	0	5 (2)
Respiratory failure	1 (<1)	5 (2)	0	0	5 (2)
Cellulitis	0	3 (1)	1 (2)	0	4 (1)
Dyspnea	2 (<1)	3 (1)	0	1 (3)	4 (1)
Hypertension	0	4 (2)	0	0	4 (1)
Neutrophil count decreased	5 (2)	3 (1)	0	1 (3)	4 (1)
Tumor lysis syndrome	0	3 (1)	1 (2)	0	4 (1)
Urticaria	1 (<1)	3 (1)	1 (2)	0	4 (1)
Chronic obstructive pulmonary disease	0	3 (1)	0	0	3 (1)
Dizziness	0	3 (1)	0	0	3 (1)
Fatigue	3 (1)	3 (1)	0	0	3 (1)
Hypersensitivity	1 (<1)	3 (1)	0	0	3 (1)
Infection	0	2 (<1)	0	1 (3)	3 (1)
Infusion related reaction	0	2 (<1)	1 (2)	0	3 (1)
Lung infection	0	2 (<1)	1 (2)	0	3 (1)
Pyrexia	5 (2)	3 (1)	0	0	3 (1)

Table 18: Treatment-related adverse events in ≥5% of patients in the O+Chemo group, safety population

	OMB110911		OMB115991	OMB111774	Integrated
Preferred Term	CHL (N=227)	O+CHL (N=217)	O+B (N=44)	O+FC (N=30)	O+Chemo (N=291)
Any event, n (%)	**148 (65)**	**182 (84)**	**42 (95)**	**30 (100)**	**254 (87)**
Neutropenia	37 (16)	56 (26)	21 (48)	23 (77)	100 (34)
Nausea	48 (21)	35 (16)	16 (36)	12 (40)	63 (22)
Rash	9 (4)	38 (18)	10 (23)	7 (23)	55 (19)
Thrombocytopenia	48 (21)	27 (12)	7 (16)	11 (37)	45 (15)
Fatigue	21 (9)	27 (12)	6 (14)	4 (13)	37 (13)
Pyrexia	5 (2)	22 (10)	7 (16)	3 (10)	32 (11)
Leukopenia	4 (2)	14 (6)	2 (5)	13 (43)	29 (10)
Urticaria	2 (<1)	21 (10)	6 (14)	2 (7)	29 (10)
Vomiting	17 (7)	18 (8)	4 (9)	5 (17)	27 (9)
Chills	0	15 (7)	4 (9)	4 (13)	23 (8)
Infusion related reaction	0	20 (9)	3 (7)	0	23 (8)
Anemia	24 (11)	13 (6)	5 (11)	3 (10)	21 (7)
Pruritus	5 (2)	15 (7)	3 (7)	1 (3)	19 (7)
Dyspnea	2 (<1)	14 (6)	2 (5)	2 (7)	18 (6)
Headache	1 (<1)	9 (4)	5 (11)	2 (7)	16 (5)
Diarrhea	12 (5)	12 (6)	2 (5)	0	14 (5)

Adverse events of special interest (AESI)

Neutropenia

In the pivotal trial 32% in the O+CHL and 25% in the CHL group had an AE associated with decreased neutrophil count, with neutropenia reported as the most common AE. Of the patients with an AE associated with decreased neutrophil count, the majority (29% in the O+CHL and 19% in the CHL group) had a ≥Grade 3 AE. There was also an imbalance in prolonged neutropenia (11% O+CHL vs. 8% CHL) and late-onset neutropenia (4% O+CHL vs. 1% CHL). However, the incidences of febrile neutropenia ≥Grade 3 (1% O+CHL vs. 3% CHL) and neutropenic sepsis (<1% O+CHL vs. 2% CHL) were low.

In the supportive studies the incidence of neutropenia AEs and SAEs was highest in the treatment group receiving the more myelosuppressive O+FC regimen where febrile neutropenia ≥Grade 3 occurred in 13% in the O+FC group. However, there were no incidences of neutropenic sepsis in the supportive studies.

Infections

In the pivotal trial the overall occurrence of any infection was quite similar as for the whole O+Chemo population. In the O+CHL arm and CHL arm any infection occurred in approximately 50% of the patients. Only lower respiratory tract infections occurred more frequently in the O+CHL arm (mainly caused by imbalance in bronchitis: 6% vs. 4% CHL). Infections grade ≥3 were balanced between treatment arms (15% vs. 14%). However, data could be affected by the fact that there was a higher frequency of prophylactic anti-microbial agent treatment in the O+CHL arm compared with CHL alone. Acyclovir was the most common (26% O+CHL vs. 11% CHL).

Infusion reactions

In total, 146 of 217 subjects (67%) in the pivotal study experienced infusion reactions (commonly rash/nausea/urticarial/pyrexia) at any infusion (56% with first infusion). This is higher than frequencies reported in the pivotal study Hx CD20 406 investigating ofatumumab monotherapy in refractory CLL patients (43% with first infusion). However, the reactions primarily occurred during Cycles 1 and 2 and were considered mild to moderate in severity. There were 3% infusion-related SAEs, of these 2 lead to discontinuation of study treatment.

Two anaphylactic reactions and no fatal SAEs due to infusion reactions were registered in the whole O+Chemo group.

Cardiovascular events

In the pivotal study, cardiovascular events were reported in a higher proportion of patients in the O+CHL arm (9% vs. 6% CHL). SAE's were also more frequently reported (6% vs. 3%). The frequency of fatal cardiac SAE's was also higher with O+CHL combination treatment: 2% (n=4) vs. <1% (n=2) in the CHL arm. In the O+Chemo treatment group cardiac disorder AEs were reported for 21 patients, which included 20 patients in the O+CHL group and 1 patient treated with O+B. The most common cardiac AE in the O+Chemo and O+CHL group was tachycardia (2% O+CHL, <1% CHL); all other cardiac events (palpitations, atrial fibrillation, cardiac failure, myocardial ischemia, pericarditis etc.) occurred in <1% of subjects.

In the pivotal study, overall vascular disorders were also reported more frequently in the O+CHL arm (20% vs. 6% CHL). Hypertension, hypotension and flushing were the most frequent events reported as vascular disorders.

Secondary malignancies/neoplasms

Secondary malignancies/neoplasms occurred in 10 patients in the O+Chemo group: 7 in the O+CHL group and 3 in the O+FC group. In the pivotal study the incidence was similar in the comparator arm (4% in each arm), indicating that there was no new safety signal with ofatumumab treatment. The reported neoplasms were all of different types. The majority of these events occurred more than 60 days after the last dose of study treatment and were considered not related to study treatment.

Other AESI

The infrequent AESI's associated with ofatumumab treatment: tumour lysis syndrome, progressive multifocal leukoencephalopathy, reactivation of Hepatitis B and small bowel obstruction, did not show new safety signals.

Serious adverse event / deaths / other significant events

Serious adverse events (SAE)

Pivotal trial

In the O+CHL arm, more patients experienced a SAE compared with the CHl arm (39% vs. 31%), although the proportion of treatment related SAEs was almost similar (15% vs. 13%, Table 15). The only SAE occurring ≥2% frequent in the O+CHL arm was pyrexia (4% vs. <1%). With 1-2% differences between treatment arms occurred lower respiratory tract infection (2% vs. <1%), respiratory failure (2% vs. <1%) and pneumonia (6% vs. 5%). Neutropenia was the only treatment related SAE occurring ≥2% frequent in the O+CHL arm (3% vs. 1%). All other treatment related SAEs occurred in relative similar percentages between treatment arms.

Table 19: Serious treatment-related adverse events occurring in 2% or more of patients

	OMB110911		OMB115991	OMB111774	Integrated
Preferred Term	CHL (N=227)	O+CHL (N=217)	O+B (N=44)	O+FC (N=30)	O+Chemo (N=291)
Any event, n (%)	**30 (13)**	**32 (15)**	**14 (32)**	**20 (67)**	**66 (23)**
Neutropenia	3 (1)	6 (3)	2 (5)	15 (50)	23 (8)
Febrile neutropenia	4 (2)	4 (2)	1 (2)	3 (10)	8 (3)
Leukopenia	0	1 (<1)	0	6 (20)	7 (2)
Pneumonia	4 (2)	5 (2)	0	0	5 (2)

Supportive trials

In the O+Chemo group, 42% of patients had at least 1 SAE, this higher frequency compared with the pivotal study primarily reflects a large increase in SAEs in the O+FC group (77%). Neutropenia was the most frequent SAE (53%) causing this increase. Similar to the listing of AEs, there were more SAEs in the O+FC group (especially high percentages of neutropenia, leukopenia, thrombocytopenia, and febrile neutropenia) compared with O+B or O+CHL. Looking at serious treatment related events occurring in 2% or more of patients, the incidences were much higher in the supportive trials (32% O+B, 67% O+FC) compared to the pivotal trial (13% CHL, 15% O+CHL).

Deaths

Pivotal trial

In total, 34 patients (16%) in the O+CHL arm and 40 (18%) patients in the CHL arm had died in the pivotal trial. Most patients died due to other causes than disease under study (progression). Eight deaths in the O+ CHL arm and 7 in the CHL arm occurred on treatment or within 60 days of last dose. Of these 3 deaths in the O+ CHL arm and 2 in the CHL arm were considered treatment related

(Table 16). Most deaths occurred >60 days after the last dose of study medication, a time at which cases are significantly confounded by subsequent chemotherapy and concomitant medical conditions.

Table 20: Deaths, safety population

	OMB110911		OMB115991	OMB111774	Integrated
	CHL (N=227)	O+CHL (N=217)	O+B (N=44)	O+FC (N=30)	O+Chemo (N=291)
Subject Status, n (%)					
Dead	40 (18)	34 (16)	0	3[a] (10)	37[a] (13)
Alive at last contact, follow-up ended	31 (14)	22 (10)	0	27 (90)	49 (17)
Alive at last contact, follow-up ongoing	156 (69)	161 (74)	44 (100)	0	205 (70)
Primary Cause of Death[b], n (%)					
Disease under Study	17 (7)	9 (4)	0	0[b]	9 (3)
Other[b]	23[c] (10)	25[c] (12)	0	3 (10)[b]	28[b,c] (10)
Time to Death, n (%)					
On treatment[d]	5 (2)	5 (2)	0	1 (3)	6 (2)
≤60 Days after last dose	2 (<1)	3 (1)	0	0	3 (1)
>60 Days after last dose	33 (15)	26 (12)	0	2 (7)	28 (10)

In total there were more fatal SAEs in the O+CHL arm (11%) than in the CHL arm (6%), however ≤1% was considered related to study treatment. The differences in fatal SAE incidence occurred more during the follow-up period. Overall, the breakdown of events by SOC was similar between arms, with the exception of the cardiac disorders (n=4 vs. n=2) and respiratory disorders (n=4 vs. n=0) SOCs, for which the incidence was higher in the O+CHL arm than the CHL arm.

Supportive trials

Most patients in the supportive trials were still alive (follow up in the O+B arm was still on-going for all patients) only 1 patient had died on treatment (O+FC group). This was due to a fatal SAE of dyspnoea.

Laboratory findings

In the pivotal trial the incidence of laboratory abnormalities of decreased neutrophils ≥ grade 3 occurred more often in the O+CHL arm (33%) compared with the CHL arm (25%). Decreased platelet count occurred more often in the CHL arm (22% vs. 12% O+CHL). As discussed previously, highest frequencies in the O+Chemo group were observed in the O+FC group (83% decreased neutrophils, 50% decreased platelets ≥ grade 3) . Decreased hemoglobin levels ≥ grade 3 were only observed in a few patients of the pivotal study (<1% O+CHL vs. 1% CHL).

In the *pivotal trial* all grades of laboratory parameter ALT (33% vs. 23%), AST (24% vs. 18%), Alkaline Phosphatase (24% vs. 17%) occurred more often in the O+CHL arm. However, Grade 3-4 events generally occurred in ≤1%. Glucose elevations also occurred more often in the O+CHL arm (85% vs. 80%), but increased glucose levels grade 3 were observed in only 7% of O+CHL treated patients (similar in CHL arm: 6%). Similar percentages of elevated laboratory parameters were reported in the O+Chemo group (most pronounced increase in O+FC treated patients). In the O+B and O+FC groups, less patients experienced high glucose levels and more patients had increased bilirubin levels.

No subjects with moderate (10-20 mL/min) or severe renal failure (<10 mL/min) were enrolled in study OMB110911 or any of the other studies. The changes in creatinine clearance as a marker for

renal function over time for all subjects and for subjects with mild renal impairment (20-50 mL/min) are presented in Table 21.

Table 21: Change in creatinine clearance from baseline

Median change from baseline [mL/min]	CHL	O+CHL	O+B	O+F	O+Alk	O+Chemo
All subjects	**(n=227)**	**(n=217)**	**(n=44)**	**(n=30)**	**(n=261)**	**(n=291)**
CYCLE 2:DAY 1	-1.0	-6.0	-7.1	-6.2	-6.6	-6.2
CYCLE 3:DAY 1	-3.0	-6.0	-12.4	-8.0	-7.0	-7.0
CYCLE 4:DAY 1	-7.0	-7.5	-11.5	-9.7	-8.0	-8.0
CYCLE 5:DAY 1	-7.0	-8.0	-8.8	-8.8	-8.4	-8.8
CYCLE 6:DAY 1	-8.0	-8.0	-7.1	-6.2	-8.0	-8.0
CYCLE 7:DAY 1	-7.0	-6.0	nd	nd	-6.0	-6.0
CYCLE 8:DAY 1	-7.0	-6.0	nd	nd	-6.0	-6.0
CYCLE 9:DAY 1	-6.0	-8.0	nd	nd	-8.0	-8.0
1MFU	-6.0	-7.0	nd	-9.7	-7.0	-7.0
3MFU	-6.0	-7.0	-2.2	-6.2	-6.0	-6.0
6MFU	-2.0	-4.0	-4.9	-10.2	-4.0	-5.0
9MFU	-2.0	-2.0	-5.3	-6.2	-2.5	-3.0
12MFU	0.0	-4.0	nd	-6.2	-4.0	-4.7
15MFU	0.0	-2.0	nd	-5.8	-2.0	-3.0
18MFU	0.5	0.0	nd	-4.4[a]	0.0	0.0
Subjects with mild renal impairment (20-50 ml/min)	**(N=40)**	**(N=31)**	**(N=2)**	**(N=0)**	**(N=33)**	**(N=33)**
CYCLE 2:DAY 1	-4.5	-14.5	-12.8	n/a	-13.6	-13.6
CYCLE 3:DAY 1	-9.0	-14.0	-14.6	n/a	-14.0	-14.0
CYCLE 4:DAY 1	-14.0	-13.0	-8.0	n/a	-12.5	-12.5
CYCLE 5:DAY 1	-17.5	-15.0	-13.7	n/a	-15.0	-15.0
CYCLE 6:DAY 1	-11.0	-16.0	-14.1	n/a	-15.0	-15.0
CYCLE 7:DAY 1	-8.0	-16.0	n/a	n/a	-16.0	-16.0
CYCLE 8:DAY 1	-10.0	-18.5	n/a	n/a	-18.5	-18.5
CYCLE 9:DAY 1	-18.0	-15.0	n/a	n/a	-15.0	-15.0
1MFU	-8.0	-13.5	nd	n/a	-13.5	-13.5
3MFU	-11.0	-12.0	0.0	n/a	-12.0	-12.0
6MFU	-6.0	-8.0	-1.8	n/a	-7.5	-7.5
9MFU	-3.0	-9.0	nd	n/a	-9.0	-9.0
12MFU	0.0	-10.0	nd	n/a	-10.0	-10.0
15MFU	5.0	-6.0	nd	n/a	-6.0	-6.0
18MFU	3.0	-7.0	nd	n/a	-7.0	-7.0

Source data: m1 Response to Questions_Additional: Table 369.0401, Table 369.0502
a. Includes 18M FU and end of study data and was not included in O+Chemo analysis
ND = not done (no subject data available), n/a= not applicable

Immunological events

In all post-baseline visits of all subjects with available data the median IgG level was 8.025 g/L. The percent of subjects with post-baseline IgG levels below the median were quite similar in all O+Chemo groups (59% O+CHL, 55% O+B, 63% O+FC, and 59% O+Chemo) and was also quite similar in the O+CHL (59%) and CHL (51%) groups. In the pivotal trial HAHA data were available from 202 subjects in the O+CHL arm for any time point post-treatment, at the time of data cut-off. No ofatumumab-induced HAHA were detected in this study.

Five subjects (2%) in the O+Chemo group had AEs of hemolytic anemia/autoimmune hemolytic anemia (AIHA): 4 in the O+CHL group and 1 in the O+FC group. Six subjects in the CHL group had AIHA AEs. Of these patients in the CHL group, 5 were SAE's occurring up to 60 days after last dose.

Of the 5 subjects with AIHA events in the O+Chemo group, 2 subjects in the O+CHL group had 3 SAEs. All of these events occurred more than 60 days after the last study treatment and were not considered related to study treatment. One subject had a fatal SAE of AIHA.

Safety in special populations

Age

Pivotal trial

In the pivotal trial the majority of patients were over 65 years of age (O+CHL: 148 patients, CHL:156 patients) and 26% of patients were 75 years or older (O+CHL: 53 patients, CHL: 64). Although the number of treatment related AEs, AEs ≥ grade 3 and treatment related SAEs increased with age in the O+CHL arm, similar or higher increases were observed in the CHL treatment arm. The type of AEs were mainly similar in patients over and under 65 years of age.

Supportive trials

In the O+B study, any adverse event occurred in 96% (n=23/24 patients) of patients under 65 years and in 100% (n=20/20 patients) of patients over 65 years. In the O+FC trial any adverse event occurred in 100% of patients both over and under age 65, but only 7 patients were over 65 years.

The incidence of ≥Grade 3 AEs in patients of the O+Chemo group increased in the age subgroups; 50% in the <65 years, 71% in the ≥65 years and 79% ≥75 years of age. The types of events were similar in both groups. In both the O+Chemo and CHL arm, most patients died in the ≥65 years of age subgroup: 17% of patients ≥65 vs. 6% of patients <65 years of age in the O+Chemo arm; and 21% vs. 10% in the CHL arm.

Age and comorbidities

Table 22: Adverse event overview by age and comorbidity

	CHL (n=227)	O+CHL (n=217)	O+B (n=44)	O+F (n=30)	O+Alk (n=261)	O+Chemo (n=291)
Age <65 and <2 comorbidities	N=41	N=38	N=7	N=10	N=45	N=55
Any AE, n (%)	31 (76%)	33 (87%)	7 (100%)	10 (100%)	40 (89%)	50 (91%)
AE related to treatment, n (%)	16 (39%)	27(71%)	7 (100%)	10 (100%)	34 (76%)	44 (80%)
AE ≥Grade 3	8 (20%)	13 (34%)	3 (43%)	8 (80%)	16 (36%)	24 (44%)
Any SAE, n (%)	3 (7%)	9 (24%)	2 (29%)	7 (70%)	11 (24%)	18 (33%)
Age <65 and ≥2 comorbidities	N=30	N=31	N=17	N=13	N=48	N=61
Any AE, n (%)	27 (90%)	31 (100%)	16 (94%)	13 (100%)	47 (98%)	60 (98%)
AE related to treatment, n (%)	21 (70%)	26 (84%)	16 (94%)	13 (100%)	42 (88%)	55 (90%)
AE ≥Grade 3	12 (40%)	15 (48%)	8 (47%)	12 (92%)	23 (48%)	35 (57%)
Any SAE, n (%)	7 (23%)	7 (23%)	5 (29%)	11 (85%)	12 (25%)	23 (38%)
Age ≥65 and <2 comorbidities	N=27	N=19	N=1	N=0	N=20	N=20
Any AE, n (%)	24 (89%)	19 (100%)	1 (100%)	n/a	20 (100%)	20 (100%)
AE related to treatment, n (%)	24 (89%)	19 (100%)	1 (100%)	n/a	19 (95%)	19 (95%)
AE ≥Grade 3	15 (56%)	13 (68%)	0	n/a	13 (65%)	13 (65%)
Any SAE, n (%)	12 (44%)	10 (53%)	0	n/a	10 (50%)	10 (50%)
Age ≥65 and ≥2 comorbidities	N=129	N=129	N=19	N=7	N=148	N=155
Any AE, n (%)	121 (94%)	123 (95%)	19 (100%)	7 (100%)	142 (96%)	149 (96%)
AE related to treatment, n (%)	95 (74%)	111 (86%)	18 (95%)	7 (100%)	129 (87%)	136 (88%)
AE ≥Grade 3	68 (53%)	90 (70%)	14 (74%)	7 (100%)	104 (70%)	111 (72%)
Any SAE, n (%)	49 (38%)	58 (45%)	8 (42%)	6 (86%)	66 (45%)	72 (46%)
Age <70 and <2 comorbidities	N=51	N=46	N=7	N=10	N=53	N=63
Any AE, n (%)	41 (80%)	41 (89%)	7 (100%)	10 (100%)	48 (91%)	58 (92%)
AE related to treatment, n (%)	22 (43%)	34 (74%)	7 (100%)	10 (100%)	41 (77%)	51 (81%)
AE ≥Grade 3	14 (27%)	16 (35%)	3 (43%)	8 (80%)	19 (36%)	27 (43%)
Any SAE, n (%)	7 (14%)	10 (22%)	2 (29%)	7 (70%)	12 (23%)	19 (30%)

	CHL (n=227)	O+CHL (n=217)	O+B (n=44)	O+F (n=30)	O+Alk (n=261)	O+Chemo (n=291)
Age <70 and ≥2 comorbidities	N=58	N=70	N=24	N=17	N=94	N=111
Any AE, n (%)	51 (88%)	69 (99%)	23 (96%)	17 (100%)	92 (98%)	109 (98%)
AE related to treatment, n (%)	38 (66%)	60 (86%)	22 (92%)	17 (100%)	82 (87%)	99 (89%)
AE ≥Grade 3	26 (45%)	39 (56%)	13 (54%)	16 (94%)	52 (55%)	68 (61%)
Any SAE, n (%)	15 (26%)	21 (30%)	9 (38%)	15 (88%)	30 (32%)	45 (41%)
Age ≥70 and <2 comorbidities	N=17	N=11	N=1	N=0	N=12	N=12
Any AE, n (%)	14 (82%)	11 (100%)	1 (100%)	n/a	12 (100%)	12 (100%)
AE related to treatment, n (%)	10 (59%)	11 (100%)	1 (100%)	n/a	12 (100%)	12 (100%)
AE ≥Grade 3	9 (53%)	10 (91%)	0	n/a	10 (83%)	10 (83%)
Any SAE, n (%)	8 (47%)	9 (82%)	0	n/a	9 (75%)	9 (75%)
Age ≥70 and ≥2 comorbidities	N=101	N=90	N=12	N=3	N=102	N=105
Any AE, n (%)	97 (96%)	85 (94%)	12 (100%)	3 (100%)	97 (95%)	100 (95%)
AE related to treatment, n (%)	78 (77%)	77 (86%)	12 (100%)	3 (100%)	89 (87%)	92 (88%)
AE ≥Grade 3	54 (53%)	66 (73%)	9 (75%)	3 (100%)	75 (74%)	78 (74%)
Any SAE, n (%)	41 (41%)	44 (49%)	4 (33%)	2 (67%)	48 (47%)	50 (48%)
Age <75 and <2 comorbidities	N=62	N=51	N=7	N=10	N=58	N=68
Any AE, n (%)	51 (82%)	46 (90%)	7 (100%)	10 (100%)	53 (91%)	63 (93%)
AE related to treatment, n (%)	29 (47%)	39 (76%)	7 (100%)	10 (100%)	46 (79%)	56 (82%)
AE ≥Grade 3	21 (34%)	20 (39%)	3 (43%)	8 (80%)	23 (40%)	31 (46%)
Any SAE, n (%)	13 (21%)	13 (25%)	2 (29%)	7 (70%)	15 (26%)	22 (32%)
Age <75 and ≥2 comorbidities	N=101	N=113	N=32	N=20	N=145	N=165
Any AE, n (%)	92 (91%)	110 (97%)	31 (97%)	20 (100%)	141 (97%)	161 (98%)
AE related to treatment, n (%)	71 (70%)	98 (87%)	30 (94%)	20 (100%)	128 (88%)	148 (90%)
AE ≥Grade 3	47 (47%)	67 (59%)	20 (63%)	19 (95%)	87 (60%)	106 (64%)
Any SAE, n (%)	31 (31%)	37 (33%)	11 (34%)	17 (85%)	48 (33%)	65 (39%)
Age ≥75 and <2 comorbidities	N=6	N=6	N=1	N=0	N=7	N=7
Any AE, n (%)	4 (67%)	6 (100%)	1 (100%)	n/a	7 (100%)	7 (100%)
AE related to treatment, n (%)	3 (50%)	6 (100%)	1 (100%)	n/a	7 (100%)	7 (100%)
AE ≥Grade 3	2 (33%)	6 (100%)	0	n/a	6 (86%)	6 (86%)
Any SAE, n (%)	2 (33%)	6 (100%)	0	n/a	6 (86%)	6 (86%)

	CHL (n=227)	O+CHL (n=217)	O+B (n=44)	O+F (n=30)	O+Alk (n=261)	O+Chemo (n=291)
Age ≥75 and ≥2 comorbidities	N=58	N=47	N=4	N=0	N=51	N=51
Any AE, n (%)	56 (97%)	44 (94%)	4 (100%)	n/a	48 (94%)	48 (94%)
AE related to treatment, n (%)	45 (78%)	39 (83%)	4 (100%)	n/a	43 (84%)	43 (84%)
AE ≥Grade 3	33 (57%)	38 (81%)	2 (50%)	n/a	40 (78%)	40 (78%)
Any SAE, n (%)	25 (43%)	28 (60%)	2 (50%)	n/a	30 (59%)	30 (59%)

Data Source: m1 Response to Questions_Additional: Table 369.0101, Table 369.0201, Table 369.0301
O+ALK is the integrated analysis of subjects who received O+CHL or O+B; O+ALK is the integrated analysis of subjects who received O+CHL, O+B or O+FC

Gender and race

In the O+Chemo group, 193 patients (66%) were male and 98 patients (34%) were female. The safety profile was quite similar between male and female patients in all safety populations. Due to the small number of patients in the Non-white category (9%), no meaningful conclusions regarding safety based on race could be drawn.

Safety related to drug-drug interactions and other interactions

Please refer to the clinical pharmacology section.

Discontinuation due to adverse events

Similar proportions of patients discontinued treatment due to AEs in both arms of the pivotal study (13-14%). In addition 7 patients in the O+CHL arm discontinued due to death following an SAE. The two most common adverse event leading to discontinuation of study treatment in both arms were neutropenia (O+CHL: n=7 and CHL: n=3) and thrombocytopenia (O+CHL: n=3 and CHL: n=7). Compared to the high numbers of neutropenia AE's in all groups, relatively few patients have to discontinue treatment due to this.

The frequency of discontinuations due to AE's was higher in the O+FC group (27%), and lower in the O+B group (7%). Also in these groups the primary cause was neutropenia/febrile neutropenia.

Post marketing experience

As of March/April 2013, the cumulative post-marketing exposure to ofatumumab was estimated to be approximately 4448 patients and the MAH had by the time received a total of 381 reports including 1017 AEs (serious and non-serious).

The ten most common of the reported AE's were; neutropenia (3,3%), pyrexia (2,9%), dyspnoea (2,6%), infusion related reaction (2,5%), rash (2,5%), disease progression (2,0%), urticaria (1,8%), pneumonia (1,6%), diarrhoea (1,4%), ineffective drug (1,4%).

Twenty-five of the 381 reports contained the preferred term 'infusion reaction.' In addition approximately 25% of the remaining reports were descriptive of infusion reactions. The majority of the reports describing infusion reactions were non-serious. None of the reports described a fatal infusion reaction. Eighty-four reports contained events descriptive of cytopenias, the most common being neutropenia.

Seventy-nine reports contained 107 terms within the Infections and Infestations System Organ Class (SOC). Approximately one-third of the total infectious events were related to pneumonia. There were 3 reports of HBV infection or reactivation. There were 16 reports including 21 cardiac events, all

serious. Four of these cases involved cardiac arrest. There were five cases of severe mucocutaneous reactions. Furthermore one case of tumour lysis syndrome (resolved), 5 cases of progressive multifocal leukoencephalopathy (PML) and one case of small bowel obstruction (resolved).

Fifty-three of the reported cases were fatal. The cause of death in these cases were; infectious process (22 reports), disease progression (15 reports), various (8 reports including several SOC's), unknown (8 reports).

The post-marketing data did not seem to reveal any new safety signals.

2.5.1. Discussion on clinical safety

Safety data for the evaluation of ofatumumab in the treatment of chronic lymphocytic leukemia (CLL) is derived from 518 patients in total. Overall 291 patients were exposed to ofatumumab in combination with chemotherapy (O-Chemo group). Of these, 217 patients received O+ chlorambucil (O+CHL; pivotal trial), 44 patients received O+bendamustine (O+B), and 30 patients received O+fludarabine and cyclophosphamide (O+FC). Safety data were provided for each of the three trials separately, as well as in two different integrated analyses: 1) all patients in the three trials who had received ofatumumab in combination with a chemotherapy regimen (O+Chemo, n=291), 2) only fludarabine inappropriate patients from trial OMB110911/OMB115991 (O+ALK, n=261). However, limited data were presented from the O+ALK group.

The integrated analyses (O+Chemo) with both data from F-inappropriate, as well as the generally more fit and younger F-appropriate patients is not considered very helpful in evaluating the actual frequencies of adverse events in the targeted patient population. Therefore, the emphasis of this discussion will be on the pivotal trial comparing O+CHL with CHL monotherapy.

The majority of the patients experienced AEs. Although in the pivotal study a 41% increase in AEs leading to dose interruption was observed, it is reassuring that permanent discontinuation due to AEs occurred in similar low proportions in the O+CHL and CHL arms (13-14%). The median chemotherapy dose was also similar in both arms, indicating that combination treatment with ofatumumab did not cause decreased chemotherapy exposure. Although patients received generally the planned dose of ofatumumab in each cycle, only few patients continued treatment after 6 cycles (n=70, 32%), and even less after 9 cycles (n=8, 4%). The CHMP questioned whether the proposed maximum treatment of 12 months (similar to study protocol) should be adjusted in the SmPC, since limited safety information of such long treatment duration is available. The MAH argued that CLL is a heterogeneous disease and physicians should be allowed to use clinical judgment in determining when a best response has been achieved. Best response being defined as a clinical response that could not improve with 3 additional cycles of treatment.

In addition, the safety data concerning any AE's and SAE's was further analysed showing that regardless of how many cycles are administered, the safety profile remained consistent. It can therefore be concluded that there is no evidence that administration of 9-12 cycles of ofatumumab is associated with increased toxicity.

The AEs reported were mainly representative of infusion reactions and events indicating myelosuppression, as observed previously with ofatumumab treatment. The overall most commonly reported AEs in the O+Chemo and O+CHL group were neutropenia, followed by nausea, rash and pyrexia. In the CHL group, thrombocytopenia was the most frequent AE, followed by nausea, neutropenia and fatigue. The 19% increase in treatment related AEs, and 15% increase in grade ≥3 AEs with O+CHL combination treatment compared with CHL alone could be of concern in this indolent

disease with relative long overall survival even without treatment. However, imbalances were mostly caused by neutropenia and infusion related reactions, which were considered manageable.

The imbalance in high grade neutropenia (26% O+CHL vs. 15% CHL) did not lead to an imbalance in ≥ grade 3 febrile neutropenia (1% O+CHL vs. 3% CHL) or neutropenic sepsis (<1% vs. 2%), which is reassuring. Although any serious infection occurred more frequently in the O+CHL arm (16% vs. 13%), the number of serious infections related to study treatment was lower compared to the CHL arm. As known with ofatumumab treatment, small imbalances have been observed in lower respiratory tract infection, pneumonia and sepsis. The more frequent use of prophylactic anti-microbial agents in the O+CHL arm (64% vs. 52% CHL) may have decreased the occurrence of infection-related AEs in this arm, although the distinction between prophylactic use of antimicrobials and concomitant medication should be made. The number of subjects who received one or more antimicrobial agents (includes antibiotics, antifungals and antivirals) was 32% in the O+CHL arm and 18% in the CHL arm. The two most common prophylactic regimens, acyclovir and trimethaprim/sulfamethoxazole (TMP/SMX), accounted for the difference between the two arms. Overall, acyclovir and TMP/SMX prophylaxis was each administered to approximately 20% of subjects in the O+CHL arm; thus, a majority of O+CHL arms did not receive prophylaxis. Interpretation of safety data could furthermore be hampered by the imbalance in concomitant steroid use (only patients in the O+CHL arm received steroids prior to each infusion). This could for example be reflected by the higher frequency of nausea reported in the CHL arm.

It is acknowledged that infusion-related AEs primarily occurred during Cycles 1 and 2, and were considered mild to moderate in severity. Furthermore it is reassuring that no fatal serious reactions occurred and only 3% of patients in the pivotal trial experienced serious infusion reactions leading to discontinuation of study treatment.

AEs were most common in the O+FC group (100%), followed by the O+B group (98%), the O+CHL group (95%) and 89% in the CHL group. AEs reported with O+B treatment were generally similar with the pivotal trial. The type of AEs in the O+FC group (more grade ≥3 leukopenia, thrombocytopenia, anaemia, febrile neutropenia, and lymphopenia compared with O+B or O+CHL) reflect the more myelosuppressive nature of FC.

Study OMB115991 (n=44) indicates that safety data of the combination ofatumumab + bendamustine could indicate a worse safety profile (11% increase in treatment related AEs and 13% increase in AEs leading to dose reduction) compared with the combination ofatumumab + chlorambucil. However this is in line with the higher toxicity of bendamustine as compared to chlorambucil and likely attributed to the difference in neutropenia between O+B and O+CHL resulting from bendamustine.

Although more patients experienced a SAE with O+CHL treatment compared with CHL monotherapy (39% vs. 31%), the type of AEs causing this difference is diverse and only pyrexia occurred ≥2% more frequent in the O+CHL arm. It is reassuring that the large imbalances in neutropenia and infusion related (rash, nausea) AEs did not lead to the same imbalances in reported SAEs. In addition, it is acknowledged that treatment related SAEs were reported in almost similar proportions in both treatment arms.

The overall mortality rate was similar in both treatment arms of the pivotal study. Most deaths occurred >60 days after the last dose of study medication, a time at which cases are significantly confounded by subsequent chemotherapy and concomitant medical conditions. The increase in fatal SAEs (mostly cardiac or respiratory disorders) in the O+CHL arm (11% vs. 6% CHL) could be of concern. However, all but one of these events (cardiac failure, O+CHL arm), including the three infectious respiratory disorders in the O+CHL arm were not considered treatment related.

The overall safety profile did not indicate new safety signals in the targeted patient population of F-inappropriate CLL patients. However, a substantial part of these patients is older, or does have multiple comorbidities and/or decreased renal function. Although the number of events increased with age in the O+CHL arm, similar increases have been observed in the CHL monotherapy arm. The MAH presented an analysis of the data where subjects were categorised by age group (cut-off at 65, 70 and 75 years) and comorbidity, with each subject presented in one category without overlap. In both the O+Chemo (n=291) and O+Alk (n=261) groups, a majority of subjects were in the ≥65 & ≥2 comorbidities category and one fifth of all subjects were in the ≥75 and ≥2 comorbidities category. In both the O+Chemo and O+Alk group, all 12 categories had a similar percentage (89-100%) of subjects experiencing an AE. As expected, the increased incidences of AEs ≥ grade 3 and SAEs seems to be driven by higher age and number of comorbidities. The higher incidence of AEs ≥ grade 3 and SAEs in subjects above the age cut-offs is partially due to a higher number of fatal, predominantly non-treatment related SAEs (12%, 15%, 18%) and partially due to hospitalisation for events grade <3. It is uncertain if the provided safety profile is also representative for older patients with multiple comorbidities and decreased renal function.

The observed decrease in creatinine clearance appears to be driven by the backbone of chemotherapy and that the addition of ofatumumab did not seem to cause additional deterioration of the renal function. It is noted that creatinine clearance returned to baseline during the follow-up period albeit that this recovery was only partial for subjects with mild baseline renal impairment in the O+CHL group.

2.5.2. Conclusions on the clinical safety

Combination treatment with chlorambucil did not indicate new safety signals in the targeted patient population of F-inappropriate CLL patients compared with already approved ofatumumab monotherapy in refractory CLL patients. A large part of the targeted patient population is older and has multiple comorbidities and/or reduced renal function. Although data from the supportive study OMB115991 could indicate a worst safety profile of O+B than O+CHL, this is in line with the higher toxicity of bendamustine.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged. Arzerra has been granted conditional marketing authorisation and as a result, PSURs should continue to be submitted 6-monthly

2.6. Risk management plan

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

2.6.1. PRAC advice

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 23: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infusion reactions including cytokine release syndrome • Tumour lysis syndrome (TLS) • Bowel obstruction

Summary of safety concerns	
	• Cardiovascular • Hepatitis B virus (HBV) infection and reactivation
Important potential risks	• Cytopenias • Infections • Progressive Multifocal Leukoencephalopathy (PML) • Severe mucocutaneous reactions • Effects on Immunisations, Including Interactions with Live Vaccines • Immunogenicity • Effect of Concomitant HMG-CoA Reductase Inhibitors on Ofatumumab Response • Change in safety profile following switch to acetate buffer formulation
Missing information	• Limited data in pregnant and lactating females • Limited experience in patients with other relevant co-morbidities including cardiac disease, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric diseases. • Limited experience in the heterogeneous non-white patient population. • Limited data in patients with ECOG performance status 2.

Pharmacovigilance plans

Table 24: On-going and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
OMB114242: Phase III, open-label randomized (2:1) specific obligation study for the EU investigating the safety and efficacy of ofatumumab vs. physicians' choice of therapy in subjects with bulky fludarabine refractory CLL. Category 3, Clinical	Specific obligation study for the EU investigating the safety and efficacy of ofatumumab vs. physicians' choice of therapy in subjects with bulky fludarabine refractory CLL	Safety of ofatumumab vs. physicians' choice of therapy in subjects with bulky fludarabine refractory CLL	Ongoing	CSR for primary endpoint: Jul-14 (planned) End of study report: Oct-18 (planned) Due date: 31-Dec-14

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the updated data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 25: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Infusion reactions, including CRS	Text within Sections 4.4 and 4.8 of the SmPC	None proposed
TLS	Text within Sections 4.4 and 4.8 of the SmPC	None proposed
Small bowel obstruction	Text within Sections 4.4 and 4.8 of the SmPC and TFUQ	None proposed
Cardiovascular events	Text within Sections 4.4 and 4.8 of the SmPC	None proposed
HBV infection and reactivation	Text within Sections 4.4 and 4.8 of the SmPC.	None proposed
Cytopenias	Text within Section 4.4 of the SmPC	None proposed
Risk of infections	Text within Section 4.8 of the SmPC	None proposed
PML	Text within Section 4.4 of the SmPC and TFUQ	None proposed
Severe mucocutaneous reactions	Routine activity includes monitoring of all spontaneous and clinical trial reports to further characterize this potential risk.	None proposed
Effect on immunisations	Text within Section 4.4 of the SmPC	None proposed
Immunogenicity	Text within Section 5.1 of the SmPC	None proposed
Effect of HMG-Co-A Reductase Inhibitors on Ofatumumab Response	Routine activity includes monitoring of all spontaneous AE reports and clinical trial reports of lack of efficacy in patients receiving concomitant HMG-CoA reductase inhibitors with ofatumumab compared to reports in patients not receiving those agents.	None proposed
Changes in Safety Profile Following Switch to Acetate Buffer Formulation	Routine activity includes monitoring all spontaneous event reports and clinical trial reports to confirm no change in safety profile of ofatumumab between the acetate and citrate buffer.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Limited data in pregnant and lactating females	Text within Section 4.6 of the SmPC	None proposed
Limited experience in patients with other relevant co-morbidities including cardiac disease, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric diseases.	Routine activity includes ongoing evaluation of safety data from clinical trials and spontaneous data in patients with relevant comorbidities.	None proposed
Limited experience in the heterogeneous non-white patient population.	Routine activity includes ongoing evaluation of safety data from clinical trials and spontaneous data in this patient population.	No additional risk minimisation measures.
Limited experience in patients with ECOG performance status 2.	Routine activity includes ongoing evaluation of safety data from clinical trials in patients with ECOG2, as available.	No additional risk minimisation measures.

The CHMP endorsed this advice without changes.

2.7. User consultation

A justification for not performing a user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: Amendments proposed for the PL as a result of this submission are minimal and are considered not to require further consultation with target patient groups; the proposed PL remains consistent with previous user testing recommendations for the Arzerra approved PL.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study OMB110911 met its primary endpoint: patients who received O+CHL had a statistically significant improvement of 9.3 months in IRC-assessed PFS compared with patients who received CHL alone. The median PFS improved from 13.1 months in the CHL arm to 22.4 months in the O+CHL arm, with a HR of 0.57 (95% CI 0.45,0.72, stratified log-rank p<0.001). Although the investigator-based PFS analysis showed comparable results to the primary IRC based analysis, 25% of progressive diseases were diagnosed later by investigator than by the IRC (similar percentage in CHL arm). At the time of data cut-off in March 2013, 287 events (64%, progression or death) had occurred and the median follow up was approximately 29 months. PFS subgroup analysis was consistent with the overall population analysis and demonstrated a benefit with O+CHL regardless of gender, age, number of co-morbidities, disease stage or reason for fludarabine inappropriateness.

In the analysis of secondary endpoints, benefit of O+CHL compared with CHL alone was shown in terms of:

- Objective Response Rate (ORR): 13% improvement with ofatumumab, IRC-based assessment (69% CHL vs. 82% O+CHL). Complete Remission 1% vs. 14%.
- Duration of response: 9 months longer (13.2 vs. 22.1 months, p<0.001)
- Time to progression: 10 months improvement (13.6 vs. 23.1 months, p<0.001)
- Time to next therapy: 15 months improvement (24.7 vs. 39.8 months, p<0.001)
- Event free survival: 11 months improvement (10.7 vs. 21.9 months, p<0.001)
- Tumour response
    - Minimal residual disease (MRD): Twelve of 32 patients (38%) with IRC assessed CR or CRi in the O+CHL arm became MRD negative, compared to 8 patients (4%) in CHL arm.
    - Reduction in tumor size: The median reduction from baseline was 48% CHL vs. 68% O+CHL.
    - B cell response: <2% vs. >40% near complete B cell depletion in responders, median number of CLL cells/µL 1022 vs. 7.

The improvement in PFS could not (yet) be confirmed in terms of increased overall survival (OS), since the median OS was not reached (15% died). The addition of ofatumumab does not seem to have detrimental effects on OS. No statistically significant differences were observed in time to response or quality of life related endpoints.

The primary endpoint of supportive study OMB115991 showed an investigator based ORR of 95% (82% if based on CT scans by investigator) and 43% CR rate (27% investigator, CT based), supporting results of the pivotal study. The key secondary endpoints PFS, OS, duration of response, and time to next therapy were not yet mature (median follow up 14 months, no deaths, 1 PD).

Uncertainty in the knowledge about the beneficial effects

Objective radiological/laboratory responses did not seem to result in noticeable quality of life benefit to patients, compared with CHL treated patients. In general, presence of B symptoms as part of quality of life measurements could be expected to be a relatively easy method to assess clinically relevant benefit. However, the frequency of patients with B symptoms decreased in almost similar rates in both treatment arms. Global health and fatigue scales also showed generally similar improvements in both arms.

A protocol deviation in visit schedule and assessment procedures was recorded in a high percentage of all patients (66% and 50%, respectively). However the deviation types were similar across both treatment arms with any differences primarily driven by the different assessment requirements in the two treatment arms. Timing of the visit schedule deviations was similar across both arms and timing of the CT scan to confirm response was identical for CHL and O+CHL.

Furthermore, it is questioned if the selected ofatumumab dose in the pivotal trial is the most effective dose. In the pivotal study the selected dose was half of the approved dose in refractory CLL patients. However the decrease in B-cell counts from baseline was rapid in all subjects in the O+CHL arm, when compared to B-cell depletion with chlorambucil. B-cell depletion with 1000 mg O+CHL can be considered as rapid and extensive for the majority of subjects. It is not known whether a faster response could have been achieved with a higher dose, however data are not available and the current dose is considered acceptable.

Median OS was not reached due to too short follow-up (5 yr) in this indolent disease. The CHMP gave advice on 10 yr, but this has not been taken into account by the applicant. This weakens study results as median OS data would probably have been obtained after prolonged follow up.

Risks

Unfavourable effects

The reported events were mainly expected for a treatment regimen with a monoclonal antibody and the various chemotherapies. The overall AEs occurred in almost similar frequencies in both arms of the pivotal study (95% O+CHL vs. 89% CHL), but the frequency of treatment related AEs (84% vs. 65%) and AEs ≥ grade 3 (60% vs. 45%) were substantially higher in the O+CHL arm compared with CHL alone. The percentage of dose interruptions was also higher in the combination arm (69% vs. 28%). Dose reductions occurred in similar frequencies in both arms (17%).

Imbalances in treatment related AEs and AEs ≥ grade 3 in the pivotal study were primarily caused by an imbalance in neutropenia (26% vs. 16% treatment related), and in infusion-related AEs. Other treatment related AEs occurring ≥10% more frequent in the O+CHL arm compared with the CHL arm were rash (18% vs. 4%), and urticaria (10% vs. <1%). Between 5-10% more frequent in the O+CHL arm occurred: pyrexia, leukopenia, chills, infusion related reaction, pruritus and dyspnoea. In the CHL arm thrombocytopenia (21% vs. 12%), nausea (21% vs. 16%) and anaemia (11% vs. 6%) occurred ≥5% more frequent compared to the O+CHL arm.

Grade 3 or higher AEs occurring ≥2% more frequent in the O+CHL arm were neutropenia (26% vs. 15%), leukopenia (3% vs. <1%), pneumonia (6% vs. 4%), rash (3% vs. <1%), sepsis, lower respiratory tract infection and respiratory failure (the last three all 2% vs. <1%). In the CHL arm, thrombocytopenia (10% vs. 5%) and febrile neutropenia grade 3 or higher (3% vs. 1%) occurred ≥2% more frequent.

Of note, the type of AEs in the O+B group was similar, whereas the O+FC combination caused more frequent AEs related to myelosuppression.

In the pivotal study, 3% of patients experienced serious infusion reactions leading to discontinuation of treatment. Infusion reactions were common in the whole O+Chemo group, any event occurring in 69% of patients even though premedication with steroids was used. However the reactions were mainly manageable with less than 1% of these patients experiencing an anaphylactic reaction and no fatal infusion reactions.

Any serious infection occurred more frequently in the O+CHL arm (16% vs. 13%). The number of serious infections related to study treatment was however lower compared to the CHL arm. The number of patients with fatal serious infections and fatal serious infections related to study treatment was similar in both arms. Only lower respiratory tract infections occurred slightly more frequently in the O+CHL arm (mainly caused by imbalance in bronchitis: 6% vs. 4% CHL).

The most common cardiac AE in the O+CHL group was tachycardia (2% O+CHL, <1% CHL); all other cardiac events (palpitations, atrial fibrillation, cardiac failure, myocardial ischemia, pericarditis etc.) occurred in <1% of subjects. Tachycardia was also the most common cardiac AE in the O+Chemo group.

In the O+CHL and O+Chemo group, frequencies of (S)AEs increased with higher age to a similar extent as the CHL arm of the pivotal study.

Serious adverse events were reported in 39% in the O+CHL group and 31% in the CHL group. Although in the pivotal trial more patients experienced a SAE with O+CHL treatment compared with CHL monotherapy (39% vs. 31%), the type of AEs causing this difference was diverse and only pyrexia occurred ≥2% more frequent in the O+CHL arm. In the O+FC group and O+B groups, SAEs were reported in 77% and 34% of patients, respectively.

The overall mortality rate was similar in both treatment arms of the pivotal study (16% O+CHL vs. 18% CHL; 5% treatment related in both arms). Most deaths occurred >60 days after the last dose of study medication. There was an increase in fatal SAEs in the O+CHL arm (11% vs. 6% CHL). All but one of these events (cardiac failure, O+CHL arm), including the three infectious respiratory disorders in the O+CHL arm were not considered treatment related. There were 3 reported deaths (10%) in the O+FC group and 0 deaths in the O+B group.

Uncertainty in the knowledge about the unfavourable effects

The increased number of treatment related AEs (95% vs. 84% O+CHL) and AEs leading to dose reduction (30% vs. 17%) in the small supportive O+B study (n+44) could indicate a different and possible worse safety profile compared to O+CHL, which is of concern.

Although patients received generally the planned dose of ofatumumab in each cycle in the pivotal study, only few patients continued treatment after 6 cycles (n=70, 32%), and even less after 9 cycles (n=8, 4%) however there is no evidence that administration of 9-12 cycles of ofatumumab is associated with increased toxicity.

Interpretation of safety data could furthermore be hampered by the imbalance in concomitant steroid use (only patients in the O+CHL arm received steroids prior to each infusion). This could for example be reflected by the higher frequency of nausea reported in the CHL arm.

Ofatumumab is already approved for a second line treatment of refractory CLL patients. In the pivotal trial Hx-CD20-406 evaluated in the former application, patients were given ofatumumab as monotherapy with the following dosing regimen: 300 mg×1, 2000 mg×7 (Weekly), 2000 mg ×4 (every 4 Weeks). In the present pivotal trial, patients received a lower dose, and combination therapy instead of ofatumumab monotherapy, making inter-study comparison of safety results difficult.

The overall safety profile did not indicate new safety signals in the targeted patient population of F-inappropriate CLL patients. However, a substantial part of these patients is older, or does have multiple comorbidities and/or decreased renal function. Although the number of events increased with age in the O+CHL arm, similar increases have been observed in the CHL monotherapy arm.

Benefit-risk balance

Importance of favourable and unfavourable effects

Ofatumumab + chlorambucil as analysed in the pivotal study demonstrated a significant and clinically relevant PFS improvement compared with chlorambucil alone. It is however uncertain if the effect size could have been overestimated in a proportion of the patients. This could especially be the case because of an unequal distribution of patients eligible for more aggressive treatments than chlorambucil (including fludarabine) to the different treatment arms. As requested, the MAH has performed a thorough analysis of the various reasons behind the “fludarabine-inapproriate” criteria with a forest plot. The various reasons are well balanced between arms. The 20% of subjects where the reason was “other” and the 8 % of patients where the reason was “not applicable”, were also balanced between arms. However, the MAH admit that within these two groups there could be patients

that could formally be “fludarabine-eligible”. Elimination of subjects in whom fludarabine-appropriateness could not be confirmed from the analysis showed that efficacy assessment was not impacted and consistent with the overall population. The prolonged PFS and improved ORR did not seem to result in noticeable improved quality of life to patients. However, despite that the combination is more intensive than chlorambucil alone, there seemed not to be detrimental effect on QoL by adding ofatumumab.

The number of overall and treatment related AEs was increased with ofatumumab + chlorambucil, but events were generally manageable. However, the increased number of SAEs (39% vs. 31%) and fatal SAEs (11% vs. 6%) are considered important unfavourable effects.

Benefit-risk balance

The B/R balance of ofatumumab in combination with chlorambucil or bendamustine for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy is considered positive.

Discussion on the benefit-risk balance

Efficacy has convincingly and robustly been demonstrated for the O-CHL regimen intended to be used in elderly co-morbid patients with CLL. There are no weaknesses in the pivotal study that could challenge the overall results (substantial PFS gain and increased ORR). Although clinical relevance in terms of quality of life related endpoints is not significantly demonstrated, the improved time to next therapy is considered an important benefit to CLL patients.

Ofatumumab in combination with bendamustine provides durable responses for subjects with previously untreated CLL (median follow-up of 14 months). Combination treatment with chlorambucil did not indicate new safety signals in the targeted patient population of F-inappropriate CLL patients compared with already approved ofatumumab monotherapy in refractory CLL patients.

The reported adverse events were mainly expected for a treatment regimen with a monoclonal antibody and alkylating agents and are considered manageable.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		Type
C.1.6 (a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include in previously untreated chronic lymphocytic leukaemia (CLL) patients, the treatment in combination with chlorambucil or bendamustine of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.

As a consequence, sections 2, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the SmPC, and Package Leaflet.

This CHMP recommendation is subject to the following condition:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To further investigate the relation between chromosomal abnormalities and PFS and OS in CLL studies Hx-CD20-406, Hx-CD20-407, OMB110911 and OMB110913. Furthermore, the impact on ORR, PFS and OS of other biomarkers should be further investigated through expression of CD 38 in study Hx-CD20-406; expression of CD 38 and IGHV mutation status in study Hx-CD20-407 and expression of ZAP-70 and IGHV-mutation status in studies OMB110911 and OMB110913.	31/12/2014

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To submit an open label, multicenter study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine	31/12/2014

Description	Due date
refractory chronic lymphocytic leukaemia (CLL)	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and does not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include in previously untreated chronic lymphocytic leukaemia (CLL) patients, the treatment in combination with chlorambucil or bendamustine of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.

As a consequence, sections 2, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the Scientific Discussion Arzerra EMEA/H/C/001131/II/0023.

Appendix

REVISED CHMP ASSESSMENT REPORT ON THE NOVELTY OF THE INDICATION/SIGNIFICANT CLINICAL BENEFIT IN COMPARISON WITH EXISTING THERAPIES

1. Introduction

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the Glaxo Group Ltd has applied for an additional one year marketing protection period in the framework of Arzerra (EMEA/H/C/001131/II/0023).

The request was based on the MAH's position that Arzerra represents a significant clinical benefit in the indication to the first line treatment of CLL in combination with alkylator-based regimens in patients not eligible for fludarabine-based therapy in comparison with existing therapies.

2. Justification of significant clinical benefit as presented by the MAH

2.1. Demonstration of new therapeutic indication

The European Commission approved the marketing authorisation for ofatumumab for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab on 19 April 2010. The current procedure is to request approval for the new indication:

Arzerra is indicated, in combination with an alkylator-based therapy, for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have not received prior therapy and are inappropriate for fludarabine-based therapy

Treatment of patients with CLL who have not received prior therapy differs greatly from that of heavily treated patients who are refractory to fludarabine and alemtutuzumab. Regimens which combine fludarabine with an alkylating agent and/or an anti-CD20 monoclonal antibody are utilized as the initial treatment of choice for patients with CLL [Hallek, 2010]. However, the choice of treatment depends on factors such as age, co-morbid conditions and risk stratification.

Most patients with CLL are elderly and/or have co-morbid medical conditions which make them poor candidates for fludarabine-based regimens. Thus, there is a high unmet medical need for more effective, well-tolerated therapies for elderly and/or less fit patients with untreated CLL, who cannot receive fludarabine and who constitute the majority of patients with this disease.

2.2. Details of existing therapies

Medicinal products for the initial treatment of CLL include alkylating agents (such as chlorambucil and bendamustine), purine analogues (such as fludarabine, cladribine, and pentostatin) alone or in combination, and the anti-CD20 monoclonal antibody rituximab in combination with chemotherapy. Chlorambucil is a mainstay of CLL therapy. Due to its oral administration, chlorambucil is a convenient option for elderly patients who cannot tolerate toxic chemotherapy.

Chlorambucil is no longer considered an appropriate option for younger or physically fit patients, based on randomised studies which demonstrated the superiority of other treatments such as fludarabine, fludarabine and cyclophosphamide (FC), and alemtuzumab, compared to chlorambucil. However, no Phase III study has demonstrated that any therapy is superior to chlorambucil in patients age 65 years or older or with co-morbid conditions. While fludarabine and alemtuzumab were superior to chlorambucil in younger patients, both drugs failed to show improvement in PFS compared to

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chlorambucil in patients age 65 years or older [Eichhorst, 2009; Hillmen, 2007]. Randomised studies demonstrated that FC is superior to fludarabine and FCR is superior to FC in younger or fit patients [Catovsky, 2007; Hallek, 2010], but it remains unclear whether these results can be extrapolated to older, less fit patients. Furthermore, regimens such as FC and FCR have significant toxicity in older patients. Thus, chlorambucil monotherapy remains a suitable choice for initial therapy of older or less fit patients with CLL.

Thus, elderly or less fit CLL patients who are inappropriate for fludarabine need therapies which are more effective than chlorambucil, which achieves a low complete response (CR) rate and has limited activity in patients with poor-risk prognostic factors. Given the benefit of adding rituximab to chemotherapy in younger or fit patients, it is important to examine whether the addition of an anti-CD20 monoclonal antibody to an alkylator (chlorambucil or bendamustine) improves clinical outcomes in elderly or less fit CLL patients. The German CLL Study Group recently presented results of a Phase III study [Goede, 2013] which randomised previously untreated CLL patients who were inappropriate for fludarabine-based therapy due to co-morbid conditions or renal insufficiency to chlorambucil (Chl), rituximab and chlorambucil (R+Chl), or the glycoengineered Type II anti-CD20 antibody obinutuzumab and chlorambucil (Ob+Chl).

The observed overall response (OR) rate and median progression-free survival (PFS) for both R+Chl (66%, 15.7 months) and Ob+Chl (76%, 23.0 months) were superior to those observed for Chl (30%, 10.9 months), although follow-up was limited (median < 15 months). While the efficacy results of the Ob+Chl arm were promising, 21%, 34% and 67% of subjects experienced grade 3-4 infusion reactions, grade 3-4 neutropenia and grade 3-5 adverse events (AEs), respectively, compared to 15% grade 3-4 neutropenia and 41% grade 3-5 AEs in the Chl arm. Given ofatumumab's preclinical advantages over rituximab (different epitope encompassing both the small and large extracellular loops of CD20, increased binding affinity for CD20, slower off-rate, greater complement dependent cytotoxicity, greater in vitro activity against CLL cells with low CD20 density), ofatumumab may be more active than rituximab in this clinical setting [Teeling, 2004; Teeling, 2006]. Therefore, combinations of ofatumumab with alkylator-based therapy, e.g. chlorambucil or bendamustine, were investigated to determine if these regimens can provide significant clinical benefit for elderly or less fit CLL patients who are inappropriate for fludarabine-based therapy.

2.3. Significant clinical benefit based on improved efficacy

Study OMB110911 is an ongoing, open-label, randomised Phase III study of ofatumumab and chlorambucil (O+Chl) vs. chlorambucil (Chl) in untreated patients with CLL who were inappropriate for fludarabine. Baseline patient demographics and disease characteristics were well balanced between the two arms. Median age was 69 years, and 72% of subjects had 2 or more comorbidities. Subjects were inappropriate for fludarabine due to advanced age (53%), comorbidities (33%), or advanced age and comorbidities (14%). Treatment was given for 12 cycles or until best response; median duration of treatment was 6 cycles in both treatment arms.

The primary endpoint, Independent Review Committee (IRC)-determined PFS, was significantly longer in the O+Chl arm compared to Chl (22.4 months vs. 13.1 months, HR 0.57, $p<0.001$). The results did not change with the use of CT scans (23.3 vs. 14.5 months, HR 0.54, $p<0.001$) or investigator-assessment of PFS (23.4 months vs. 14.8 months, HR 0.58, $p<0.001$). Median follow-up was 30 months. IRC-assessed overall response (OR) and CR rates were 82% and 12% for O+Chl vs. 69% and 1% for Chl, respectively. Three-year OS was 82% with O+Chl and 78% with Chl, with no statistically significant difference between treatment arms.

AEs were reported in 89% of Chl subjects and 95% of O+Chl subjects, 45% of Chl subjects and 60% of O+Chl subjects experienced a ≥ Grade 3 AE, and 65% of Chl subjects and 84% of O+Chl subjects experienced a drug-related AE. AEs led to permanent discontinuation of study treatment in 14% of Chl subjects and 13% of O+Chl subjects. The most common AEs were nausea (Chl 25%, O+Chl 21%), neutropenia (Chl 18%, O+Chl 27%), and thrombocytopenia (Chl 26%, O+Chl 14%). Thirty-one percent of Chl subjects and 39% of O+Chl subjects experienced a Serious AE (SAE), and 1% of subjects in each arm experienced a fatal drug-related SAE. AEs associated with decreased neutrophil counts occurred in 25% (21% ≥ Grade 3) of Chl subjects and 32% (30% ≥ Grade 3) of O+Chl subjects, including SAEs in 6% of subjects in each arm.

Thrombocytopenia AEs (30% vs. 18%) and ≥ Grade 3 thrombocytopenia (11% vs. 6%) were lower in the O+Chl arm, likely due to improved bone marrow function as a result of the increased efficacy in the O+Chl arm.

Thus, the addition of ofatumumab to chlorambucil in previously untreated patients with CLL who are inappropriate for fludarabine-based therapy resulted in a higher median PFS and response rates. AEs for O+Chl were characteristic of anti-CD20 based chemoimmunotherapy, with a low incidence of ≥ Grade 3 infusion related reactions, manageable neutropenia, and no increase in infections. Furthermore, the O+Chl arm demonstrated a decreased incidence of thrombocytopenia, due to improved bone marrow function. These findings demonstrate that O+Chl is an effective, safe regimen which provides significant clinical benefit for patients with previously untreated CLL who are inappropriate for fludarabine-based therapy.

Study OMB115991 is an ongoing Phase II, open-label, single arm study of ofatumumab and bendamustine in 44 subjects with previously untreated CLL and 53 subjects with relapsed CLL. The primary endpoint was investigator-assessed OR rate. Primary and secondary endpoints were reported separately for each subject population. The demographics and disease characteristics of the 44 previously untreated subjects were similar to those in Study OMB110911. Median age was 62.5 years, and 82% of subjects had 2 or more comorbidities. Treatment was given for 6 cycles; median duration of treatment was 6 cycles, and 89% of subjects received all 6 cycles.

Investigator-assessed OR and CR rates of 95% and 43% were observed following the last dose of treatment. Minimal residual disease (MRD) was assessed in bone marrow or peripheral blood 3 months after end of therapy in 16 subjects who attained CR; 9 of these 16 (56%) subjects were MRD negative. With a median follow-up time of 8.7 months, only one subject has progressed at 10.9 months. Time-to-event endpoints of duration of response and time to next anti-CLL therapy do not have clearly estimable median values due to the small number of events.

AEs were reported in 98% of untreated subjects, including 95% who experienced a drug-related AE and 7% in whom an AE led to discontinuation of study treatment. SAEs were reported in 34% of subjects, including 32% who had a drug-related SAE. The most frequently reported SAEs were hematologic or infusion-related events. There were no fatal SAEs. Neutropenia was the most common reason (20%) for bendamustine dose delay or reduction. One subject (2%) was withdrawn from treatment due to neutropenia. Infusion-related AEs occurred in 68% of subjects, primarily during Cycle 1 and 2, and were generally mild to moderate in severity. Infusion reaction SAEs occurred in 9% of subjects and led to withdrawal from study treatment in 5% of subjects. There were no fatal infusion reactions. Overall, 43% of subjects experienced infection AEs, including 11% of subjects with Grade 3 or 4 infection AEs and 9% of subjects with infection SAEs. No infection AEs or SAEs resulted in discontinuation from study treatment. Respiratory tract infections constituted the most common infection. AEs associated with decreased neutrophil counts occurred in 50% of subjects, and all were considered drug related. Decreased neutrophil count SAEs occurred in 7% of subjects. In addition, 7

subjects (5 drug-related) experienced an AE of anemia or decreased hemoglobin, and 8 subjects (7 drug-related) experienced an AE of decreased platelet count.

Thus, ofatumumab and bendamustine achieved high response rates with an acceptable safety profile in subjects with previously untreated CLL who are inappropriate for a fludarabine-based therapy. The safety profile was consistent with that of anti-CD20 chemoimmunotherapy. There were no unexpected adverse events. Neutropenia was manageable, infusion reactions were mild or moderate, and the incidence of serious infections was low. While median follow-up time is limited, the high CR and MRD negativity rates indicate that the high response rates may translate into prolonged remissions and PFS.

These findings indicate that ofatumumab and bendamustine provides clinical benefit in previously untreated, fludarabine-inappropriate CLL patients.

Summary of Therapeutic Benefit of Ofatumumab in Patients with CLL Who Have Not Received Prior Therapy and Are Inappropriate for Fludarabine-based Therapy

Ofatumumab was examined in combination with chlorambucil and bendamustine, the two predominant alkylators used to treat CLL in clinical practice, in previously untreated CLL patients who are inappropriate for fludarabine-based therapy. The addition of ofatumumab to chlorambucil resulted in a highly statistically significant, clinically meaningful improvement in PFS with an acceptable safety profile. Of note, addition of ofatumumab resulted in a decreased incidence of > Grade 3 thrombocytopenia, in contrast to worsened > Grade 3 thrombocytopenia observed with obinutuzumab [Goede, 2013]. These findings are supported by high OR and CR rates, with an acceptable safety profile, in response to ofatumumab and bendamustine in a similar population. While median follow-up time is limited, the high CR and MRD negativity rates indicate that these high response rates may translate into prolonged remissions and PFS.

In conclusion, the results of the pivotal Phase III study (OMB11091) of ofatumumab and chlorambucil vs. chlorambucil, combined with results of the supportive Phase II study (OMB115991) of ofatumumab and bendamustine, demonstrate that ofatumumab in combination with an alkylator-based therapy provides a significant clinical benefit in comparison to existing therapies in the new therapeutic indication.

2.4. Significant clinical benefit based on improved safety

NA

2.5. Significant clinical benefit based on major contribution to patient care

NA

3. Assessment of the MAH's justification of significant clinical benefit[1]

3.1. Demonstration of new therapeutic indication

Arzerra was authorised on 19 April 2010for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab. The new indication in the framework of the procedure EMEA/H/C/001131/II/0023 is in combination with chlorambucil or bendamustine for the treatment of

[1] In accordance with guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf

patients with CLL who have **not** received prior therapy and who are not eligible for fludarabine-based therapy. This represents a new indication in line with the guidance on elements requires to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period as it represents a change from the second line to first line treatment.

3.2. Details of existing therapies

It is agreed that chlorambucil is a standard backbone therapy for patients with CLL not suitable for more intensive therapy including purine analogs.

According to the most recent ESMO guideline (2011) alternatives in such patients are dose-reduced purine analog-based therapies [FC, PCR (pentostatin, cyclophosphamide and rituximab] or bendamustine.

MabThera (rituximab) has a broad CLL indication: *"in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia"* that in principle allows the antibody to be combined with any chemotherapy.

3.3. Significant clinical benefit based on improved efficacy

Patients who received O+CHL had a statistically significant improvement of 9.3 months in IRC-assessed PFS compared with patients who received CHL alone. The median PFS improved from 13.1 months in the CHL arm to 22.4 months in the O+CHL arm, with a HR of 0.57 (95% CI 0.45,0.72, stratified log-rank p<0.001). Efficacy has convincingly and robustly been demonstrated for the O-CHL regimen intended to be used in elderly co-morbid patients with CLL. Considering the known value of anti-CD20 therapy this result is not surprising. There are no weaknesses in the pivotal study that could challenge the overall results (substantial PFS gain and increased ORR).The MAH has provided the first comparative study of adding an anti-CD20 antibody to the old alkylating agent chlorambucil. No such data are currently available for the other anti-CD20 antibody rituximab.

However, in the absence of data comparing ofatumumab with rituximab as add-on to alkylating agents, the CHMP is of the view that ofatumumab did not demonstrate a significant clinical benefit over existing therapies based on improved efficacy.

3.4. Significant clinical benefit based on improved safety

The Applicant did not provide any data or rationale to substantiate a claim of significant clinical benefit based on improved safety.

3.5. Significant clinical benefit based on major contribution to patient care

The Applicant did not provide any data or rationale to substantiate a claim of significant clinical benefit based on major contribution to patient care.

4. Conclusion

Although the MAH has provided strong evidence of efficacy of the O-CHL regimen intended to be used in elderly co-morbid patients with CLL, the currently approved indication for MabThera (rituximab) allows use in the same patient population as ofatumumab. In the absence of data comparing ofatumumab with rituximab as add-on to alkylating agents, the CHMP is of the view that ofatumumab did not demonstrate a significant clinical benefit in comparison with existing therapies for the new

therapeutic indication in combination with chlorambucil or bendamustine for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.

Therefore the CHMP does not recommend one additional year of marketing protection on the basis of improved efficacy nor improved safety, of this application for a new indication in accordance with Article 14(11) of Regulation (EC) No 726/2004.

5. Recommendation

The CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004 and the "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period", and does not consider by consensus that the new therapeutic indication brings a significant clinical benefit in comparison with existing therapies.