10 November 2016
EMA/CHMP/692752/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Arzerra

International non-proprietary name: ofatumumab

Procedure No. EMEA/H/C/001131/II/0045

Marketing authorisation holder (MAH): Novartis Europharm Ltd

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List of abbreviations

AE	Adverse event
ADA	Anti-drug antibody
BR	Bendamustine and rituximab
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
DoR	Duration of response
ECOG	Eastern Cooperate Oncology Group
EMA	European Medicines Agency
EMAP	Emerging markets and Asia Pacific
FC	Fludarabine and cyclophosphamide
FCR	Fludarabine, cyclophosphamide, and rituximab
FDA	Food and drug administration
HAHA	Human anti-human antibody
HBV	Hepatitis B virus
HR	Hazard ratio
IGVH	Immunoglobulin variable region heavy chain
IRC	Independent review committee
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
LLN	Lower limit of normal
mAb(s)	monoclonal antibody(es)
MRD	Minimal residual disease
NCI-WG	National Cancer Institute-Sponsored Working Group
O+B	Ofatumumab plus bendamustine
O+FC	Ofatumumab plus fludarabine and cyclophosphamide
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	Partial response
SAE	Serious adverse event
SCT	Stem cell transplantation
TTNT	Time to next therapy
TTP	Time to progression
ZAP70	Zeta-chain-associated protein kinase 70

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 9 March 2016 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the combination of Arzerra with fludarabine and cyclophosphamide or in combination with bendamustine for the treatment of adult patients with relapsed Chronic Lymphocytic Leukaemia (CLL); as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 and 9 of the SmPC are updated based on the analysis of the pivotal studies OMB110913 (COMPLEMENT 2) and OMB115991. The Package Leaflet and Risk Management Plan (v.13) are updated in accordance.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Arzerra was designated as an orphan medicinal product EU/3/08/581 on 07/11/2008. Arzerra was designated as an orphan medicinal product in the following indication: Treatment of chronic lymphocytic leukaemia

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

On 08 November 2016, on the basis that the CHMP had raised an objection regarding the study design and patient population for OMB115991, the MAH withdrew the following variation:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the combination of Arzerra with bendamustine for the treatment of adult patients with relapsed Chronic Lymphocytic Leukaemia (CLL) based on the analysis of the pivotal study OMB115991.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on 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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Hanne Lomholt Larsen Co-Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on:	26 May 2016
CoRapporteur's preliminary assessment report circulated on:	23 May 2016
Joint Rapporteur's updated assessment report circulated on:	17 June 2016
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 June 2016
MAH's responses submitted to the CHMP on:	08 September 2016
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 October 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	04 November 2016
PRAC RMP advice and assessment overview adopted by PRAC	27 October 2016
The MAH withdrew the variation pertaining to Study OMB115991 on:	08 November 2016
CHMP opinion:	10 November 2016
The CHMP adopted a report on similarity of Arzerra with Imbruvica, Gazyvaro and Venclyst on date (Appendix 1)	10 November 2016

2. Scientific discussion

2.1. Introduction

Chronic Lymphocytic Leukaemia (CLL) is the most common type of leukemia in the western world, with an incidence rate of approximately 4.5 cases per 100.000 in the US in 2012. The median age at presentation is 71 years, and 11% of patients are diagnosed under the age of 55 years. The etiology is uncertain with progressively accumulation of clonal B-cells co-expressing T-cell (CD5+) and B-cell (CD19+, CD23+) cell surface markers, with a low expression of the otherwise typical B-cell marker CD20. The clinical course of CLL is variable and influenced in great part to genetic, epigenetic, and biochemical properties of the tumour cells and clinical features at time of diagnosis. CLL is a chronic disease; some patients have indolent disease

and could have a normal life expectancy, whereas others have advanced disease, rapid disease progression and poor outcome. The overall survival (OS) ranges from months to decades. Although patients with early-stage disease have a life expectancy of more than 10 years, those who progress or have advanced disease (Binet stage B or C, or RAI stage II – IV) have shorter median survival. Constitutional symptoms such as fever, night sweats, unintended weight loss and fatigue are common in advances disease and can significantly impact quality of life. CLL is non-curative, with the exception of allogeneic stem cell transplantation, which is only an option for very few patients. Even with newer treatments, CLL is marked by relentless relapses and remissions of decreasing duration and quality.

Advanced age and disease stage, more than 2 prior therapies, and the presence of chromosomal abnormalities such as 17p and 11q deletions mutations in the IGVH gene and over-expression of CD38 and/orZAP70 are associated with decreased duration and quality of response to therapy. Immunosuppression, which increases the risk of infections, is typical in CLL patients; further, the treatment often is complicated by increased susceptibility to infections, which may lead to death in many patients.

The combination of fludarabine, cyclophosphamide, and the CD20-targeted mAb rituximab (FCR) is the most potent commonly used regimen in previously untreated and relapsed patients with CLL. The combination was approved on the basis of a randomized phase III trial which demonstrated a median PFS of 30.6 months for FCR, compared with 20.6 months for FC. More fragile patients with comorbidities might not tolerate the FC regimen, less toxic regimen as bendamustine and rituximab (BR) are therefore commonly used in this clinical setting. A phase II study of BR demonstrated a median event-free survival of 14.7 months, and results from retrospective, observational studies indicate, that BR has a therapeutic value in older, less fit patients with CLL. Which treatment to use for relapsed CLL, is dependent on multiple factors based on a risk based approach and prognostic factors such as presence of 17p13 deletion and/or tumour protein 53 mutation, co-morbidity and physical fitness of the patient, duration and type of previous remission and complications to prior treatments.

Arzerra (ofatumumab; GSK1841157, OMB157) is a human monoclonal antibody (mAb) that recognizes an epitope of the CD20 molecule expressed on human B cells and B cell tumours that is distinct from the rituximab binding site. It induces cell lysis primarily through complement-dependent cytotoxicity (CDS) and antibody-dependent cell-mediated cytotoxicity (ADCC), especially in low CD20 expressing cells, such as CLL. Based on this, it is suggested that ofatumumab's stronger B-cell depletion potential compared to rituximab may translate into longer duration of treatment response.

Ofatumumab has shown activity in patients with previously untreated CLL, as well as refractory disease, both as single agent and as chemoimmunotherapy with fludarabine and cyclophosphamide (Wierda et al 2011). Ofatumumab has a well-established safety profile and was well tolerated in clinical trials, based upon 2.603 haematology patients, including 1.555 patients with CLL (as of December 2014) (GSK Document Number GM2008/00147/10, 2015). Ofatumumab is currently approved in more than 50 countries worldwide for use as monotherapy in patients with CLL refractory to fludarabine and alemtuzumab, and in EU in combination with chlorambucil or bendamustine for patients with CLL who have not received prior therapy and are inappropriate for fludarabine-based therapy (3 July 2014).

This is a type II variation application for an extension of the indication for Arzerra to include:

<u>*Relapsed CLL:*</u>

Arzerra is indicated in combination with fludarabine and cyclophosphamide or in combination with bendamustine for the treatment of adult patients with relapsed CLL.

On the basis of the pivotal Study OMB110913 (COMPLEMENT 2): A Phase 3 study of ofatumumab in combination with fludarabine and cyclophosphamide in subjects with relapsed CLL and supportive study OMB115991: A Phase 2 study of ofatumumab in combination with bendamustine in subjects with relapsed

CLL. This study also enrolled patients with previously untreated CLL, these results have previously been reported and are not reported in this application.

With the response to Request for supplementary information the applicant has withdrawn the claim for the combination of ofatumumab with bendamustine in the treatment of relapsed CLL, as follows which was the final agreed indication:

> Arzerra is indicated in combination with fludarabine and cyclophosphamide for the treatment of adult patients with relapsed CLL (SmPC, section 4.1).

For relapsed CLL, the recommended dosage and schedule is 300 mg on day 1 followed 1 week later by 1,000 mg on day 8 (cycle 1), followed by 1,000 mg on day 1 of subsequent cycles every 4 weeks for up to a maximum of 6 cycles (SmPC section 4.2).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

An environmental risk assessment was not submitted (see discussion on non-clinical aspects).

2.2.2. Discussion on non-clinical aspects

No new clinical data have been submitted in this application.

An ERA is not required as therapeutic antibodies such as ofatumumab being proteins they do not impose a risk to the environment and are not excreted unchanged and do not give rise to metabolites with potential biological activity and are highly unlikely to be environmentally persistent. On the basis of these observations it has been concluded that it is exempted from the obligation to submit an ERA . according to Directive 2001/83/EC and Guideline EMEA/CHMP/SWP/4447/00 corr2.

2.2.3. Conclusion on the non-clinical aspects

No new nonclinical data have been submitted in this application, which is considered acceptable.

Considering the above data, ofatumumab is not expected to pose a risk to the environment and is exempted from ERA submission.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

Tabular overview of clinical studies

The studies supporting the efficacy and safety of ofatumumab in combination with chemotherapy in subjects with relapsed CLL are:

- **OMB110913** (COMPLEMENT 2, Novartis internal code OMB157A2301), a Phase 3 study of ofatumumab in combination with FC vs. FC in subjects with relapsed CLL (N=365)

- **OMB115991** (Novartis internal code OMB157B2201), a Phase 2 study of ofatumumab in combination with bendamustine in subjects with untreated or relapsed CLL (N=97, of which n=53 in the relapsed CLL cohort).

These studies are referred to hereafter with the abbreviated study codes Study OMB913 and Study OMB991, respectively.

Table 1 Ofatumumab clinical development program in CLL

Administration	Previously untreated CLL	Relapsed CLL	Refractory CLL
Monotherapy	No studies	OMB112517: Phase III, maintenance 1000 mg	OMB111773*: Phase II, 2000 mg OMB111827*: Phase II, 2000 mg OMB114242: Phase III, 2000 mg OMB112855*: QTc, 2000 mg
		Hx-CD20-402*: Phase I/II, 500 mg, 1000 mg, 2000 mg OMB111148* (Japan): Phase I, 500 mg or 1000 mg OMB112758* (Japan and Korea): Phase I/II, 2000 mg	
Combination therapy	OMB110911: Phase II O+CHL vs. CHL, 1000 mg OMB111774*: Phase II O+FC, 500 mg & 1000 mg OMB115601 (Japan): Phase I/II O+CHL, 1000 mg	**OMB110913 (Study OMB913): Phase IIIA O+FC vs. FC, 1000 mg**	No studies
	OMB115991 (Study OMB991): Phase II O+B, 1000 mg		

B=bendamustine; CHL=chlorambucil; FC=fludarabine/cyclophosphamide; O=ofatumumab; O+FC=ofatumumab plus fludarabine/cyclophosphamide; QTc=corrected QT interval.
Note: Information provided for each study includes study phase and ofatumumab dose, not including any initial dose.
* Completed studies (no subjects in follow-up).

2.3.2. Pharmacokinetics

The clinical pharmacology of ofatumumab has been previously characterized, and previously submitted data are not repeated in this document. New data presented in this submission are from Study OMB913, A brief overview of the clinical pharmacology of ofatumumab is given in the following sections.

Bioanalytical methods

The concentrations of ofatumumab in human plasma in both studies were determined by an antibody capture sandwich ELISA that has been previously submitted (original method: GlaxoSmithKline Document Numbers CD2008/00745/00, CD2008/01624/00, and 2012N145316_00; and transferred to Alliance Pharma: GlaxoSmithKline Document Number 2011N118243_01). Briefly, the method was precise, accurate and reproducible, with a lower limit of quantification of 100 ng/mL and an upper limit of quantification of 1606500 ng/mL. At all validation sample concentrations examined, the run accuracy (expressed by the percent bias) was less than 20% (maximum bias observed was 16.2%), and was therefore acceptable. At all validation sample concentrations examined, the intra- and inter-run precision values (represented by the coefficient of variation) were less than or equal to 20%, and were therefore acceptable. The maximum intra- and inter-run precision observed were 3.1% and 14.4% respectively. The method transferred to Alliance met the acceptance criteria for accuracy and precision. The maximum inter-and intra-run accuracy were 6.0% and 4.6%, respectively, which were less than 20% and hence acceptable. The maximum inter- and

intra- run precision were 6.6% and 2.8%, respectively, which were less than 20% and hence acceptable. Ofatumumab was shown to be stable in human plasma for up to 10 freeze-thaw cycles. Longterm stability was established for up to 1743 days at -20ºC (2012N145316_00).

The anti-drug antibody assay validated for clinical sample analysis has been previously submitted (original method: GlaxoSmithKline Document Number 2011N118034_00 and subsequently transferred to Alliance Pharma: GlaxoSmithKline Document Number 2015N230890_00). Briefly, this was a bridging electroluminescence assay with a relative sensitivity of 2.5 ng/mL of affinity-purified anti-ofatumumab rabbit polyclonal positive control. The assay tolerates a drug concentration of at least 200 µg/mL of human serum. All patients with available PK and ADA data in studies OMB913 and OMB991 had at least one ADA sample with a corresponding ofatumumab concentration below 200 µg/mL, allowing conclusive determination of the ADA status. The confirmatory assay involved addition of both ofatumumab and rituximab, hence reducing the false positive signals caused by CD20 bearing cell membrane fragments and confirming the specificity of antibodies that bind to ofatumumab.

PKPD methods

The population PK analysis was performed using the NONMEM software system, NONMEM VII version 3 (ICON, Gaithersburg, MD, USA). All modelling was performed using the first order conditional estimation with interaction (FOCEI) method.

The exposure response analysis were performed by numerical or graphical exploration of the data mainly in quartiles of the exposure endpoints as well as Kaplan-Meier. The datasets were prepared using SAS and validated for the analysis. Validated R codes were used to generate the figures for graphical exploration and the tables for exposure quartiles. All figures were generated in R version 3.0.2.

Statistical methods

ANCOVA was used for exploring the potential interaction between ofatumumab and F-ara-A and C.

Absorption

Ofatumumab is administered as an iv solution, and the usual considerations of bioavailability and bioequivalence do not apply. The currently marketed acetate-buffered formulation of ofatumumab was used in studies included in the current submission. Therefore, bioavailability and bioequivalence studies to characterize the biopharmaceutics of ofatumumab were not performed during the clinical development program.

Distribution

In clinical studies with ofatumumab, the half-life was 17.1 days and the volume of distribution at steady state ranged from 1.7 to 8.1 L across studies, dose levels, and infusion number.

Elimination

Ofatumumab is eliminated through a non-linear target-mediated route as well as a target independent route mediated by non-specific endocytosis followed by intracellular catabolism. Higher numbers of B cells result in greater component of target-mediated elimination clearance and shorter ofatumumab half-life at the start of therapy.

In patients with relapsed CLL receiving ofatumumab in combination with fludarabine and cyclophosphamide, geometric mean CL and t½ values for ofatumumab were 11.2 ml/h (3.7–105 ml/h) and 19.9 days (1.4 47.1 days) after the fourth infusion.

Dose proportionality and time dependencies

Subsequent ofatumumab dosing leads to potent depletion of B cells resulting in reduced overall clearance at later cycles. Following multiple doses, ofatumumab pharmacokinetics exhibits a long half-life and low volume of distribution similar to that of other mAbs.

Target population

Ofatumumab pharmacokinetics in study OMB913 was investigated using a population pharmacokinetic approach, and were consistent with those reported previously in subjects with CLL.

By estimating just a single parameter (BOND_adj) and updating another parameter (BIN) based on the data in Study OMB110913, the published ofatumumab population PK model resulted in the successful fitting of the ofatumumab PK data from Study OMB110913. Following the update of the BIN parameter based on the ratio of the baseline CD20 levels in Study OMB110913 compared to that in Study OMB111773/Hx CD20-406, a BOND_adj parameter of 0.8 was estimated. Given the baseline CD19+ levels in Study OMB110913 were aligned to the relapsed/refractory population published by Struemper (0.0901 (95% CI: 0.0603-0.12)), the estimate of the BOND_adj parameter was in line with expectations. The data were described well, and there was good agreement between individual post-hoc parameter estimates for the ofatumumab model from Study OMB110913 and previous ofatumumab studies. Additionally, the derived ofatumumab PK parameters were also comparable to previously reported values, with the average estimated half-life after repeat dosing of 19.9 days, which closely matches estimates from other studies, as well as the expected half-life of monoclonal antibodies.

Ofatumumab population pharmacokinetics has been studied in combination with chemotherapeutic regimens in CLL subjects. Whilst Study OMB110913 was not designed, powered, nor sampled to formally assess a potential DDI between ofatumumab and either FC component, the potential for a DDI was assessed using several methodologies. For both F-ara-A and C, concentration-time profiles and a formal comparison (ANOVA) of derived AUC(0-τ) by treatment group indicated comparable PK in the absence and presence of ofatumumab.

For F-ara-A, the point estimates for AUC(0-τ) comparison between treatments at both cycles suggested similar exposure in both treatment arms. The CI were wide and included the null value of 1.0, for no change in parameter suggesting lack of DDI of ofatumumab on F-ara-A exposure.

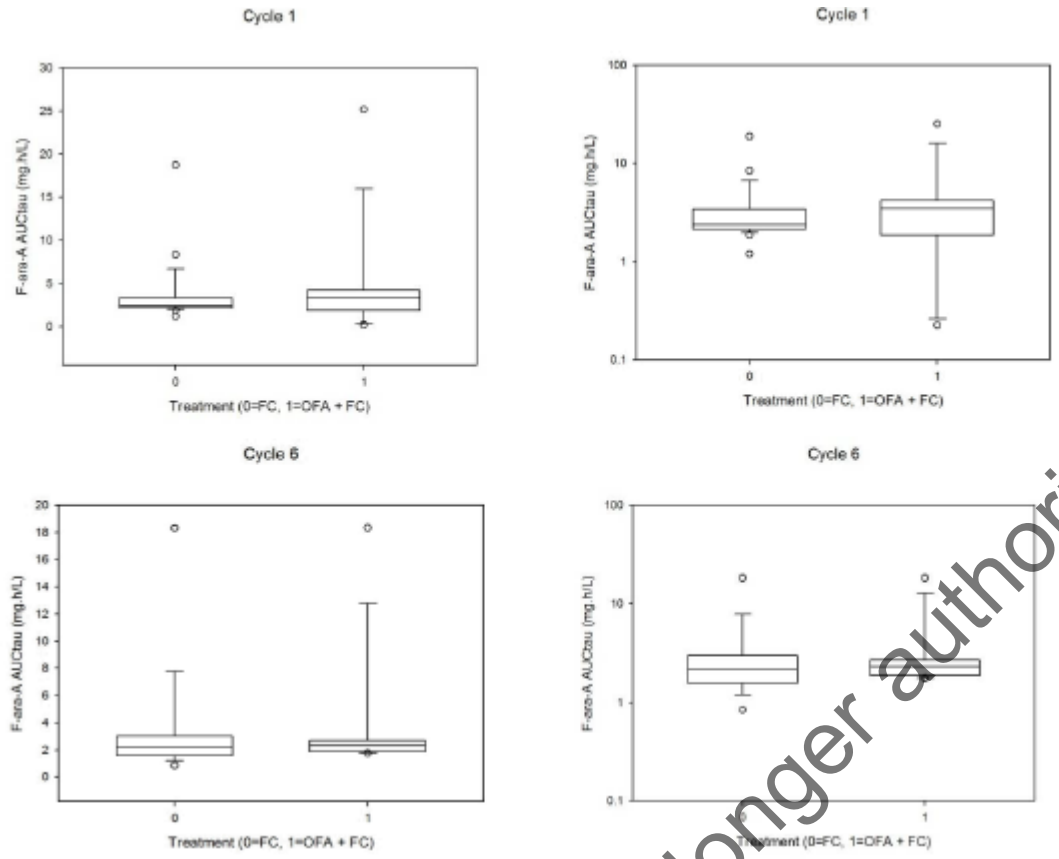


Figure 1: F-ara-A concentration-time after dose profiles by cycle

For C, the point estimates for AUC(0-τ) comparison at Cycle 1 was 0.959 suggesting lack of DDI of ofatumumab on C exposure. At Cycle 6, the point estimates for AUC(0-τ) comparison was 0.68 suggesting lower C exposure with concurrent ofatumumab treatment. The CI around the point estimate at Cycle 6 was wide and included the null value. The population PK model estimates of clearance were slightly higher with ofatumumab co-administration.

Table 2: Summary of cyclophosphamide individual derived PK parameters by cycle and treatment

Parameter	FC				Ofatumumab+FC			
	Cycle 1		Cycle 6		Cycle 1		Cycle 6	
	N[b]	Geomean (%CVb)	N[b]	Geomean (%CVb)	N[b]	Geomean (%CVb)	N[b]	Geomean (%CVb)
Cmax (mg/L)	26	11.1 (122)	18	5.63 (512)	12	8.05 (29.7)	12	7.13 (43.0)
Tmax (h)[a]	26	1.29 (0.320 - 5.00)	18	1.77 (0.360 - 21.5)	12	0.730 (0.280- 17.2)	12	0.875 (0.420- 19.2)
AUC(0-τ) (mg.h/L)	27	85.2 (63.7)	19	101 (129)	14	81.7 (44.5)	13	68.6 (42.5)

a Median (range)
b Some EOI samples not taken hence Cmax and Tmax not summarised

In this small DDI substudy, parameter estimates may have been influenced by the consistent differences in sample collection between the two treatment arms and a very sparse sampling scheme, which could make it difficult to definitively draw conclusions based on derived parameters from this limited dataset.

Based on the results of Study OMB913 included in this submission, ofatumumab exposure was similar when administered alone or in combination with C in relapsed CLL subjects. In a sub-study assessment, no effect

of ofatumumab was seen on either fludarabine or cyclophosphamide exposure. Cumulative drug-drug interaction data available therefore suggests a lack of interaction between ofatumumab and chemotherapy agents.

Special populations

No new data on special populations have been provided. This is found acceptable.

Pharmacokinetic interaction studies

No new dedicated drug interactions studies have been submitted with this application. The potential interaction between ofatumumab and F-ara-A and C were investigated based on population analysis of the exposures.

Population pharmacokinetics

Model description: The analysis was performed using the NONMEM software system, NONMEM VII version 3 (ICON, Gaithersburg, MD, USA). All modelling was performed using the first order conditional estimation with interaction (FOCEI) method.

Prior modeling: The population pharmacokinetic model the current analysis was built on was previously submitted. The prior population pharmacokinetic model was based on data from 252 patients with CLL, 38 patients with FL, and 187 patients with RA who received multiple infusions of ofatumumab as a single agent at doses ranging from 100 to 2000 mg in Study Hx-CD20-001, Study Hx- CD20-402, Study Hx-CD20-403, and Study OMB773/Hx-CD20-406.

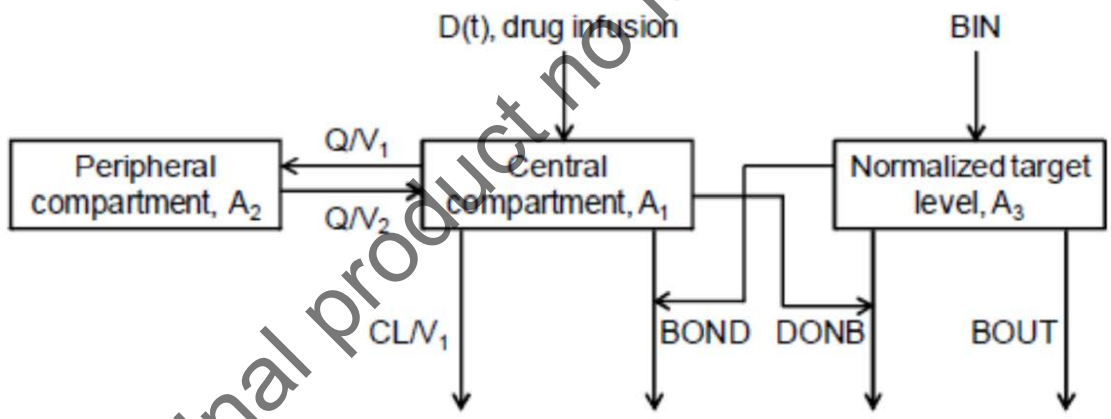


Figure 2: Diagram of Pharmacokinetic Model

Database: The population PK dataset for ofatumumab included 2478 observations from 176 subjects. Of these subjects, 103 were male and 73 female and 151 were White, 2 Black/African American, 19 Asian, 3 American Indian/Alaskan and 1 multi-race. A summary of subject demographic and immunological characteristics is provided in ***Table 3***.

Table 3: Summary of demographic and immunological characteristics

	Age (years)	Height (cm)	Weight (kg)	CR_{CL} (mL/min)	IgG (g/L)	CD19	CD5P19	CD5M19	CH50
N	176	176	176	170	172	176	176	176	163
Mean	61.2	168	75.7	79.5	8.87	52000	46500	5490	262
SD	8.74	9.64	15.8	26.5	5.22	52800	48900	18700	122
Min	38.0	147	40.0	1.00	0.710	63.0	43.0	0.00	0.00
Median	62.0	168	73.5	77.9	8.04	41600	34400	255	246
Max	81.0	202	140	197	41.8	234000	234000	160000	400
CV%	14.3	5.75	20.9	33.3	58.8	101	105	341	46.3
Geomean	60.6	167	74.1	72.6	7.52	23200	19900	NC	NC
%CVb	14.9	5.72	20.5	62.4	68.6	372	409	NC	NC

CR_{CL} = Creatinine clearance; IGG = Immunoglobulin G; NC = not calculable
%CVb is the coefficient variation of the geometric mean
CD19=cluster of differentiation (CD) 19, CD5P19=CD45+CD19+CD5+, CD5M19=CD45+CD19+CD5-, CH50 = Complement concentration

Data missingness: In individual concentration-time profiles, non-quantifiable (NQ) values which occurred in a profile before the first measurable concentration were assigned a value of zero concentration. Additionally, if an NQ value occurred after a measurable concentration in a profile and was followed by a value above the lower limit of quantification (LLQ), then the NQ value was generally omitted. If two NQ values occurred in succession (after maximum observed concentration (Cmax)), the profile was deemed to have terminated at the first NQ value, and any subsequent concentrations were omitted. The mean/median value at a time with NQ values was reported (in tabular or graphical fashion) unless the resulting mean/median value was <LLQ of the assay, in which case the value was assigned NQ.

Outliers: There were six, one and three quantifiable concentrations for ofatumumab, F-ara-A and C, respectively measured prior to the first doses that were excluded from the analysis. Additionally, all trailing dose records, following the last available PK sample were also excluded from the analysis.

Methodology: For ofatumumab, a population PK model has been previously reported using a target-mediated clearance model developed based on four phase I/II studies in subjects with CLL, follicular lymphoma, and rheumatoid arthritis (Struemper 2014, Patel 2015). This model was applied to the data in the present study to determine the post hoc estimates of individual parameters.

Due to the limited sampling for both F-ara-A and C in Study OMB110913 following both ofatumumab + FC and FC, literature models characterizing the PK of both compounds were used to support pseudo-Bayesian analysis of available F-ara-A and C concentrations. For F-ara-A, the model published by Salinger et al (Salinger 2009) was employed and for C, the models by Kim et al (Kim 2013) and Hassan et al (Hassan 1999) were used as the basis for the Bayesian analysis. The models presented for both F-ara-A and C were two-compartment models describing concentrations following IV infusions, as was the case in Study OMB110913.

For all three analytes, prior to fitting, the suitability of existing/published models to the Study OMB110913 data was assessed using a visual predictive check (VPC). A previously developed nonlinear mixed-effects model describing the PK of ofatumumab was used to characterize ofatumumab exposure. The population parameter estimates (fixed effects) and variability (random effects) from the previous model were used to generate the empirical Bayesian estimates of individual parameters. The B cell synthesis rate (BIN) was set to the relative ratio of the geometric mean B-cell count in Study OMB110913 compared to that in Study OMB111773/Hx-CD20-406. An adjustment factor for B-cell target on drug interaction rate constant was estimated. Model applicability was assessed by visual inspection of goodness-of-fit plots and visual predictive checks. For F-ara-A and C, previously developed non-linear mixed-effects models were used to provide supporting prior information on parameter estimates and variances. Individual post hoc parameter

estimates were generated. Assessment of DDI potential was conducted via visual comparison of concentrations vs. time plots after dose by cycle, visual inspection of the CI-VPC by treatment, evaluation of the statistical significance of including treatment as a covariate on CL and V1 in the population PK model, and comparison of AUC(0-τ) by treatment using box and whisker plots and conducting a formal assessment using an analysis of variance (ANOVA). For F-ara-A and C, the $PRIORS procedure in NONMEM was employed such that the literature data are used to provide supporting prior information on parameter estimates and variances. A sensitivity analysis using differing arbitrary variances in conjunction with a review of the Study OMB110913 data in relation to the published data and comparability of the literature population to a CLL population was used to determine the variance supplied for the fitting.

The applicability of the values used as prior information for the C model was checked using a CI-VPC (500 replicates) using parameter and variability values. Given the uncertainty in the priors, the different publications, the lack of Q and V2 estimates in duplicate, and the relatively high IIV observed in both the Hassan, et al and Kim, et al publications, the $THETAPV was set at 10,000 for the estimation of population PK model parameters of C from study OMB110913. The high value for $THETAPV allowed minimal influence of the prior estimates on the final parameter estimates given the high variability and the low compatibility with Study OMB110913.

Verification of modelling software: Not reported.

Deviations from MAP: Not applicable.

Structural model: as described in ***Figure 2*** for ofatumumab. For both F-ara-A og C, linear two-compartment models with first-order elimination was fitted to the data, respectively.

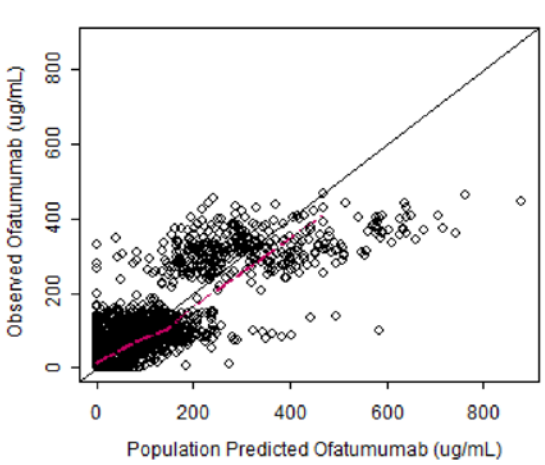
Co-variate model: For ofatumumab, the base and final models contained fixed covariate effects. For both F-ara-A and C, no formal covariate testing was evaluated. However, as detailed in the population PK report, ofatumumab co-administration was investigated as a covariate in the population PK model to assess the potential DDI. Only treatment on CL and V1 was evaluated as a covariate in the population PK model for F-ara-A and C.

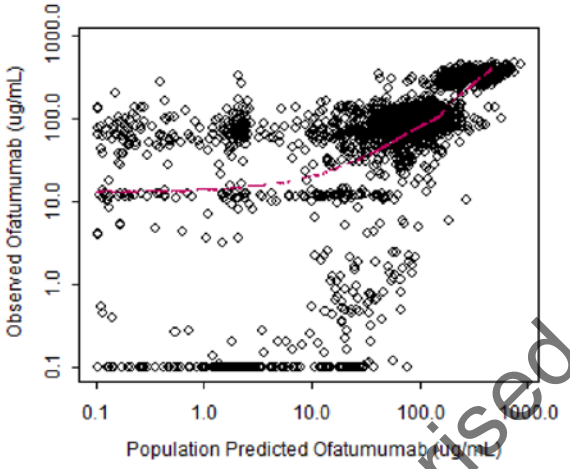
Error model: All inter-individual variability (IIV) terms in the analysis were described by an exponential error model, or log-normal parameter distribution. For PK observations of ofatumumab and F-ara-A, the residual error model was described by a combined proportional and additive error model. For PK observations of C, the residual error model was described by a simplified version of above with just the proportional component.

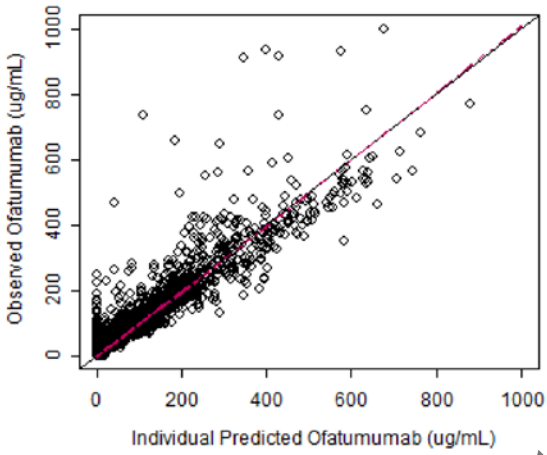
Assumptions:

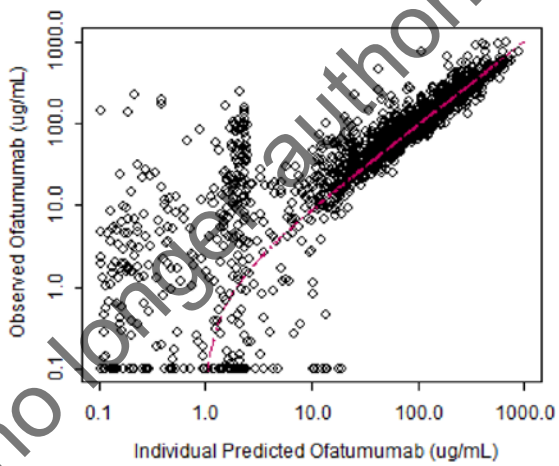
- Domains explored by the collected data/the incorporation of prior knowledge sufficiently sound to allow describing the PK of ofatumumab, F-ara-A and C in the target population with regards to selected patient population, population samples size, sample timing and numbers
- PK/PD target appropriate
- parametric distribution for the random effects (log-normal parameter distribution)

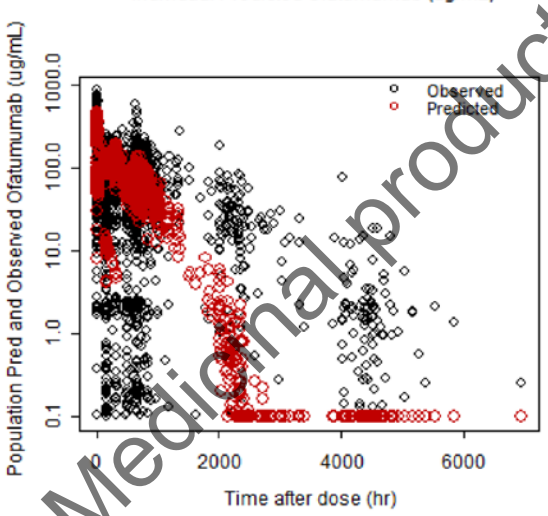
Model diagnostics: Goodness of fit plots are given for otatumumab, F-ara-A and C are given in the following figures (***Figure 3*** to ***Figure 8***). For other diagnostic plots please refer to the model report.

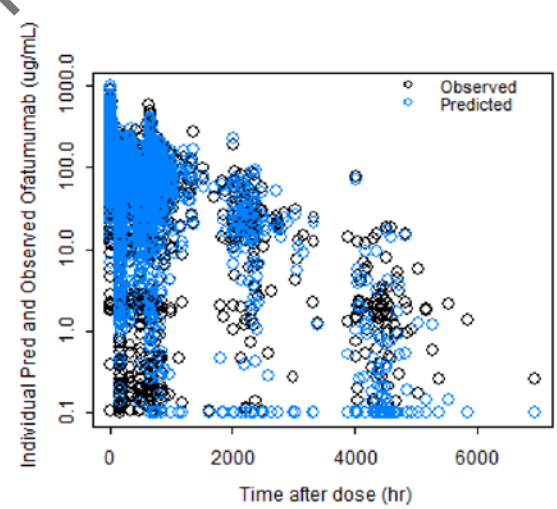


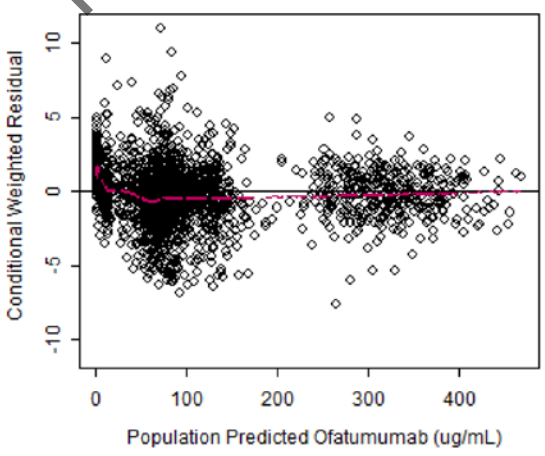












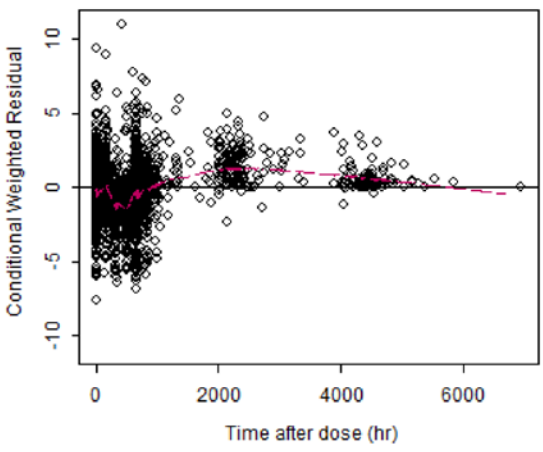
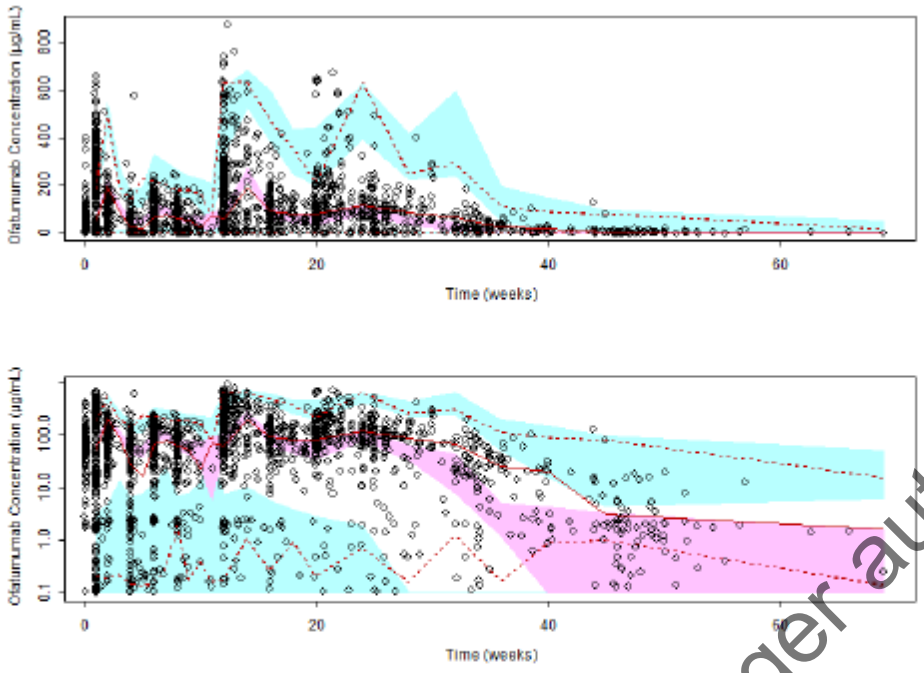


Figure 3: Ofatumumab diagnostic plots



Circles=observations; Solid line is median of observed. Dotted lines are 2.5th and 97.5th of observed.
Shaded areas are 95% CI around median, 2.5th and 97.5th of simulated.

Figure 4: Ofatumumab visual predictive check overall vs. time from first dose

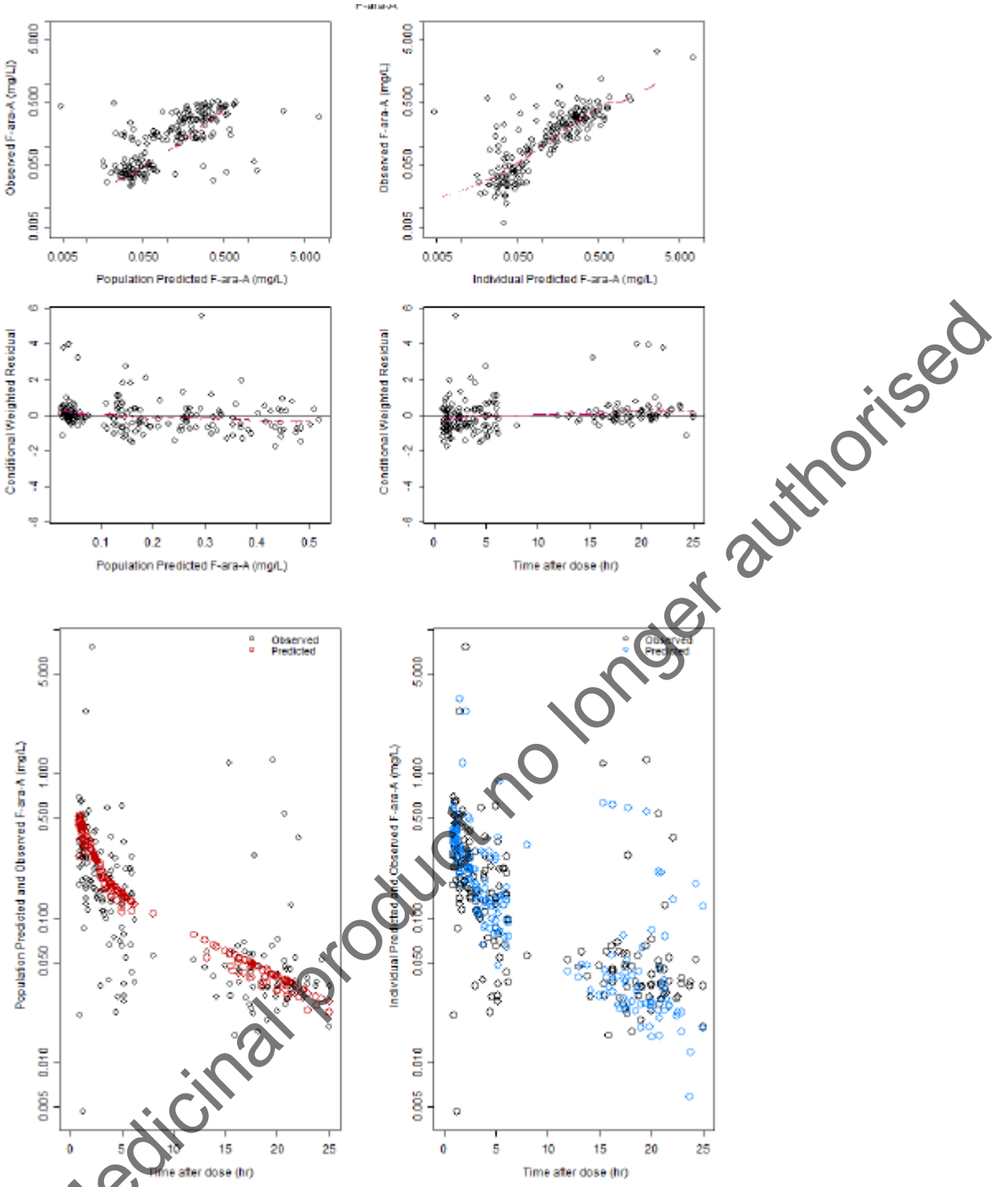
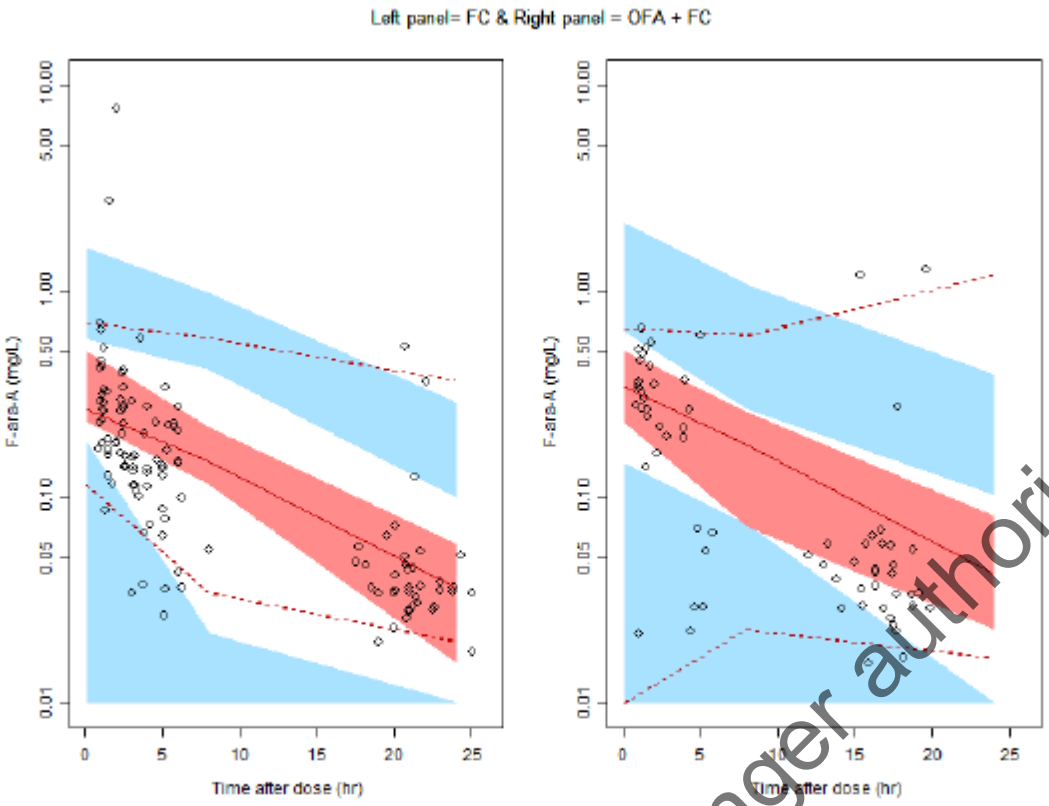


Figure 5: F-ara-A diagnostic plots



Circles=observations; Solid line is median of observed. Dotted lines are 2.5th and 97.5th of observed. Shaded areas are 95% CI around median, 2.5th and 97.5th of simulated.

Figure 6: F-ara-A CI-VPC by treatment

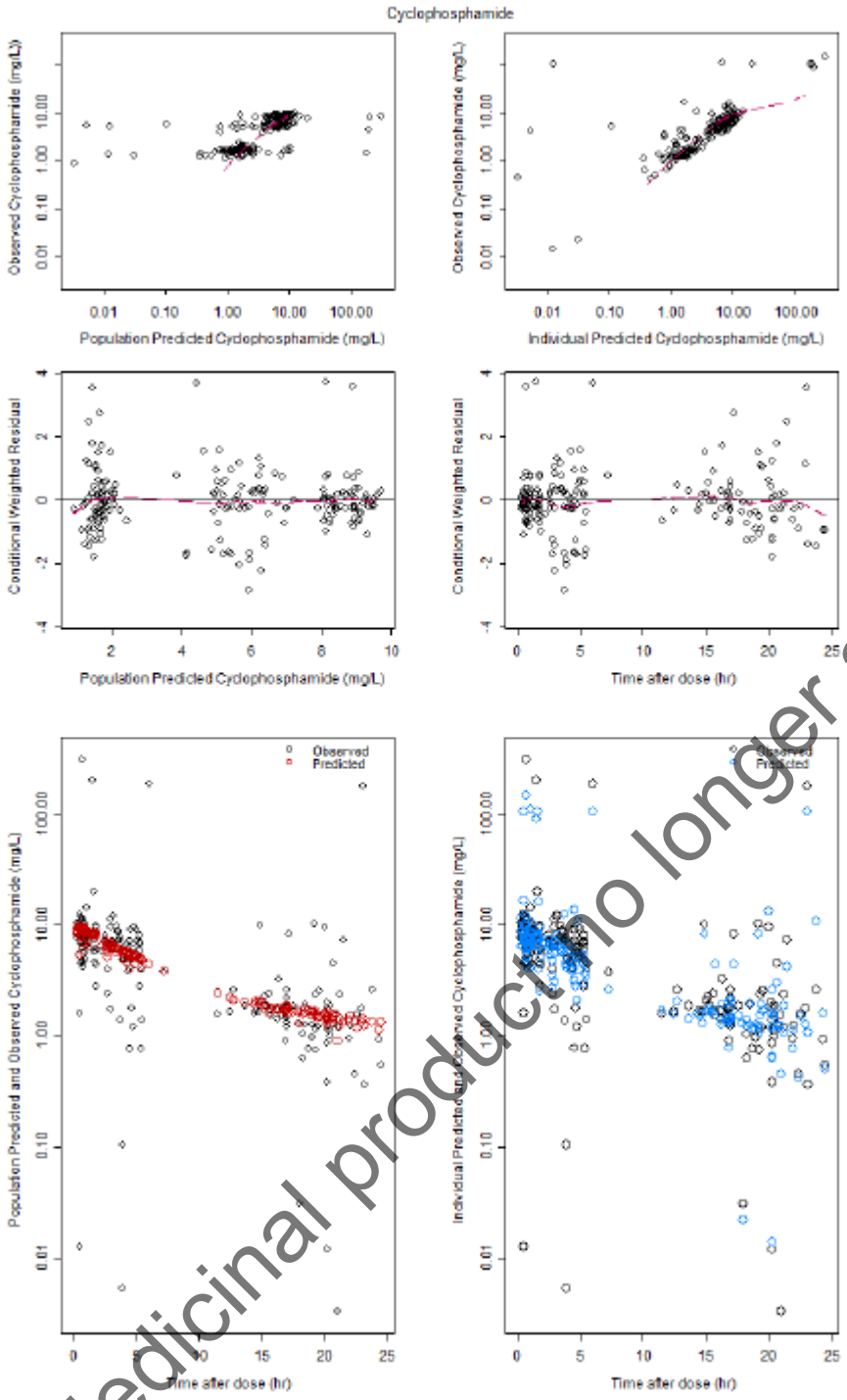


Figure 7: Cyclophosphamide diagnostic plots

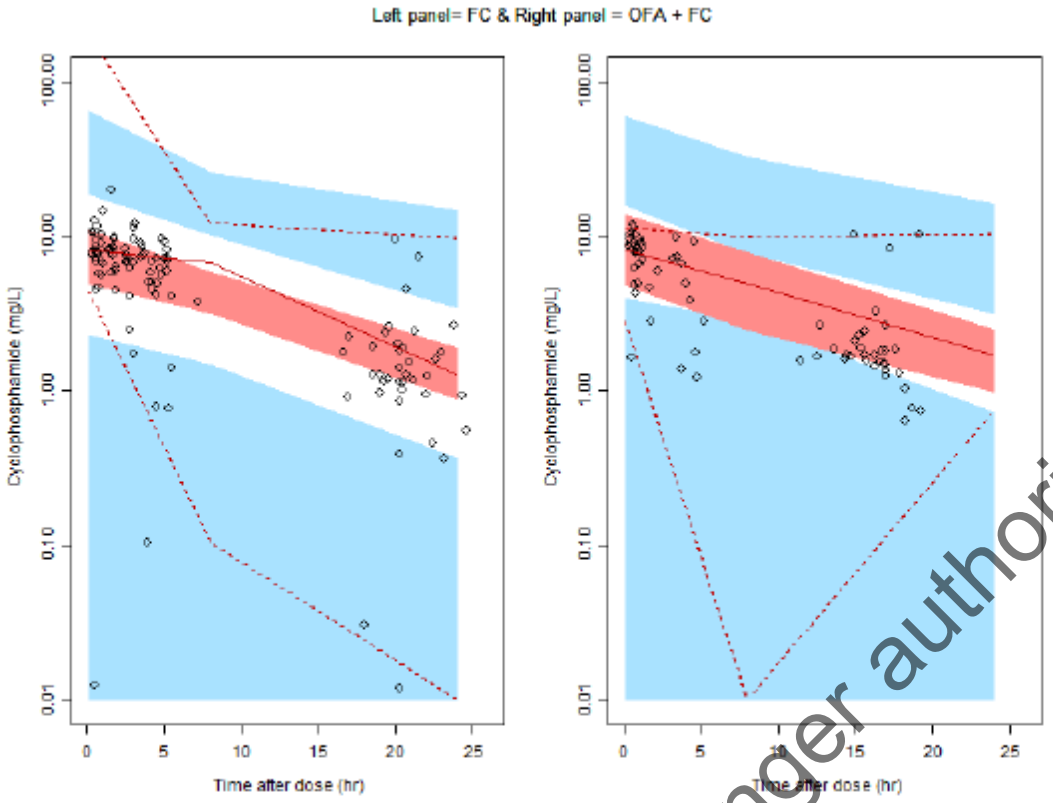


Figure 8: Cyclophosphamide CI-VPC by treatment

Decision criteria: CI-VPCs, parameter estimates and their variability, diagnostics plots and parameters plots, where appropriate, were used to confirm the suitability of models to the available Study OMB110913 data.

2.3.3. Pharmacodynamics

Pharmacodynamics and exposure-response relationship

No new data related to the mechanism of action of ofatumumab have been submitted.

Rapid, efficient, and sustained depletion of peripheral B cells was observed for the majority of CLL patients at all ofatumumab dosing regimens tested, beginning with the first infusion. In patients with relapsed or refractory CLL, previously untreated CLL as well as patients receiving maintenance therapy, ≥ 80% reductions in B cell counts were seen following multiple doses. In Study OMB913, the ofatumumab, fludarabine and cyclophosphamide combination elicited complete (40% of responders) or near-complete (80% of responders) Bcell depletion in relapsed CLL patients.

Previously, a trend of longer PFS was observed with higher ofatumumab AUC and was also noted with Cmax and Ctrough at certain time points (Summary of clinical pharmacology in maintenance CLL). In Study OMB913, higher ofatumumab exposure was also associated with greater reduction of B-cells, and longer PFS. No relationship could be discerned between exposure of ofatumumab and occurrence of adverse events.

Antibodies

In Study OMB913, 1 patient out of 170 with conclusive ADA data was confirmed ADA positive. In Study OMB991, no patients with positive ADA were identified (0 out of 42 with conclusive ADA data). In total, 2483 patients have been treated with ofatumumab; 2225 patients received ofatumumab by IV infusion. To date, 14/1882 patients were confirmed ADA positive across the clinical development program (0.7%). In CLL, 2/926 patients were confirmed ADA positive (0.2%). For patients with positive ADA results, there were no safety, pharmacokinetic, or pharmacodynamic consequences associated with the positive results in immunogenicity assays, where this could be assessed. The safety profile in patients with positive ADA results was similar to that in patients with all negative results.

2.3.4. PK/PD modelling

Exposure-response

Rapid, efficient, and sustained depletion of peripheral B cells was observed for the majority of CLL patients at all ofatumumab dosing regimens tested, beginning with the first infusion. In patients with relapsed or refractory CLL, previously untreated CLL as well as patients receiving maintenance therapy, ≥ 80% reductions in B cell counts were seen following multiple doses. In Study OMB913, the ofatumumab, fludarabine and cyclophosphamide combination elicited complete (40% of responders) or near-complete (80% of responders) B-cell depletion in relapsed CLL patients. Previously, a trend of longer PFS was observed with higher ofatumumab AUC and was also noted with Cmax and Ctrough at certain time points.

Database: All patients from study OMB110913 (data cut off: December 17, 2014) with at least one exposure variables and with the respective efficacy/safety endpoint were included in the analysis.

Data missingness, outliers: For exposures; as described for the population-PK model. For the response endpoints; as described in the clinical study report.

Methodology: Visual inspection of the exposure response relationship.

The previously developed population PK model was applied to the data and used to generate post hoc ofatumumab PK parameter estimates for the individual subjects in Study OMB110913, including AUC(0-τ). Cmax and Ctrough were observed directly from the raw data. Ofatumumab exposure parameters (Cycle 4 AUC(0-τ) and Ctrough) were divided into quartiles and the relationship between exposure and PFS was explored using Kaplan-Meier plots. Cycle 4 AUC(0-τ) and Ctrough were chosen as the measures of exposure for the analyses because these exposure levels approximate steady state exposure.

The relationship between ofatumumab exposure and B cell counts over time was also explored graphically by quartiles of Cycle 1 Week 2 AUC(0-τ) and Ctrough, and Cycle 4 AUC(0-τ) and Ctrough. Cycle 1 Week 2 AUC(0-τ) and Ctrough and Cycle 4 AUC(0-τ) and Ctrough were chosen as the measures of exposure for the analyses to examine both the early and steady state ofatumumab exposure effect on the B cell count, respectively.

The relationship between exposure and safety was assessed graphically by examining early and late onset AEs as follows: Cycle 1 Week 2 AUC(0-τ), Cmax, and Ctrough vs. adverse events occurring on or before 1 month of treatment, and Cycle 4 AUC(0-τ), Cmax, and Ctrough vs. adverse events occurring on or before 6 months of treatment. The assumption of this analysis is that the measure of exposure is representative of the exposure at the time of the AE regardless if the AE occurred before or after the exposure assessment.

Finally, the proportion of subjects with ofatumumab Ctrough > 10 µg/mL by cycle was computed directly from observed data. This target level was determined based on preclinical data where peripheral B-cell recovery in cynomolgus monkeys and tumour cell growth in tumour-bearing SCID mice were suppressed [Bleeker, 2008].

Purpose of use:

1. To explore the relationship between ofatumumab exposure and:
    - Progression free survival (PFS) in subjects with relapsed CLL
    - B cell count over time in subjects with relapsed CLL
    - Selected adverse events (AEs) in subjects with relapsed CLL (all infections, Grade 3+ infections, pneumonia, decreased neutrophil count, decreased platelet count, decreased haemoglobin, other cytopenias and serious adverse events)
2. To determine the proportion of subjects with ofatumumab trough concentrations above 10 ug/mL, established as a target concentration based on peripheral B cell suppression data in the preclinical setting.

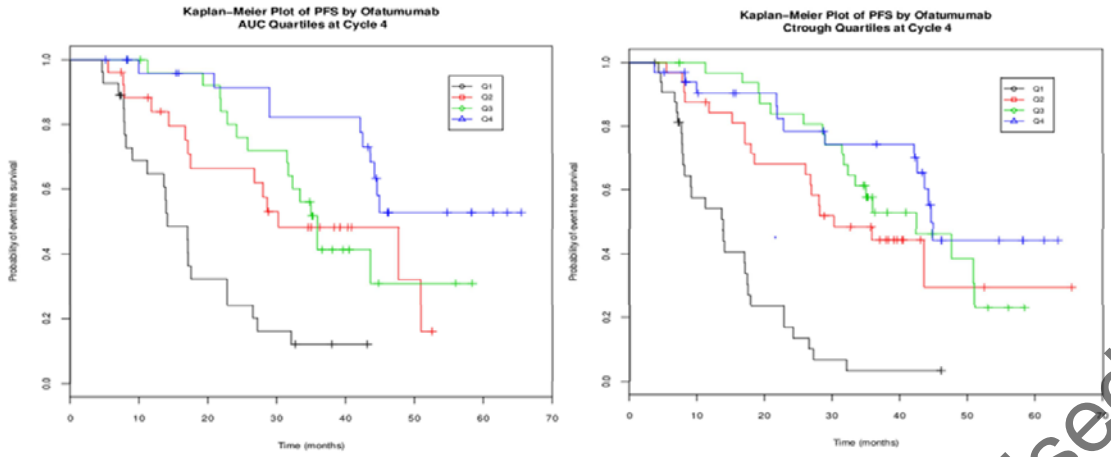
Outcome:

1. Exposure response analysis showed
    a. A general trend of longer PFS was observed with higher ofatumumab exposure (Cycle 4 AUC(0-τ) and Ctrough), an observation that is possibly attributable to response-induced decrease in drug clearance (Figure 9).
    b. B cell depletion was observed at all exposures, however, higher exposures were overall associated with a greater reduction of B cells (Figure 10). The exposure-related differences in B cell depletion across exposure quartiles are consistent with the drug mechanism of action and the observed exposure-related differences in PFS.
    c. There was no apparent relationship between exposure and the occurrence of selected adverse events. A high proportion of subjects (>88%) in the study achieved Ctrough concentrations above the target of 10 ug/mL at steady state.
2. In Study OMB110913, simulations based on an existing model suggested that ofatumumab administered as 2 doses in the first cycle (300 mg on Day 1 and 1000 mg on Day 8), then 1000 mg on Day 1 of each 4-week cycle would maintain plasma concentrations above a target trough concentration of 10 µg/mL in the majority of subjects. Trough concentrations were measured at the end of Cycles 1 to 5 on the day of the next dose, but before the start of the infusion. The vast majority of subjects (>88%) had Ctrough values above 10 µg/mL at steady state (after Cycle 3) (Table 4**: Summary of Ofatumumab Trough Concentrations across Cycles** Table 4).

Table 4: Summary of Ofatumumab Trough Concentrations across Cycles

	N	Mean	SD	Median	G.Mean	n≥10 ug/mL	Percentage (%)
Cycle 2	162	51.2	48.1	36.9	24.3	120	74.1
Cycle 3	150	60.2	55.0	51.6	25.6	110	73.3
Cycle 4	130	93.9	68.2	81.9	58.6	115	88.5
Cycle 5	113	99.9	78.8	91.9	70.4	103	91.2

Source: OMB110913 Table 5.1010 and Table 5.0022



Source: vob/COMB157A/COMB157A2301/csr_1/util/ER/Figures/PFS_C4_AUC.pdf and vob/COMB157A/COMB157A2301/csr_1/util/ER/Figures/PFS_C4_Ctrough.pdf

Figure 9: Kaplan-Meier Plot of PFS by ofatumumab AUC(tesla) and Ctrough quartiles at Cycle 4

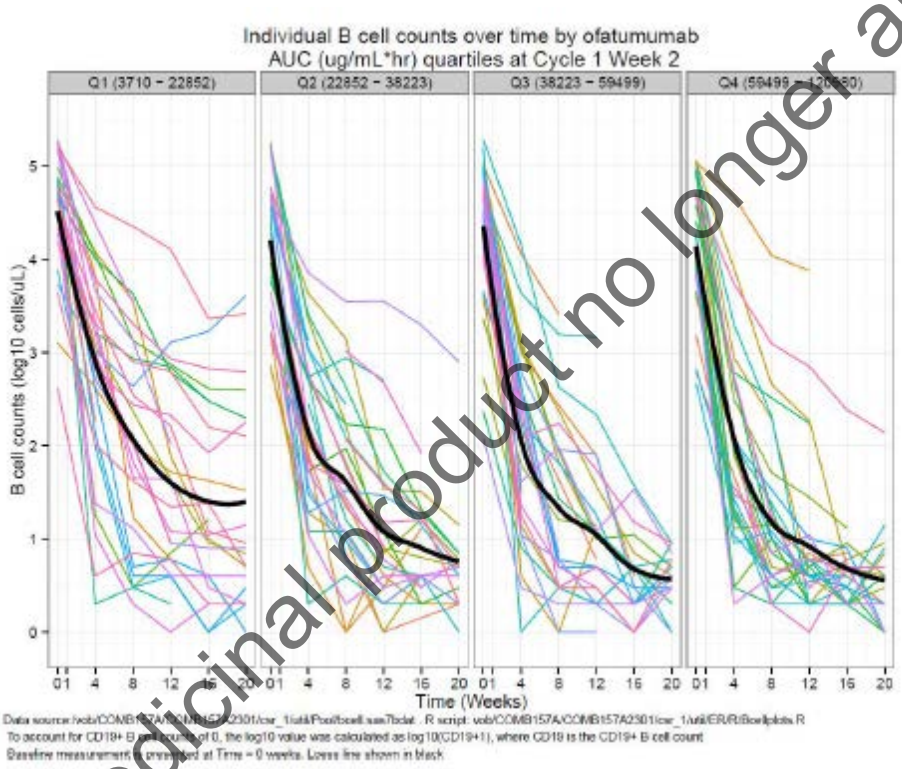


Figure 10: B cell count over time by quartiles of ofatumumab AUC at Cycle 1 Week 2

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology of ofatumumab has been previously characterized, and previously submitted data are not reassessed. The new clinical pharmacology data presented in this submission are from Study OMB913, and consists of a population PK analysis as well as visual investigation by quartiles and Kaplan-Mayer plots to explore the exposure response relationship. The presented data and analysis do not alter the understanding of ofatumumab pharmacokinetics, pharmacodynamics, or immunogenicity.

Based on the results of Study OMB913, ofatumumab exposure was similar when administered alone or in combination with fludarabine in relapsed CLL subjects, however there was indications of an interaction with cyclophosphamide at later cycles.

In patients with relapsed CLL receiving ofatumumab in combination with fludarabine and cyclophosphamide, the geometric mean C_{max} values after the first infusion (300 mg), the 1000 mg infusion on day 8, and the 1000 mg infusion at the fourth cycle were 61.4 µg/ml, 241 µg/ml and 313 µg/ml, respectively; the geometric mean $AUC_{(0-\tau)}$ value at the fourth cycle was 89,091 µg.h./ml. The geometric mean CL and t½ values for ofatumumab were 11.2 ml/h (3.7–105 ml/h) and 19.9 days (1.4-47.1 days) after the fourth infusion.

The above information has been included in the SmPC section 5.2.

An exposure-response analysis in the form of cross-sectional visual inspections was presented to explore the potential relationship of exposure with both efficacy and safety. As expected due to B-cell mediated DD higher ofatumumab exposure was also associated with greater reduction of B-cells, and longer PFS. No relationship could be discerned between exposure of ofatumumab and occurrence of adverse events.

2.3.6. Conclusions on clinical pharmacology

The presented data and analysis do not alter the understanding of ofatumumab pharmacokinetics, pharmacodynamics, or immunogenicity. The results are in general consistency with previous findings of exposure to ofatumumab in subjects with CLL. Relevant information is included in the SmPC section 5.2.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No new dose response studies have been submitted with this application. The selected dose in the pivotal study is in line with the approved dose for previously untreated CLL patients (except that the maximum recommended number of cycles for relapsed CLL patients are 6 as opposed to 12 for previously untreated patients).

The dose of ofatumumab, 1000 mg, was selected based on the tolerability of the 1000 mg dose in previous and ongoing studies as well as PK modelling and simulation results that indicated that the proposed dosing regimen would maintain the target exposure in a high proportion of subjects. An initial dose of 300 mg of ofatumumab was given on Day 1, cycle 1 to minimize infusion-related events before introducing the higher dose at Day 8 cycle 1. The six cycle dosing schema at four week intervals was based on prior clinical experience with rituximab combined with fludarabine or FC [Byrd, 2005; Keating, 2005; Wierda, 2005] and was also thought to maximize the duration of ofatumumab exposure, and maintain chemosensitization of CLL to fludarabine and cyclophosphamide while enhancing response duration without causing additional toxicities.

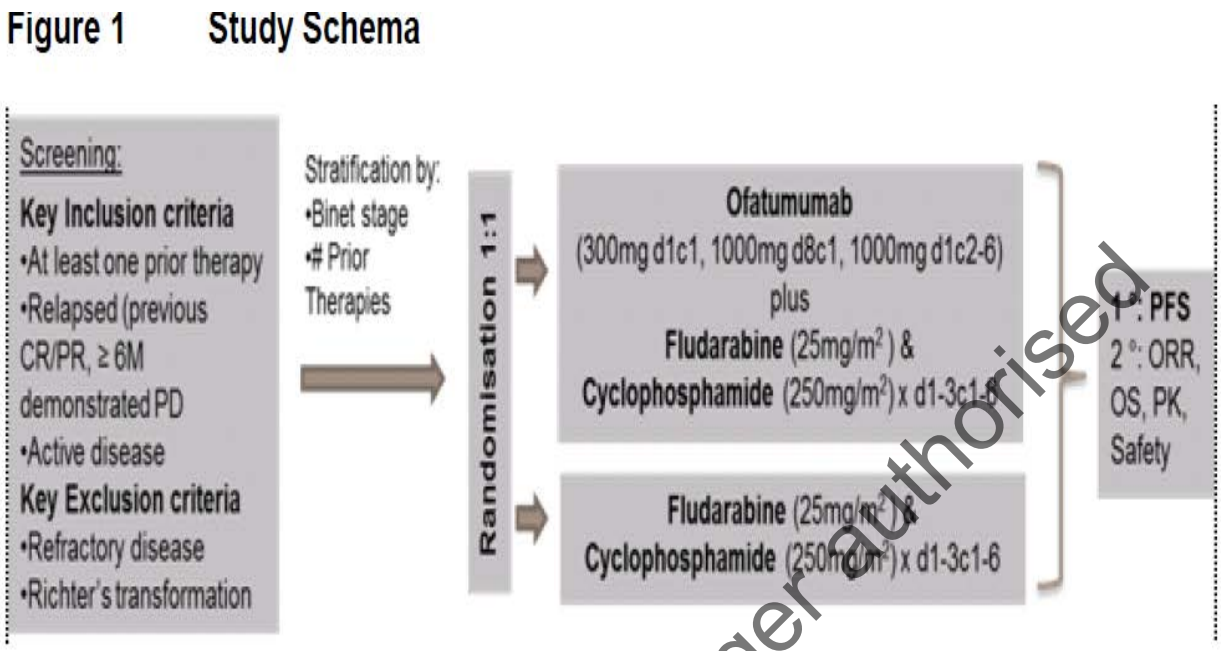
2.4.2. Main study

***Study* OMB110913/COMPLEMENT 2.**

A Phase III, Open Label, Randomized Trial of Ofatumumab Added to Fludarabine-Cyclophosphamide vs. Fludarabine-Cyclophosphamide Combination in Subjects with Relapsed Chronic Lymphocytic Leukemia.

Methods

Figure 1: Study outline.



Study participants

Key Inclusion Criteria:

- Diagnosis of CLL by flow cytometry confirmation of immunophenotype with CD5, CD19, CD20, CD23, CD79b, and surface immunoglobulin
- Active disease and indication for treatment based on modified IWCLL updated National Cancer Institute-Working Group (NCI-WG) guidelines
- Relapsed CLL: defined as a subject who received at least one prior CLL therapy and previously achieved a complete or partial remission/response, but after a period of 6 or more months, demonstrated evidence of disease progression

Key Exclusion Criteria:

- Subjects who were refractory to prior CLL treatment and other B cell disorders (e.g., small lymphocytic leukemia [SLL)], monoclonal B cell lymphocytosis [MBL] or diffuse large B cell lymphoma [DLBCL]) were excluded; Refractory CLL: defined as treatment failure (failure to achieve a CR or PR) or disease progression within 6 months of last anti-leukemic therapy
- Subjects with platelet count less than 50,000/microliter and ANC less than or equal to 1000/microliter
- Chronic or current active infectious disease requiring systemic antibiotics, antiviral, or antiviral 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 unless given in doses ≤100mg/day hydrocortisone (or equivalent dose of other

glucocorticoid) for less than 7 days for exacerbations other than CLL (e.g. asthma)

Treatments

Treatment Arm A (O+FC)

Ofatumumab: Cycle 1: 300 mg IV Day 1 (to minimize infusion-related reactions), 1000 mg IV on Day 8

Cycles 2-6: 1000 mg IV (1 dose every 28 days). Subjects were premedicated at 30 minutes to 2 hours before each infusion of ofatumumab to reduce the incidence and severity of infusion reactions.

Fludarabine: 25 mg/m2 IV, Days 1-3 every 28 days for 6 cycles

Cyclophosphamide: 250 mg/m2 IV, Days 1-3 every 28 days for 6 cycles

OR

Treatment Arm B (FC)

Fludarabine: 25 mg/m2 IV, Days 1-3 every 28 days for 6 cycles

Cyclophosphamide: 250 mg/m2 IV, Days 1-3 every 28 days for 6 cycles

In both treatment arms, disease status assessments to determine subject response or progression were performed monthly according to NCI Criteria.

Patient Reported Outcome (PRO) measures (EORTC QLQ-C30, EORTC QLQ-CLL16,EQ-5D) were performed at Baseline (screening visit) and at Cycle 4-Day 85 treatment visit. A Health Change Questionnaire was performed at all post baseline visits, as per Protocol Section 6. If a subject experienced progressive disease during treatment, PRO measures were assessed at the time progressive disease (PD) was assessed.

Follow-up Phase

After completion of the treatment phase (for subjects achieving CR, PR, or SD), survival and disease status assessments were performed 1 month post treatment and every 3 months for up to 5 years, as well safety, efficacy and pharmacokinetics.

Bone marrow examination with Minimal Residual Disease (MRD) assessment was required for confirmation of CR at least three months post final treatment. CT-Scans were performed for subjects achieving a CR or PR three months post final treatment.

PRO measures (EORTC QLQ-C30, EORTC QLQ-CLL16, EQ-5D and a Health Change Questionnaire) were performed at time points indicated in the Time and Events Schedule. Subjects that had disease progression during the follow-up phase were required to complete a PD follow-up visit. In subsequent visits the subject continued to be followed for survival status only, as per post PD follow-up schedule, until the end of the 5 years follow-up phase.

Post PD follow-up

Follow-up assessment for subjects experiencing disease progression during the treatment phase required a 1-month post-treatment safety assessment. Subsequent follow-up visits included assessment of survival status, date of next CLL therapy, type of therapy and response to therapy, and could be either clinic visit or telephone visits.

Disease status assessment - screening phase

Blood samples, physical examination, computed tomography (CT) scan and bone marrow examination were performed to determine baseline disease status and study eligibility. All examinations had to be

performed ≤14 days prior to randomization, with the exception of the CT scan and bone marrow examination. The CT scan was performed within 6 weeks and the bone marrow examination within 6 months prior to randomization.

Disease status assessment – during study period

In both treatment arms, disease status assessments to determine subject response or progression were performed monthly according to NCI criteria [Hallek, 2008] and included:

- Physical examination including lymph node examination, spleen and liver measurement
- Detection of constitutional symptoms
- Peripheral blood sample evaluation of complete blood count (CBC) and differentialMonitoring and treatment of potential tumour lysis syndrome was performed as per routine oncology standard of care.

Quality of life assessment

The following patient reported outcome (PRO) measures were used in the study:

- European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (EORTC QLQ-C30)
- EORTC QLQ Chronic Lymphocytic Leukaemia 16 item module (EORTC QLQ-CLL 16)
- EuroQoL Five-Dimension (EQ-5D)
- Health Change Questionnaire (HCQ)

The EORTC QLQ-C30, EORTC QLQ-CLL 16, and EQ-5D questionnaires were collected at study Baseline, Day 1 of Cycle 4, at the 1-month follow-up visit and every 3 months during follow-up. The HCQ was administered at Day 1 of Cycle 4, at the 1-month follow-up visit and every 3 months during follow-up.

If a subject demonstrated disease progression, the measures should be completed at the progression visit and again one time after determination of progression. If a subject withdrew from the study then the questionnaires was administered at the point of withdrawal.

Disease status assessment - follow-up phase

After completion of the treatment phase (for subjects achieving CR, PR, or SD), survival and disease status assessments were performed 1-month post treatment and every 3 months for up to 5 years. Bone marrow examination was required for confirmation of CR at least three months post final treatment. Minimal Residual Disease (MRD) assessment of the bone marrow aspirate was also performed for subjects demonstrating a CR. CT-Scans were performed for subjects achieving a CR or PR three months post final treatment.

Disease status assessment - post PD follow-up

Follow-up assessment for subjects experiencing disease progression during the treatment phase required a 1-month post-treatment safety assessment. Subsequent follow-up visits included assessment of survival status, date of next CLL therapy, type of therapy and response to therapy, and could be either clinic visit or telephone visits.

Subjects that had disease progression during the follow-up phase were required to complete a PD follow-up visit. In subsequent visits, the subject continued to be followed for survival status only, as per post PD follow-up schedule, until the end of the 5 years follow-up phase.

Objectives

Primary objective:

The primary objective of this study (OMB110913/COMPLEMENT 2) was to evaluate and compare whether treatment with ofatumumab (GSK1841157) plus fludarabine and cyclophosphamide (O+FC) improved the progression-free survival (PFS) compared to fludarabine and cyclophosphamide (FC) alone in patients with relapsed chronic lymphocytic leukaemia (CLL).

Secondary objectives:

- To evaluate and compare the overall response rate, overall survival, time to and duration of response, time to next therapy, and time to progression in subjects treated with O+FC to those treated with FC
- To evaluate and compare the two treatment arms with respect to changes in scores of patient reported outcome (PRO) measures
- To evaluate and compare the safety, tolerability, and clinical benefit in subjects treated with O+FC to those treated with FC
- To evaluate and compare biological disease progression with clinical response in subjects treated with O+FC to those treated with FC
- To evaluate and compare prognostic and biological markers correlation with clinical response in subjects treated with O+FC to those treated with FC. To evaluate ofatumumab pharmacokinetics added to fludarabine and cyclophosphamide in subjects with relapsed CLL

Other/Exploratory Objectives:

Among others, to compare the clinical outcomes of subjects treated with O+FC to those treated with FC by the pre-treatment Cumulative Illness Rating Scale (CIRS) scores. To explore whether relevant transcriptomic/pharmacogenomics biomarkers or genetic markers could identify factors that may be associated with the development or progression of CLL to better understand response to ofatumumab.

Outcomes/endpoints

The primary efficacy endpoint was defined as the time from randomization until progression or death, whichever occurred first. The PFS was assessed by the investigator and an Independent Review Committee.

Secondary Endpoints

Clinical:

- Time to progression (TTP), defined as the time from randomization until disease progression.
- Time to next therapy (TTNT), defined as the time from randomization until next-line treatment
- Overall response rate (ORR) defined as the percentage of subjects who achieved a best overall response of CR, CRi, nPR, or PR and calculated for IRC and investigator-assessed response.
- Time to response (TTR), defined as time from randomization to the first response (CR, PR).
- Duration of response (DOR), defined as the time from the initial response (CR, PR) to first documented sign of disease progression or death due to any cause.
- Overall Survival (OS), defined as the interval between randomization date and date of death due to any cause. Subjects who had not died were censored at the date of last contact.
- Improvement of constitutional/B-Symptoms

- Improvement of Eastern Cooperative Oncology Group (ECOG) performance status
- Incidence and severity of AEs, SAEs, and other safety parameters including frequency of transfusions, incidence of autoimmune haemolytic anaemia (AIHA), development of human anti-human antibodies (HAHA), incidences of subjects with Grade 3 and Grade 4 infections and myelosuppression (anaemia, neutropenia, thrombocytopenia)
- Quantitative IgG, IgA, IgM
- Changes in patient reported outcomes (PRO) domain scores

Disease Markers:

- B-cell monitoring
- Minimal Residual Disease (MRD)
- Prognostic and biological markers correlating with clinical response

Pharmacokinetics

- Plasma ofatumumab concentrations

Exploratory Endpoints:

- Exploratory pharmacogenetics biomarkers
- Cumulative illness rating scale (CIRS), a tool to measure comorbidity burden by assessing organ class functionality, more frequently used for assessment of previously untreated patients. For the present study, the CIRS-G (G=geriatric) was used.
- Type of and response to next line treatment
- Exploratory transcriptomic/pharmacogenomics biomarkers

Randomisation

Subjects were randomized with a block size of 2 to receive treatment arm A or B in a 1:1 ratio for the duration of the treatment period. Assignment of study drug was stratified according to two stratification factors: the number of prior CLL therapies (1 to 2 vs. ≥3) and Binet stage at Screening (A vs. B vs. C), resulting in six strata in total.

Blinding

Because of distinct infusion reaction profile of ofatumumab, blinding was not possible. In order to minimize potential bias, the primary endpoint was assessed by an IRC blinded to subjects' treatment. The blinded IRC was conducted by Perceptive Informatics, Inc. (Perceptive), utilizing electronic CRF-collected data. The IRC reviewer did not receive subjects' AE data to avoid compromising the blinded treatment group.

Sample size

Study OMB110913 was an event-driven study (disease progression as determined by a blinded Independent Review Committee or death), and the original protocol required 234 IRC-confirmed events to occur to trigger primary analysis. Blinded data were submitted to the IRC on an ongoing basis and the total number of events (i.e., blinded and irrespective of treatment arm) were returned to GSK to allow monitoring of the event rate. During this process, it became evident that the original study assumptions (13 vs. 9 months) underestimated the actual PFS and that events were occurring at a slower rate than projected. In addition, as data began to return from the IRC, more subjects than expected were found to have been censored for reasons such as withdrawal from study, starting new anti-cancer therapy prior

to disease progression, extended time without adequate assessment, and disease progression determined by the investigator but not by the IRC. It was also determined that among completed subjects, the drop-out rate was 31%. Thus, the event rate was anticipated to decrease further over time, due to the declining number of evaluable subjects who have not progressed or have been lost to follow-up. The delay in events, the lower event rate projections due to the decreasing pool of subjects over time, and the risk of losing additional subjects during follow-up resulted in a smaller evaluable subject population and prompted the re-evaluation of the sample size assumptions for median PFS for the study.

The following assumptions were made in the estimation of the required sample size in protocol amendment 02:

- Event times are exponentially distributed.
- A median PFS for fludarabine + cyclophosphamide is 20 months.
- A median PFS for ofatumumab 1000 mg + fludarabine + cyclophosphamide is 30 months.
- A 1:1 stratified randomization scheme.
- An 80% chance of successfully declaring a difference in the presence of a true underlying difference (power).
- A 5% two-sided risk of erroneously claiming a difference in the presence of no true underlying difference.
- Accrual rate is 10 subjects per month.

Under the above assumptions, a minimum of 194 total events from both treatment arms combined were needed for the study to have 80% power. With a total sample size of 316 evaluable subjects, the total duration of the study was estimated to be approximately 50.5 months (under H1) to obtain the 194 total events. Assuming a drop-out rate of 10%, the total sample size for both arms combined was expected to be about 352 subjects and the total duration of the study will be about 54 months. Assuming a screening failure rate of 15%, the total number of subjects expected to be screened was approximately 416 subjects.

The robustness and sensitivity of the above sample size calculation was considered in order to assess the impact on power should the assumed median PFS vary. The following table shows the estimated power for different median values of PFS for ofatumumab 1000mg + fludarabine + cyclophosphamide. The total number of events is 194 and the total number of evaluable subjects is 316.

Median PFS for Ofatumumab 1000 mg + Fludarabine + Cyclophosphamide	Median PFS for Fludarabine + Cyclophosphamide	Estimated Power
26 months (30% improvement)	20	0.45
28 months (40% improvement)	20	0.65
30 months (50% improvement)	20	0.80
32 months (60% improvement)	20	0.90

Statistical analysis

The Intent-to-treat (ITT) Analysis Set included data from all subjects who were randomized, regardless to which treatment arm they were randomized or which treatment they received. The ITT population was

used for all efficacy assessments.

A Safety Analysis Set included data from subjects who received ≥ 1 dose of a study drug, with treatment assignments designated according to the actual treatment received.

The Per-protocol (PP) population was used in the primary endpoint analysis to check the robustness of the results for the ITT population, it was only used if the difference in the total number of subjects was >10% of the ITT population.

No interim analysis was planned for the study. PFS was tested based on a two-sided test, with a significance alpha level of 0.05. The Kaplan Meier method was used for survival distributions, and the curved were compared using a stratified log-rank test. A Cox regression model was used and included covariates for treatment, stratification factors (Binet Stage (A vs. B vs. C) and number of prior therapies (1-2 vs >3). Analytical results included the estimated hazard ratios along with 95% confidence intervals, and associated probabilities for the effect of treatment, stratification factors and the covariates. The hazard ratio for treatment expressed the risk of experiencing disease progression or death for O+FC vs. FC. The primary efficacy hypothesis (the null hypothesis) was to be rejected at the 2-sided significance level before the efficacy hypothesis for the secondary efficacy endpoints could be evaluated. If the primary hypothesis was rejected, the 5 secondary endpoints were to be sequentially tested at the 2-sided significance level of 0.03 as listed previously. The significance level was chosen in such a way that the overall Type 1 error rate of significance level was preserved at the 2sided significance level of 0.05.

Five sensitivity analyses of PFS were conducted to confirm the robustness of the primary PFS analysis.

Subgroup analyses were conducted for IRC-assessed PFS for the stratification factors (number of prior therapies and Binet stage) as well as gender, age, race, geographical distribution, Rai staging, ECOG performance status, presence of constitutional symptoms, presence of comorbidities, creatinine clearance, type of previous therapy, and time to first diagnosis.

Secondary efficacy analyses of IRC-assessed ORR and OS were considered as inferential secondary endpoints for this study, and were only tested if the primary endpoint was significant to control overall type I error rate based on the sequential gatekeeping strategy.

Patient reported outcomes (PRO) analyses were performed using the ITT. The mixed model repeated measures (MMRM) was used to assess the treatment effect in the changes from baseline score in Global Health Status/HRQoL and in the B symptom index for data up to 9 months, 12 months, and 18 months.

Results

Participant flow

Table *5*: Subject disposition, treatment and follow-up status with reason for discontinuation

Phase/Status	O+FC (N=183)	FC (N=182)	Total (N=365)
Treatment Completion Status, n (%)			
Entered	183 (100)	182 (100)	365 (100)
Treatment received[a]	181 (99)	178 (98)	359 (98)
Ongoing	0	0	0
Completed scheduled treatment	119 (65)	93 (51)	212 (58)
Treatment discontinued[b]	64 (35)	89 (49)	153 (42)
Primary Reason for Study Drug Discontinuation, n (%)			
Adverse event[c]	50 (27)	52 (29)	102 (28)
Physician decision	6 (3)	12 (7)	18 (5)
Subject decision	6 (3)	15 (8)	21 (6)
Disease progression	0	9 (5)	9 (2)
Lost to follow-up	1 (<1)	1 (<1)	2 (<1)
Protocol deviation	1 (<1)	0	1 (<1)
Follow-Up Status, n (%)			
Ongoing	82 (45)	57 (31)	139 (38)
Follow-up	44 (24)	26 (14)	70 (19)
Survival follow-up	38 (21)	31 (17)	69 (19)
Died	67 (37)	69 (39)	136 (38)
Completed 5 years follow-up	3 (2)	0	3 (1)
Withdrawn from study	31 (17)	56 (31)	87 (24)
Primary Reason for Study Withdrawal, n (%)			
Withdrawal by subject/consent withdrawn	19 (10)	40 (22)	59 (16)
Physician decision	3 (2)	4 (2)	7 (2)
Lost to follow-up	7 (4)	9 (5)	16 (4)
Randomized in error[a]	2 (1)	2 (1)	4 (1)
Unknown	0	1 (<1)	1 (<1)

Data Source: Table 1.0000, Table 1.1120, Table 1.1130, Table 3.1630, Listing 21.0030
Abbreviations: eCRF=electronic case report form; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

a. 6 subjects entered the treatment phase, but did not receive study treatment (O+FC: Subject 266, Subject 1925; FC: Subject 3, Subject 270, Subject 282, Subject 915). Four of these subjects were randomized in error (O+FC: Subject 266, Subject 1925; FC: Subject 270, Subject 915), and 2 subjects in the FC arm were withdrawn (Subject 3, Subject 282).
b. Includes subjects who did not initiate treatment and subjects who discontinued early due to PD (FC: 9 subjects, Table 1.1130 [not included in Table 1.1120]).
c. Data based on study treatment discontinuation details provided in the eCRF and includes subjects with fatal SAEs. This summary includes 4 additional subjects compared with Table 36, which included subjects with AEs and 'action taken' indicated as 'study drug discontinued'. This discrepancy is due to 2 subjects with AEs leading to drug discontinuation, but the primary reason for study drug discontinuation was provided as 'investigator decision' (O+FC: Subject 785, Subject 2082), and 6 subjects who discontinued study drug due to AEs, but had fatal SAEs for which 'action taken' was recorded as 'not applicable' (O+FC: Subject 291, Subject 835, Subject 1880; FC: Subject 821, Subject 837, Subject 1750). For death during treatment, please see Section 7.2.

Post-treatment anti-cancer therapy

Administration of subsequent CLL therapy was at the discretion of the treating investigator per local standard of care.

Rituximab, as monotherapy or in combination with chemotherapy, was the most frequently prescribed

anti-cancer drug, see table below. Ofatumumab was not offered as part of a crossover or extension study, but was administered to 2% of subjects, primarily in the FC arm.

Table 6: Post-treatment anti-cancer therapy received by more than 1% of subjects

	O+FC (N=183)	FC (N=182)	Total (N=365)
Any Anti-Cancer Therapy, n (%)			
Yes	62 (34)	59 (32)	121 (33)
No	121 (66)	123 (68)	244 (67)
Medication, n (%)			
Rituximab	40 (22)	41 (23)	81 (22)
Bendamustine	30 (16)	25 (14)	55 (15)
Cyclophosphamide	26 (14)	31 (17)	57 (16)
Vincristine	18 (10)	15 (8)	33 (9)
Fludarabine	13 (7)	14 (8)	27 (7)
Doxorubicin	9 (5)	8 (4)	17 (5)
Chlorambucil	6 (3)	10 (5)	16 (4)
Alemtuzumab	2 (1)	6 (3)	8 (2)
Ofatumumab	1 (<1)	7 (4)	8 (2)
Vinblastine	1 (<1)	5 (3)	6 (2)
Median Time from Study Drug Discontinuation to Start of Subsequent Anti-Cancer Therapy, days	667	447	532

Data Source: Table 1.4050, Table 1.4224
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

Concomitant medications

The majority of subjects used concomitant medications during the study (O+FC: 96%, FC: 93%). The most commonly reported concomitant medications that were not a component of the infusion-pre-medication were antibiotics or antivirals, which were predominantly taken for prophylaxis. The same percentage of subjects in both treatment arms received antimicrobials (84%). Since known AEs associated with FC treatment include nausea and vomiting, anti-emetic drugs were commonly reported.

Sixty-two percent of subjects received at least 1 transfusion (blood products or blood supportive care products) during the trial with a higher proportion of subjects receiving transfusions in the O+FC arm (69%) compared with the FC arm (56%). Red blood cells and/or platelets were administered to 26% of subjects in the O+FC arm and 30% of subjects in the FC arm. Blood products were administered to 29% of subjects (O+FC: 28%, FC: 31%) and blood supportive care products were administered to 50% of subjects (O+FC: 59%, FC: 40%). Granulocyte colony stimulating factor (G-CSF) for the treatment and prevention of neutropenia was administered to 56% of subjects in the O+FC arm and 40% of subjects in the FC arm. Erythropoietin was administered to 7% of subjects in the O+FC arm and 5% in the FC arm.

Exposure

Table 7: Exposure to study treatment

	O+FC (N=181)	FC (N=178)
Treatment Duration, days		
Mean (SD)	127.7 (48.1)	117.7 (48.5)
Median (min-max)	143 (1-273)	143 (3-242)
Number of Cycles Treated, n (%)		
Mean (SD)	5.1 (1.52)	4.8 (1.58)
Median (min-max)	6 (1-6)	6 (1-6)
<3 Cycles	18 (10)	21 (12)
3-6 Cycles	163 (90)	157 (88)
Completed 6 full cycles	119 (66)	93 (52)

Data Source: Table 3.0050, Table 3.0150, Table 3.0010
Abbreviations: FC=fludarabine and cyclophosphamide; max=maximum; min=minimum; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SD=standard deviation

Median administered dose of cyclophosphamide per infusion was between 442.5 and 460 mg among all subjects treated. Median administered dose of fludarabine per infusion was between 43 and 45 mg.

The median exposure to ofatumumab was 1300 mg for Cycle 1 (300 mg initial dose and 1000 mg subsequent dose for Cycle 1) and 1000 mg for all subsequent cycles.

Table 8: Study drug dose reductions, delays or interruptions

Study Drug Dosing Modification Number of Modifications	O+FC (N=181) n (%)	FC (N=178) n (%)
Any Ofatumumab Interruption or Stop	**91 (50)**	**n/a**
0	90 (50)	n/a
1	67 (37)	n/a
2	14 (8)	n/a
≥3	10 (6)	n/a
Any Ofatumumab Dose Delay	**129 (71)**	**n/a**
0	52 (29)	n/a
1	48 (27)	n/a
2	38 (21)	n/a
≥3	43 (24)	n/a
Any Fludarabine Dose Delay	**127 (70)**	**120 (67)**
0	54 (30)	58 (33)
1	47 (26)	60 (34)
2	44 (24)	27 (15)
≥3	36 (20)	33 (19)
Any Fludarabine Dose Reduction	**60 (33)**	**55 (31)**
0	121 (67)	123 (69)
1	45 (25)	45 (25)
2	15 (8)	10 (6)
≥3	0	0

Study Drug Dosing Modification Number of Modifications	O+FC (N=181) n (%)	FC (N=178) n (%)
Any Cyclophosphamide Dose Delay	**127 (70)**	**120 (67)**
0	54 (30)	58 (33)
1	46 (25)	60 (34)
2	45 (25)	27 (15)
≥3	36 (20)	33 (19)
Any Cyclophosphamide Dose Reductions	**50 (28)**	**44 (25)**
0	131 (72)	134 (75)
1	37 (20)	37 (21)
2	13 (7)	7 (4)
≥3	0	0

Data Source: Table 3.0060, Table 3.0090, Table 3.0092, Table 3.0094, Table 3.0096, Table 3.0098
Abbreviation: FC=fludarabine and cyclophosphamide; n/a=not applicable; O+FC=ofatumumab plus fludarabine and cyclophosphamide.
Note: Data for dose interruption or stop for fludarabine or cyclophosphamide were not collected.

Treatment compliance

The majority (>90%) of subjects randomized to receive ofatumumab received 100% of the expected total dose. Similarly compliance with the FC regimen was also good with >95% of subjects receiving between 80% and 120% of the expected total daily dose. Variations in this range were expected due to the requirement to calculate dose based on body surface area.

Conduct of the study

Recruitment

This is an International multicentre study where 365 subjects were included at 87 sites in 18 countries in USA, Canada, Bulgaria, Germany, Greece, Italy, Poland, UK, Spain, Netherlands, Romania, Brazil, India, Mexico, Russia, Thailand and Ukraine. It was initiated at 12th March 2009 and completed at 17th December 2014.

Table 9: Subjects by geographical region

Region	O+FC (N=183) n (%)	FC (N=182) n (%)	Total (N=365) n (%)
Europe[a], n (%)	96 (52)	92 (51)	188 (52)
North America[b]	13 (7)	9 (5)	22 (6)
EMAP[c]	74 (40)	81 (45)	155 (42)

Data Source: Table 2.0040
Abbreviation: EMAP=emerging markets and Asia Pacific; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.
a. Europe: Bulgaria, Germany, Greece, Italy, Poland, Romania, Spain, Netherlands, and United Kingdom.
b. North America: United States, Canada.
c. EMAP: Brazil, India, Mexico, Russia, Taiwan, Thailand, and Ukraine.

Protocol amendments

An overview of the protocol amendments is given below.

GlaxoSmithKline Document Number	Date	Version
UM2007/00310/00	2008-AUG-22	Original
UM2007/00310/01	2014-APR-09	Amendment No. 1
• Study Name and Logo added • Name of Physician Study Leader updated • Investigator Agreement Page updated • SAEs no longer reported after commencement of subsequent anti-CLL therapy • Prohibited concomitant medication, Glucocorticoid dosing amended • Requirement to collect anticancer and anti-infectious concomitant medications after 1 month follow-up amended to collect only if associated with an SAE and only until subsequent anti-CLL therapy is initiated		
• Details regarding reporting of study results to investigators, to a publically available register, and for publication updated • Investigator responsibilities with regard to Quality Compliance and Quality Assurance updated • Minor clarifications and typographical errors addressed		
UM2007/00310/02	2014-SEP-30	Amendment No. 2
• Clinical Investigational Leader and associated contact information updated • Introduction updated with current published data • Statistical assumptions for event rate projection updated		
UM2007/00310/03	2015-FEB-20	Amendment No. 3 (India only)
• Name of Physician Project Lead and Sponsor Signatory updated • The requirement to report SAEs after commencement of subsequent anti-CLL therapy has been reinstated in India only, to comply with changed country-specific requirements		

Protocol deviations

An overview of the protocol deviations are given below.

Table *10*: Protocol deviations

Deviation Category	O+FC (N=183)	FC (N=182)	Total (N=365)
Any Protocol Deviation[a], n (%)	**81 (44)**	**68 (37)**	**149 (41)**
Visit completion	29 (16)	38 (21)	67 (18)
Wrong study treatment/administration/dose	31 (17)	14 (8)	45 (12)
Assessment or time point completion	11 (6)	14 (8)	25 (7)
Failure to report safety events per protocol	7 (4)	5 (3)	12 (3)
Eligibility criteria not met[b]	8 (4)	2 (1)	10 (3)
Excluded medication, vaccine or device	5 (3)	5 (3)	10 (3)
Informed consent[c]	4 (2)	3 (2)	7 (2)
Study procedures	1 (<1)	0	1 (<1)
Any Per Protocol Deviation, n (%)	**9 (5)**	**5 (3)**	**14 (4)**
Failure to demonstrate diagnosis of relapsed CLL	3 (2)	2 (1)	5 (1)
Prohibited therapies or procedures	3 (2)	1 (<1)	4 (1)
Subject exposed to <80% or >120% planned total dose[d]	3 (2)	2 (1)	5 (1)

Data Source: Table 1.1410, Table 1.1412, Listing 21.0050, Listing 21.0020

Abbreviations: CLL=chronic lymphocytic leukemia; FC=fludarabine and cyclophosphamide; ICF=informed consent form; O+FC=ofatumumab plus fludarabine and cyclophosphamide; PGx=pharmacogenomic.

a. Important deviations were summarized from study protocol deviation tracker; deviation tracker was completed by site monitors and data management, and deviations were categorized as important by the study team in accordance with ICH E3.

b. Ten subjects had 11 deviations of protocol eligibility criteria, including deviations for refractory CLL, AIHA requiring treatment, Hepatitis B status, and inappropriate screening lab values.

c. All 7 subjects signed the ICF version 1 prior to study start, but did not sign ICF version 2 or signed late. In version 2, the risk of CT scan was changed from low to moderate. In addition, 1 subject did not sign the PGx section of the ICF, but a sample was taken. The sample was subsequently destroyed.

d. Includes exposure to either study treatment, unless due to AE and/or protocol-defined dose reductions.

Baseline data

Baseline demographic characteristics can be found in the table below.

Table *11*: Demographic characteristics

		O+FC (N=183)	FC (N=182)	Total (N=365)
Age, years	Median (min-max)	62 (38-83)	61 (32-90)	61 (32-90)
	<65, n (%)	121 (66)	110 (60)	231 (63)
	≥65, n (%)	62 (34)	72 (40)	134 (37)
	≥70, n (%)	36 (20)	48 (26)	84 (23)
	≥75, n (%)	10 (5)	17 (9)	27 (7)
Sex, n (%)	Male	104 (57)	116 (64)	220 (60)
	Female	79 (43)	66 (36)	145 (40)
Ethnicity, n (%)	Not Hispanic/Latino	172 (94)	169 (93)	341 (93)
	Hispanic/Latino	11 (6)	13 (7)	24 (7)
Race, n (%)	White	158 (86)	154 (85)	312 (85)
	Asian	19 (10)	22 (12)	41 (11)
	Central/South Asian	13 (7)	16 (9)	29 (8)
	Japanese/East Asian/SE Asian	6 (3)	6 (3)	12 (3)
	African American/African	3 (2)	5 (3)	8 (2)
	American Indian or Alaskan Native	3 (2)	1 (<1)	4 (1)

Data Source: Table 1.2010, Table 1.2020, Table 1.2040
Abbreviations: FC=fludarabine and cyclophosphamide; max=maximum; min=minimum; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SE=southeast

Table *12*: Disease characteristics at screening / baseline

		O+FC (N=183)	FC (N=182)	Total (N=365)
Time from First Diagnosis to Randomization, Median (min-max), years		4.6 (1-26)	4.6 (0-19)	4.6 (0-26)
Time from Last Progression to Randomization, Median (min-max), months		2.0 (0-83)	1.8 (0-49)	1.9 (0-83)
Rai Stage, n (%)	Low risk (stage 0)	6 (3)	6 (3)	12 (3)
	Intermediate (I, II)	118 (64)	111 (61)	229 (63)
	High risk (III,IV)	59 (32)	64 (35)	123 (34)
	Missing	0	1 (<1)	1 (<1)
Binet Stage, n (%)	A	30 (16)	29 (16)	59 (16)
	B	102 (56)	100 (55)	202 (55)
	C	51 (28)	53 (29)	104 (28)
ECOG Status, n (%)	0,1	170 (93)	170 (93)	340 (93)
	2	13 (7)	12 (7)	25 (7)
Lymphocytes, Median (min-max), 10^9/L	Screening	42.9 (1-251)	41.9 (2-338)	42.0 (1-338)
	Baseline	41.9 (2-221)	44.3 (1-551)	42.4 (1-551)
Evidence of Bone Marrow Failure, n (%)		56 (31)	58 (32)	114 (31)
Splenomegaly[a], n (%)		44 (24)	51 (28)	95 (26)
Lymphadenopathy[b], n (%)		91 (50)	82 (45)	173 (47)
Lymphocytosis, n (%)	>50% increase over 2 mos	54 (30)	64 (35)	118 (32)
	Doubling over <6 mos	84 (46)	88 (48)	172 (47)
B-Symptoms, n (%)	Weight loss[c]	21 (11)	20 (11)	41 (11)
	Fevers[d]	18 (10)	18 (10)	36 (10)
	Night sweats[e]	107 (58)	107 (59)	214 (59)

Data Source: Table 1.3210, Table 1.3211, Table 1.8000, Table 1.8002, Table 2.0076
Abbreviations: ECOG=Eastern Cooperative Oncology Group; FC=fludarabine and cyclophosphamide; max=maximum; min=minimum; mos=months; O+FC=ofatumumab plus fludarabine and cyclophosphamide.
Note: All assessments were completed at Screening, with the exception of ECOG status, which was determined on Day 1 (baseline).

a. Defined as massive (≥6 cm below the left costal margin) or progressive splenomegaly.
b. Defined as massive nodal clusters (≥10 cm longest diameter), symptomatic or progressive lymphadenopathy.
c. Unintentional weight loss ≥10% in the prior 6 months.
d. Fevers 100.5 °F (38.5 °C) for 2 weeks without evidence of infection.
e. Night sweats without evidence of infection.

Table *13*: Prognostic markers at baseline

	O+FC (N=183)	FC (N=182)	Total (N=365)
IGHV Mutational Status (98% cut-off), N	167	169	336
Sequence homology >98%, n (%)	115 (69)	116 (69)	231 (69)
Sequence homology ≤98%, n (%)	52 (31)	53 (31)	105 (31)
IGHV Mutational Status (97% cut-off), N	167	169	336
Sequence homology ≥97%, n (%)	127 (76)	126 (75)	253 (75)
Sequence homology <97%, n (%)	40 (24)	43 (25)	83 (25)
V_H3-21 Usage, N	168	169	337
Yes, n (%)	9 (5)	7 (4)	16 (5)
Chromosomal Aberration			
6q deletion, N	177	171	348
≥20%, n (%)	5 (3)	4 (2)	9 (3)
11q deletion[a], N	176	172	348
≥20%, n (%)	40 (23)	31 (18)	71 (20)
12q trisomy, N	177	172	349
≥20%, n (%)	20 (11)	24 (14)	44 (13)
17p deletion, N	177	172	349
≥20%, n (%)	7 (4)	13 (8)	20 (6)
13q deletion, N	177	172	349
≥20%, n (%)	97 (55)	90 (52)	187 (54)
CH_{50}, N	168	168	336
<LLN, n (%)	16 (10)	21 (13)	37 (11)
LLN-ULN, n (%)	88 (52)	99 (59)	187 (56)
>ULN, n (%)	64 (38)	48 (29)	112 (33)
CD20 Expression (MFI), N	180	176	356
<LLN, n (%)	178 (99)	168 (95)	346 (97)
β2 microglobulin, N	178	174	352
Median, µg/L	4505	4425	4445
β2 microglobulin (4000 µg/L cut-off)			
≤4000 µg/L, n (%)	67 (38)	69 (40)	136 (39)
>4000 µg/L, n (%)	111 (62)	105 (60)	216 (61)
β2 microglobulin (3500 µg/L cut-off)			
≤3500 µg/L, n (%)	51 (29)	47 (27)	98 (28)
>3500 µg/L, n (%)	127 (71)	127 (73)	254 (72)
ZAP-70, N	176	169	345
Positive, n (%)	94 (53)	91 (54)	185 (54)
Negative, n (%)	28 (16)	32 (19)	60 (17)
Intermediate, n (%)	54 (31)	46 (27)	100 (29)

Data Source: Table 1.4700, Table 2.0058
Abbreviations: FC=fludarabine and cyclophosphamide; LLN=lower limit of normal; MFI=mean fluorescence intensity; O+FC=ofatumumab plus fludarabine and cyclophosphamide; ULN=upper limit of normal.
a. No subject with 11q deletion also had 17p deletion.

Table *14*: Screening/baseline fitness, creatinine clearance and comorbid conditions

	O+FC (N=183)	FC (N=182)	Total (N=365)
Presence of Comorbidities, median (min-max)	2 (0-9)	2 (0-9)	2 (0-9)
0, n (%)	42 (23)	43 (24)	85 (23)
1, n (%)	41 (22)	44 (24)	85 (23)
≥2, n (%)	100 (55)	95 (52)	195 (53)
Creatinine, µmol/L, median (min-max)	86 (46-168)	83 (51-164)	85 (46-168)
CrCl, median (min-max), mL/min	79 (31-193)	82 (29-176)	79 (29-193)
CrCl <70 mL/min, n (%)	68 (37)	63 (35)	131 (36)
CIRS-G total score, median (min-max)	7 (4-17)	7 (4-16)	7 (4-17)
>10, n (%)	30 (16)	23 (13)	53 (15)

Data Source: Table 1.4500, Table 1.3212, Table 1.3213, Table 3.2150
Abbreviations: CIRS-G=Cumulative Illness Rating Scale-Geriatric, CrCl=creatinine clearance; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

Table *15*: Summary of pre-treatment anti-chronic lymphocytic leukemia therapy

	O+FC (N=183)	FC (N=182)	Total (N=365)
Number of Prior Therapies, n (%)			
1-2	149 (81)	147 (81)	296 (81)
≥3	34 (19)	35 (19)	69 (19)
n	183	181[a]	364
Median (min-max)	1.0 (1-8)	1.0 (1-6)	1.0 (1-8)
Type of Anti-CLL Therapy, n (%)			
Chemotherapy[b]	183 (100)	179 (98)	362 (>99)
Biologic Therapy[c]	53 (29)	39 (21)	92 (25)
Hormonal Therapy[d]	5 (3)	4 (2)	9 (2)
Immunotherapy[e]	2 (1)	3 (2)	5 (1)
Unknown[f]	4 (2)	3 (2)	7 (2)
Rituximab-containing Therapies, n (%)	43 (23)	35 (19)	78 (21)
Bendamustine-containing Therapies, n (%)	3 (2)	8 (4)	11 (3)
Alemtuzumab-containing Therapies, n (%)	14 (8)	9 (5)	23 (6)
Fludarabine-containing Therapies, n (%)	100 (55)	100 (55)	200 (55)
Alkylator-containing Therapies, n (%)	144 (79)	131 (72)	275 (75)

Data Source: Table 1.2210, Table 1.4011, Table 1.4012, Table 1.4013, Table 1.4014, Table 1.4015, Table 1.4020, Table 1.4032, Listing 21.0080

Abbreviations: CLL=chronic lymphocytic leukemia; max=maximum, minimum=minimum; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

a. The pre-treatment anti-CLL therapy for Subject 915 was not reported.
b. Chemotherapy included: cyclophosphamide, fludarabine, chlorambucil, vincristine, doxorubicin, cladribine.
c. Biologic Therapy included: rituximab and alemtuzumab.
d. Hormonal Therapy included: prednisolone, prednisone, dexamethasone, methylprednisolone.
e. Immunotherapy included: interferon.
f. Therapy reported as unknown include: prednisolone, allopurinol, methylprednisolone, radiotherapy, dexamethasone.

Table *16*: Summary of pre-treatment dictionary anti-cancer therapy

ATC Level 1 Ingredient	OFA + FC (N=183)	FC (N=182)	Total (N=365)
Any medication	183 (100%)	181 (>99%)	364 (>99%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS			
Any medication	183 (100%)	181 (>99%)	364 (>99%)
CYCLOPHOSPHAMIDE	125 (68%)	113 (62%)	238 (65%)
FLUDARABINE	101 (55%)	100 (55%)	201 (55%)
CHLORAMBUCIL	86 (47%)	78 (43%)	164 (45%)
VINCRISTINE	49 (27%)	45 (25%)	94 (26%)
RITUXIMAB	43 (23%)	35 (19%)	78 (21%)
DOXORUBICIN	20 (11%)	13 (7%)	33 (9%)
CLADRIBINE	17 (9%)	15 (8%)	32 (9%)
ALEMTUZUMAB	14 (8%)	9 (5%)	23 (6%)
VINBLASTINE	6 (3%)	8 (4%)	14 (4%)
BENDAMUSTINE	3 (2%)	9 (5%)	12 (3%)
MITOXANTRONE	5 (3%)	5 (3%)	10 (3%)
CYTARABINE	2 (1%)	4 (2%)	6 (2%)
ETOPOSIDE	2 (1%)	2 (1%)	4 (1%)
IDARUBICIN	2 (1%)	1 (<1%)	3 (<1%)
CISPLATIN	0	2 (1%)	2 (<1%)
OXALIPLATIN	2 (1%)	0	2 (<1%)
PROCARBAZINE	0	2 (1%)	2 (<1%)
BLEOMYCIN	1 (<1%)	0	1 (<1%)
CARBOPLATIN	0	1 (<1%)	1 (<1%)
EPIRUBICIN	1 (<1%)	0	1 (<1%)
IFOSFAMIDE	1 (<1%)	0	1 (<1%)
INTERFERON	1 (<1%)	0	1 (<1%)
LOMUSTINE	0	1 (<1%)	1 (<1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS			
Any medication	65 (36%)	54 (30%)	119 (33%)
PREDNISOLONE	31 (17%)	30 (16%)	61 (17%)

Table *17*: Summary of number of prior anti-cancer therapy regimens

	OFA + FC (N=183)	FC (N=182)	Total (N=365)
Number of Chemotherapy Regimens			
1	97 (53%)	102 (56%)	199 (55%)
2	53 (29%)	47 (26%)	100 (27%)
3	24 (13%)	16 (9%)	40 (11%)
4	3 (2%)	10 (5%)	13 (4%)
>4	6 (3%)	4 (2%)	10 (3%)
Number of Hormonal Therapy Regimens			
1	2 (1%)	1 (<1%)	3 (<1%)
2	2 (1%)	3 (2%)	5 (1%)
3	1 (<1%)	0	1 (<1%)
4	0	0	0
>4	0	0	0
Number of Biologic Therapy Regimens			
1	46 (25%)	30 (16%)	76 (21%)
2	6 (3%)	7 (4%)	13 (4%)
3	1 (<1%)	2 (1%)	3 (<1%)
4	0	0	0
>4	0	0	0
Number of Immunotherapy Regimens			
1	2 (1%)	3 (2%)	5 (1%)
2	0	0	0
3	0	0	0
4	0	0	0
>4	0	0	0

Table *18*: Summary of best response to most recent prior anti-cancer therapy

	OFA + FC (N=183)	FC (N=182)	Total (N=365)
Best Response			
Complete Response	81 (44%)	55 (30%)	136 (37%)
Partial Response	99 (54%)	125 (69%)	224 (61%)
Stable Disease	0	0	0
Progressive Disea	0	0	0
Unknown	0	1 (<1%)	1 (<1%)
Not Evaluable	0	0	0
Not Applicable	3 (2%)	0	3 (<1%)
Missing	0	1 (<1%)	1 (<1%)
Response Rate	180 (98%)	180 (99%)	360 (99%)

Numbers analysed

Efficacy and PRO analysis were conducted on the ITT population, which comprised all 365 randomized subjects (O+FC: N=183, FC: N=182) (see table below). The PP population (N=351) was a subset of subjects from the ITT population who did not have an important protocol deviation (see under “Statistical methods”). The Safety population included 359 subjects (O+FC: N=181, FC: N=178) who were randomized and received at least 1 dose of study drug. The 6 subjects excluded from the Safety population were randomized, but did not receive any study treatment.

Table *19*: Study populations

Study Populations	O+FC (N=183)	FC (N=182)	Total (N=365)
Intent-to-treat (ITT) population[a]	183	182	365
Safety population[b]	181	178	359
Per protocol (PP) population[c]	174	177	351
PK population	176	27	203
PGx population	176	162	338

Data Source: Table 1.0000, Listing 25.1000, Listing 25.1010, Listing 25.1020
Abbreviations: FC=fludarabine and cyclophosphamide; ITT=intent-to-treat; O+FC=ofatumumab plus fludarabine and cyclophosphamide; PK=pharmacokinetic; PGx=pharmacogenomic; PP=per protocol.

a. All randomized subjects regardless of whether or not they received study treatment.
b. Subjects that took at least 1 dose of study drug; grouping was based on the actual treatment subjects received.
c. Subjects with no important protocol deviations.

Outcomes and estimation

Efficacy results were based on all available subject data for the ITT population (N=183 subjects randomized to O+FC and N=182 subjects randomized to FC) with a data cut-off of 17 December 2014. Median follow-up at the data cut-off was 1034 days (approximately 34 months) for the total ITT population, with 1067 days (approximately 35 months) in the O+FC arm and 701 days (approximately 23 months) in the FC arm.

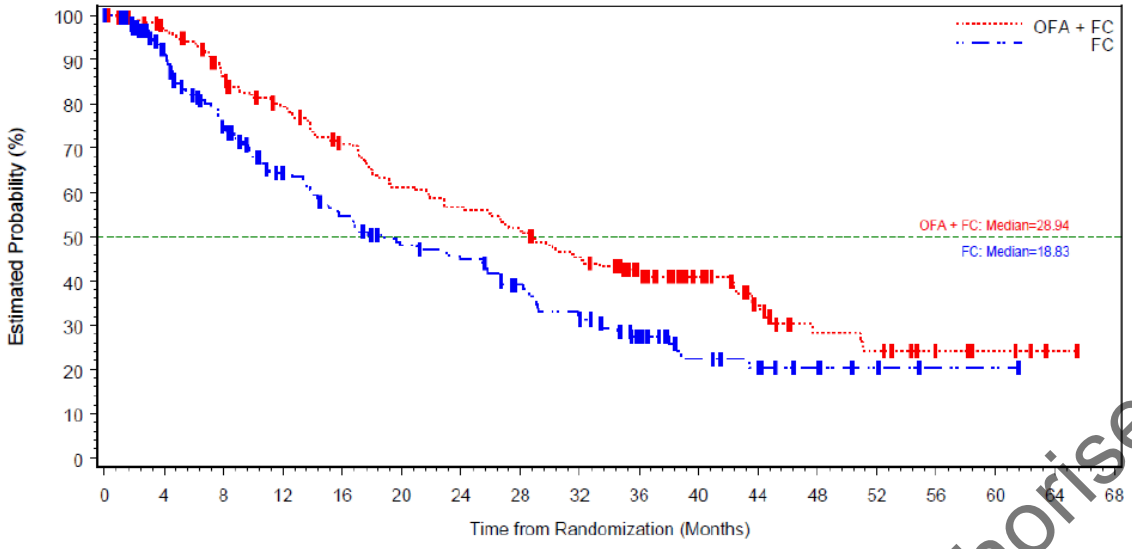
Primary endpoint – IRC-assessed progression-free survival (PFS)

Table 20: IRC-assessed Kaplan-Meier estimates of PFS

	O+FC (N=183)	FC (N=182)
Subject Classification, n (%)		
Progressed or died (event)	103 (56)	105 (58)
Death	30 (16)	28 (15)
Progression	73 (40)	77 (42)
Censored, last adequate assessment (LAA)[a]	62 (34)	51 (28)
Censored, LAA before or on anti-cancer therapy[b]	10 (5)	17 (9)
Censored, randomization[c]	6 (3)	7 (4)
Censored, LAA before death[d]	1 (<1)	2 (1)
Censored, LAA before progression[d]	1 (<1)	0
Kaplan-Meier Estimate for PFS (Months)[e]		
1st Quartile (95% CI)	13.8 (10.0, 17.1)	7.9 (6.3, 10.0)
Median (95% CI)	**28.9 (22.8, 35.9)**	**18.8 (14.4, 25.8)**
3rd Quartile (95% CI)	51.1 (44.16, NC)	38.5 (31.9, NC)
Hazard Ratio Estimate[f] (95% CI)	0.67 (0.51,0.88)	
Stratified Log-Rank p-Value	0.0032	

Data Source: Table 2.0010
Abbreviations: CI=confidence interval; FC=fludarabine and cyclophosphamide; LAA=last adequate assessment; NC=not calculable; O+FC=ofatumumab plus fludarabine and cyclophosphamide.
Note: LAA was defined as a visit where all components (blood, lymph nodes, organ and constitutional symptoms) for the response assessment were 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 (death or progression) 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+FC compared with FC. The hazard ratio and p-value from the stratified log-rank test are adjusted for Binet stage and number of prior therapies.



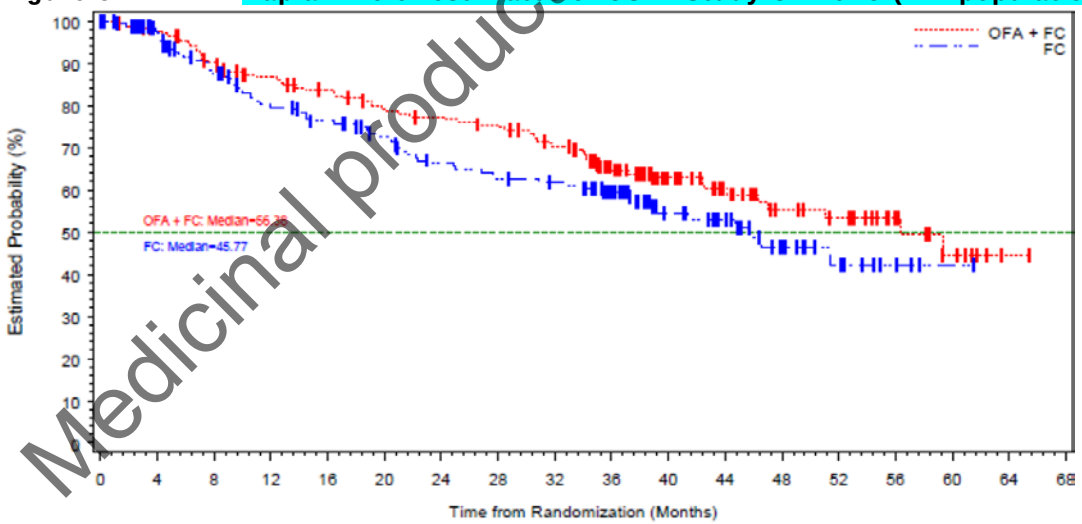
Subjects at risk

O+FC	183	164	141	124	108	93	86	78	67	51	37	25	14	12	7	4	1	0
FC	182	145	112	88	73	61	56	45	37	24	13	10	6	3	1	1	0	0

Data Source: Figure 12.0010
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; OFA+FC=ofatumumab plus fludarabine and cyclophosphamide.

Figure 11: Kaplan-Meier estimates of IRC-assessed PFS

Figure 3-12 **Kaplan-Meier estimates of OS in Study OMB913 (ITT population)**

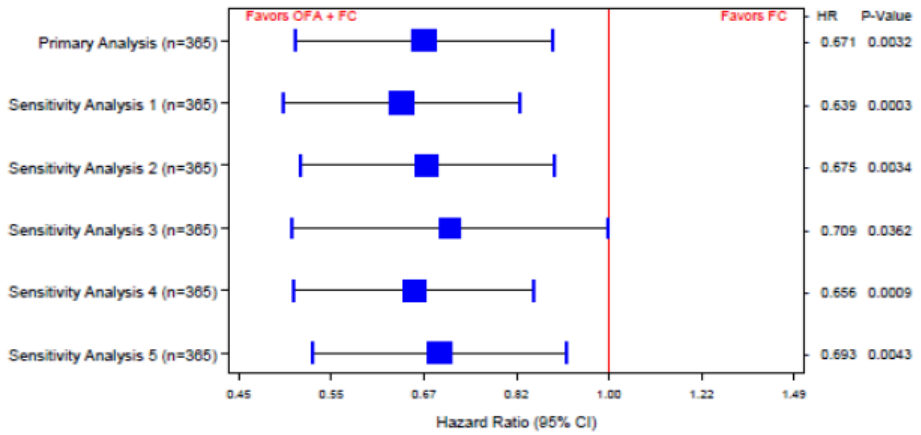


Subjects at risk

O+FC	183	171	154	143	135	126	122	117	107	80	55	43	29	25	15	8	1	0
FC	182	159	136	120	112	102	90	85	82	61	38	30	17	10	4	1	0	0

FC: fludarabine and cyclophosphamide; ITT: intent-to-treat; O+FC: ofatumumab plus fludarabine and cyclophosphamide; OS: overall survival.
Source: [Study OMB913-Figure 12.0090]

PFS sensitivity and supportive analyses



Data Source: Figure 12.0110
Abbreviations: CT=computed tomography; FC=fludarabine and cyclophosphamide; HR=hazard ratio; IRC=independent review committee; OFA+FC=ofatumumab plus fludarabine and cyclophosphamide; PFS=progression-free survival.
Primary analysis: IRC-assessed PFS
Sensitivity Analysis 1: IRC-assessed PFS adjusted for progression proclaimed by the investigator
Sensitivity Analysis 2: IRC-assessed PFS with differential censoring based on treatment arm
Sensitivity Analysis 3: IRC-assessed PFS censored for subjects who discontinued study treatment due to undocumented progression or toxicity
Sensitivity Analysis 4: Investigator assessed PFS
Sensitivity Analysis 5: IRC-assessed PFS based on common visits

Figure 13: Forest plot of hazard ratios and 95% confidence intervals for primary and sensitivity analysis of PFS

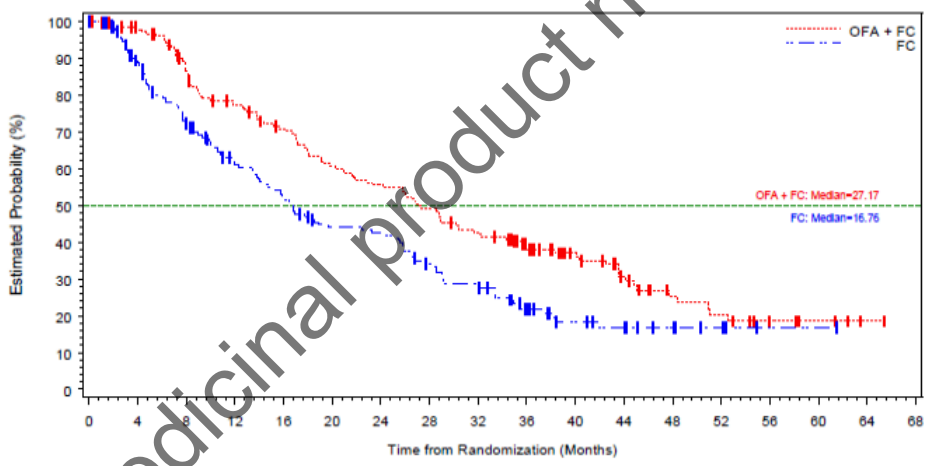
PFS by investigator assessment

Table *21*: Investigator-assessed Kaplan-Meier estimates of PFS

	O+FC (N=183)	FC (N=182)
Subject Classification, n (%)		
Progressed or died (event)	114 (62)	121 (66)
Death	29 (16)	27 (15)
Progression	85 (46)	94 (52)
Censored, last adequate assessment (LAA)[a]	60 (33)	50 (27)
Censored, randomization[b]	6 (3)	7 (4)
Censored, LAA before or on anti-cancer therapy[c]	3 (2)	3 (2)
Censored, LAA before death[d]	0	1 (<1)
Kaplan-Meier Estimate for PFS (Months)[e]		
1st Quartile (95% CI)	13.8 (8.8, 17.1)	7.6 (4.9, 9.3)
Median (95% CI)	**27.2 (21.8, 32.1)**	**16.8 (13.8, 24.0)**
3rd Quartile (95% CI)	48.4 (43.6, NC)	34.5 (28.6, 41.8)
Hazard Ratio Estimate[f] (95% CI)	0.66 (0.51,0.85)	
Stratified Log-Rank p-Value	0.0009	

Data Source: Table 2.1400
Abbreviations: CI=confidence interval; FC=fludarabine and cyclophosphamide; LAA=last adequate assessment; NC=not calculable; O+FC=ofatumumab plus fludarabine and cyclophosphamide.
Note: LAA was defined as a visit where all components (blood, lymph nodes, organ and constitutional symptoms) for response assessment were available.

a. Subjects alive and progression-free, censored at LAA.
b. No disease assessment after randomization.
c. Subjects took alternative therapy prior to documented progression, censored at LAA.
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+FC compared with FC. The hazard ratio and p-value from the stratified log-rank test are adjusted for Binet stage and number of prior therapies.



Data Source: Figure 12.0020
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; OFA+FC= ofatumumab plus fludarabine and cyclophosphamide.

Figure 14: Kaplan-Meier estimates of investigator-assessed PFS

Table *22*: Comparison of IRC- and investigator-assessed PFS timing

PFS Events	O+FC (N=183)	FC (N=182)
PFS Events (progression or death) by IRC, n (%)	**103 (56)**	**105 (58)**
PFS Events (progression or death) by Investigator, n (%)	**114 (62)**	**121 (66)**
Complete agreement with investigator	73 (40)	73 (40)
PFS events earlier by investigator	18 (10)	18 (10)
PFS events later by investigator	8 (4)	9 (5)

Data Source: Table 2.7020
Abbreviations: FC=fludarabine and cyclophosphamide; IRC=independent review committee; O+FC=ofatumumab plus fludarabine and cyclophosphamide; PFS=progression-free survival.

IRC-assessed event-free survival

Event-free survival – where PD, death, and the start of alternative CLL therapy prior to PD were considered events – resulted in a higher number of events compared with the primary PFS analysis (n=231). Median EFS in both treatment arms was 27.2 months in the O+FC arm and 16.5 months in the FC arm; HR=0.66, 95% CI: [0.51, 0.86], p=0.0012.

IRC-assessed PFS without new anti-cancer therapy as an event or censored

The analysis of PFS, where the start of alternative therapy was neither censored (like in the primary analysis of PFS) nor counted as event (like in EFS), resulted in a median PFS consistent with the primary analysis (28.1 months in the O+FC arm and 18.8 months in the FC arm; HR=0.68, 95% CI: [0.52, 0.90], p=0.0045).

Covariates

Cox regression with stepwise selection was conducted for IRC-assessed PFS with the following covariates: stratification factors, treatment, baseline characteristics, and prognostic factors. Covariates with p<0.20 were selected by the model.

The HR for O+FC compared with FC was significant, adjusting for other covariates (HR=0.67, 95% CI: [0.50, 0.92], p=0.011). This result was consistent with the primary PFS analysis. Additionally, the Cox regression showed a significant p-value for 17p deletion (reference='no aberration'; HR=6.29, 95% CI: [3.26, 12.16], p<0.0001), controlling for other covariates.

Potential bias related to timing of disease assessment

Sensitivity analysis 5 was performed to address a potential assessment time bias introduced in the PFS analysis due to the follow-up visits being counted from the last dosing date for each subject. To investigate this, the progression dates and censoring dates were set to the protocol defined time points for scheduled visits ('common visits').

The median PFS for O+FC occurred in 'interval 12,' which corresponds to approximately 28.6 to 31.6 months. The median PFS for FC occurred in 'interval 8,' which corresponds to approximately 16.6 to 19.6 months. The HR for this analysis was 0.69 (95% CI: [0.53 to 0.91]; p=0.0043; which is consistent with the primary analysis.

IRC-assessed PFS by number of prior therapies and class of prior therapy

Table *23*: Summary of IRC-assessed PFS by number of prior anti-cancer therapies

	O+FC (N=183)	FC (N=182)
Number of Prior Anti-cancer Therapies: 1-2		
Event (progressed or died), n (%)	81/149 (54)	82/147 (56)
Kaplan-Meier Estimate for PFS (Months)[a] Median (95% CI)	31.6 (26.7, 42.5)	24.0 (15.1, 28.6)
Hazard Ratio[b] Estimate (95% CI)	0.65 (0.48, 0.89)	
Number of Prior Anti-cancer Therapies: ≥3		
Event (progressed or died), n (%)	22/34 (65)	23/35 (66)
Kaplan-Meier Estimate for PFS (Months)[a] Median (95% CI)	17.6 (11.8, 19.3)	13.9 (9.3, 16.8)
Hazard Ratio[b] Estimate (95% CI)	0.72 (0.40, 1.29)	

Data Source: Table 2.0078

Abbreviations: CI=confidence interval; FC=fludarabine and cyclophosphamide; IRC=independent review committee; NC=not calculable; O+FC=ofatumumab plus fludarabine and cyclophosphamide; PFS=progression-free survival.

a. Confidence intervals estimated using the Brookmeyer Crowley method.
b. Hazard ratios are estimated using the Pike estimator.

Table *24*: Summary of PFS by type of prior rituximab therapy

	O+FC (N=183)	FC (N=182)
Prior Exposure to Rituximab-based Therapy		
Event (progressed or died), n (%)	26/43 (60)	17/35 (49)
Kaplan-Meier Estimate for PFS (Months)[a] Median (95% CI)	26.8 (16.7, 42.4)	14.4 (6.3, 25.8)
Hazard Ratio[b] Estimate (95% CI)	0.66 (0.34, 1.26)	
No Prior Exposure to Rituximab-based Therapy		
Event (progressed or died), n (%)	77/140 (55)	88/147 (60)
Kaplan-Meier Estimate for PFS (Months)[a] Median (95% CI)	29.7 (22.8, 42.1)	21.0 (14.7, 28.1)
Hazard Ratio[b] Estimate (95% CI)	0.65 (0.47, 0.88)	

Data Source: Table 2.0082, Table 2.0104

Abbreviations: CI=confidence interval; FC=fludarabine and cyclophosphamide; NC=not calculable; O+FC=ofatumumab plus fludarabine and cyclophosphamide; PFS=progression-free survival.

a. Confidence intervals estimated using the Brookmeyer Crowley method.
b. Hazard ratios are estimated using the Pike estimator, adjusted for stratum.

IRC-assessed PFS by response to most recent prior anti-cancer therapies

Table *25*: Summary of IRC-assessed PFS by response to most recent prior anti-cancer therapies

	O+FC (N=183)	FC (N=182)
Best Response to Prior Therapy: CR/Cri		
Event (progressed or died), n (%)	45/83 (54)	27/55 (49)
Kaplan-Meier Estimate for PFS (Months)[a] Median (95% CI)	30.4 (25.8, 43.6)	29.0 (16.7, 38.8)
Hazard Ratio[b] Estimate (95% CI)	0.85 (0.52, 1.38)	
Best Response to Prior Therapy: PR/nPR		
Event (progressed or died), n (%)	58/100 (58)	78/125 (62)
Kaplan-Meier Estimate for PFS (Months)[a] Median (95% CI)	24.2 (17.5, 32.3)	15.7 (12.6, 23.2)
Hazard Ratio[b] Estimate (95% CI)	0.64 (0.45, 0.89)	

Data Source: Table 2.0100, Table 2.0102 Abbreviations: CI=confidence interval; CR=complete response; Cri=complete response with incomplete bone marrow recovery; FC=fludarabine and cyclophosphamide; IRC=independent review committee; NC=not calculable; nPR=nodular partial response; O+FC=ofatumumab plus fludarabine and cyclophosphamide PFS=progression-free survival; PR=partial response. a. Confidence intervals estimated using the Brookmeyer Crowley method. b. Hazard ratios are estimated using the Pike estimator.

Secondary endpoints

The overall response rate (ORR) was also assessed by an IRC using the 2008 NCI-WG guidelines. The ORR was higher for OFA+FC versus FC (84% versus 68%, p=0.0003).

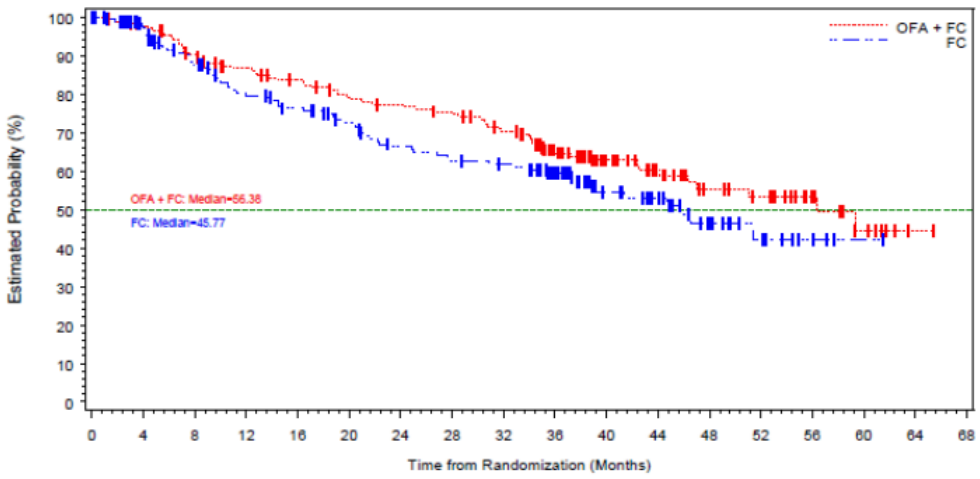
Overall Survival

The number of deaths reported was 67 (37%) in the O+FC group and 69 (38%) in the FC group. The OS data are still immature at the time of reporting. With a median follow-up of 34 months median OS was 56.4 months for O+FC and 45.8 months for FC but the difference was not significant (see table and figure below).

Table *26*: Kaplan-Meier estimates of overall survival

	O+FC (N=183)	FC (N=182)
Median OS (95% CI), months[a]	56.4 (44.2, NC)	45.8 (37.3, NC)
Events (death), n (%)	67 (37)	69 (38)
Hazard Ratio[b] Estimate (95% CI)	0.78 (0.56, 1.09)	
Stratified Log-Rank p-Value	0.1410	

Data Source: Table 2.9070
Abbreviations: CI=confidence interval; FC=fludarabine and cyclophosphamide; NC=not calculable; O+FC=ofatumumab plus fludarabine and cyclophosphamide; OS=overall survival.
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 FC.



Subjects at risk

O+F	183	17	15	14	13	12	12	11	10	80	55	43	29	25	15	8	1	0
C		1	4	3	5	6	2	7	7									
FC	182	15	13	12	11	10	90	85	82	61	38	30	17	10	4	1	0	0
		9	6	0	2	2												

Data Source: Figure 12.0090

Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide OFA+FC=ofatumumab plus fludarabine and cyclophosphamide.

Figure 15: Kaplan-Meier Estimates of Overall Survival

Time to progression and time to next therapy

Time to progression as assessed by the IRC was significantly increased for subjects treated with O+FC compared with subjects treated with FC (table below). Investigator-assessed median time to progression was also significantly improved in the O+FC arm (32.3 months) compared with the FC arm (25.8 months) (HR=0.62, 95% CI: 0.46, 0.83; p=0.0009). These results were consistent with the primary PFS endpoint analysis. Median time to next therapy was extended for subjects in the O+FC arm who required subsequent therapy approximately 8 months later than subjects in the FC arm (table below).

Table 27: IRC-assessed time to progression and time to next therapy

	O+FC (N=183)	FC (N=182)
Median Time to Progression (95% CI)[a], months	**42.1 (28.9, 47.7)**	**26.8 (22.5, 31.9)**
Events (progression), n (%)	73 (40)	77 (42)
Hazard Ratio[b] Estimate (95% CI)	0.63 (0.45, 0.87)	
Stratified Log-Rank p-Value	0.0036	
Median Time to Next Therapy (95% CI)[a], months	**48.1 (40.5, 60.4)**	**40.1 (32.1, 48.4)**
Events (next therapy), n (%)	62 (34)	59 (32)
Hazard Ratio[b] Estimate (95% CI)	0.73 (0.51, 1.05)	
Stratified Log-Rank p-Value	0.0735	

Data Source: Table 2.2050, Table 2.7040

Abbreviations: CI=confidence interval; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

a. Confidence intervals were obtained using the Brookmeyer-Crowley method.
b. Hazard ratios were obtained using the Pike estimator, adjusted for stratum.

Minimal residual disease

Negativity for MRD 6 months after the last treatment was 26% in the O+FC arm (48/183) compared with 6% in the FC arm (11/182) (Study OMB913). Three months after the last treatment, 39/183 subjects (21%) in the O+FC arm were negative for MRD, compared with 15/182 (8%) in the FC arm.

Over all Follow-up visits, 65 subjects (36%) in the O+FC arm and 21 subjects (12%) in the FC arm were MRD negative. Thirty-one of 52 subjects (60%) subjects who achieved an IRC assessed CR or CRi in the O+FC arm became MRD negative, compared to 33 of 101 (33%) subjects who achieved PR or nPR. In the O+B study (OMB991) 6% (3) were MRD negative during Follow-up.

B cell response

Approximately 80% of responders in the O+FC arm (study OMB913) showed near-complete B cell depletion and almost 40% showed complete B cell depletion (whether IRC or Investigator assessed). Of non-responders in the O-FC arm, 7% and 20% had complete and near complete B-cell depletion respectively (IRC assessed). The proportion of responders in the FC arm with B cell depletion (complete or near-complete) was 4% and 23% respectively. Few non-responders in the FC arm had complete (2%) or near complete B cell depletion (8%), as assessed by the IRC. Depletion of CD5+CD19+ (CLL cells) after treatment was higher in the O+FC arm. The median CD5+CD19+ concentration at the 1-month Follow-up for subjects in the O+FC arm was 1 cell/µL compared with 64 cells/µL for subjects in the FC arm.

B-symptoms and reduction of lymph node size

In the Study OMB913, approximately two-thirds of subjects presented with 1 or more B-symptoms at Baseline. In both treatment arms, the number of subjects with B-symptoms decreased over time during treatment and over the course of follow-up. More subjects in the O+FC arm were B-symptom free and at earlier time points compared with the FC arm. In both treatment arms, the majority of subjects with a decrease in lymph node size had a reduction of >50% compared with Baseline. A larger decrease in median lymph node size was noted in the O+FC arm (-3140.9 mm^2; range -9984 to -558) compared to the FC arm (-2177.9 mm^2; range -15991 to -111). In the Study OMB991 following the last dose of study treatment, 100% maximum reductions in lymph node size were reported for 30 of the 36 subjects (83%) who had lymphadenopathy reported at Baseline.

Richter's transformation

A total of 5 subjects, O+FC: 2/114 (1.8%), and FC 3/121 (2.5%) subjects had PD due to Richter's transformation.

Patient reported outcomes

Baseline HRQoL values were collected at screening and were similar for both treatment arms as determined from the EORTC QLQ-C30, EORTC QLQ-CLL16, 'B-symptoms' score, and EQ-5D for the ITT population.

Ancillary analyses

Post-hoc analyses of TTP and TTNT.

Adding ofatumumab to FC resulted in an apparently larger gain in median TTP (approximately 15 months) than in median PFS (approximately 10 months). In the analysis of PFS 208 events were observed, of which 58 events were deaths (approximately 30% of all PFS events). These deaths (which occurred without progressive disease [PD]) were not considered as TTP events, but were censored in the TTP analysis. Among

these deaths (30 in the O+FC arm and 28 in the FC arm), the time to death is longer in the O+FC arm (median 8.2 months) than the FC arm (7.4 months).

Time to next therapy

The benefit seen across progression-related endpoints (PFS, EFS, and TTP) translated into a median prolongation in TTNT of approximately 8 months in the main analysis of TTNT (where death was censored). In a sensitivity analysis of TTNT where death was considered an event, the median prolongation in TTNT (approximately 9 months) is similar to the median prolongation in PFS (approximately 10 months). Furthermore, similar results were seen for PFS with and without censoring for NTX. Different definitions for event and censoring are employed for progression-related endpoints (PFS, EFS and TTP) and TTNT. To further explore the relationship between TTP and TTNT endpoints, subjects enrolled in Study OMB913 were categorized into 4 groups, as shown in the table below.

Table *28*: Categorization of subjects based on progression and NTX events in Study OMB913 (ITT population)

Group	O+FC N=183	FC N=182
a) Subjects with PD and who received NTX	51 (28%)	42 (23%)
b) Subjects without PD and who did not receive NTX	99 (54%)	88 (48%)
c) Subjects without PD but received NTX	11 (6%)	17 (9%)
d) Subjects with PD but did not receive NTX	22 (12%)	35 (19%)

FC: fludarabine plus cyclophosphamide; IRC: independent review committee; ITT: intent-to-treat; O+FC: ofatumumab plus fludarabine plus cyclophosphamide; PD: progressive disease; NTX: next line therapy.

Source: [SCE-Appendix 1-Table 2.9980]

Two of these groups can be considered as expected: a) subjects with PD who received NTX, and b) subjects who did not have PD and who did not receive NTX. The two other groups can be considered as being influenced by local clinical practice: c) subject who did not have PD but who received NTX, d) subjects who had PD but did not receive NTX. Depending on the balance in subjects categorized in groups c and d between the two arms, discrepant results for TTP and TTNT can be expected. Such a discrepancy is not truly reflective of a lack in consistency between the study endpoints and may be influenced by patient's condition and decisions, alternative available treatments or physician's judgement. When the influence of local clinical practice is removed from the analysis of TTNT (i.e., subjects in groups c and d), the median prolongation in TTNT (16.8 months) was similar to that observed for TTP (median 15.3 months), see table below.

Table *29*: Sensitivity analyses of TTNT removing effects due to local clinical practice in study OMB913 (ITT population)

Endpoint	Key feature	O+FC N=183	FC N=182	KM median difference (O+FC) – FC (month)	HR (95% CI)
Time to progression					
TTP (IRC) *	Event: PD Censoring: death, LAA Note: NTX used as a censoring point	42.1	26.8	15.3	0.63 (0.45, 0.87)
Time to next therapy					
TTNT *	Event: NTX Censoring: death, last contact date	48.1	40.1	8.0	0.73 (0.51, 1.05)
TTNT excluding group c (no PD, received NTX)	Event: NTX Censoring: death, last contact date	57.6	46.8	10.8	0.80 (0.43, 1.21)
TTNT excluding group d (had PD, no NTX)	Event: NTX Censoring: death, last contact date	44.9	32.1	12.8	0.61 (0.42, 0.88)
TTNT excluding groups c and d (no PD, received NTX, and had PD, no NTX)	Event: NTX Censoring: death, last contact date	53.0	36.2	16.8	0.64 (0.41, 0.98)

* Pre-specified analyses in the reporting and analysis plan.

CI: confidence interval; FC: fludarabine plus cyclophosphamide; HR: hazard ration; IRC: independent review committee; ITT: intent-to-treat; KM: Kaplan–Meier; LAA: last adequate assessment; O+FC: ofatumumab plus fludarabine plus cyclophosphamide; PD: progressive disease; NTX: next line therapy; TTNT: time to next therapy; TTP: time-to-progression.

Source: [SCE-Appendix 1-Table 2.9986], [SCE-Appendix 1-Table 2.9988], [SCE-Appendix 1-Table 2.9990].

Summary of main study

The following table summarises the efficacy results from the main study 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 *30*: Summary of Efficacy for trial OMB110913

Title: A Phase III, Open Label, Randomized Trial of Ofatumumab Added to Fludarabine-Cyclophosphamide vs. Fludarabine- Cyclophosphamide Combination in Subjects with Relapsed Chronic Lymphocytic Leukemia		
Study identifier	OMB110913	
Design	This is an open-label, two-arm, randomised, Phase III study of ofatumumab in combination with fludarabine and cyclophosphamide in subjects with relapsed chronic lymphocytic leukemia.	
	Duration of main phase:	6 cycles of treatment followed by 5 years follow-up phase
Hypothesis	superiority of ofatumumab (GSK1841157) plus FC over FC (fludarabine and cyclophosphamide).	
Treatments groups	Treatment Arm A (O+FC)	Ofatumumab plus fludarabine and cyclophosphamide Number of patients randomised: 183 subjects
	Treatment Arm B (FC)	Fludarabine and cyclophosphamide Number of patients randomised: 182 subjects

Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	The time from randomisation until progression or death due to any cause. Calculated for IRC and investigator-assessed, with IRC-assessed as primary endpoint.
	Secondary endpoint	Overall response rate (ORR)	The percentage of subjects who achieved a best overall response of CR, CRi, nPR, or PR. Calculated for IRC and investigator-assessed response.
	Secondary endpoint	Overall Survival (OS)	The time from randomisation until death due to any cause.
	Other Secondary endpoint	Time to progression (TTP)	The time from randomisation until disease progression. Calculated for IRC and investigator-assessed response.
	Other Secondary endpoint	Time to next therapy (TTNT)	The time from randomisation until next-line therapy
	Other Secondary endpoint	Time to response (TTR)	The time from randomisation to the first response. Calculated for IRC and investigator-assessed response.
	Other Secondary endpoint	Duration of response (DOR)	The time from the first response to the first documented disease progression or death due to any cause, for responders only. Calculated for IRC and investigator-assessed response.
Database cut-off	17 Dec 2014 + OS Updated 21 December 2015.		

Results and Analysis

Analysis description:	**Primary Analysis: Progression- free survival (PFS) assessed by IRC**		
Analysis population and time point description	The Intent-to-Treat (ITT) Population Timepoint: Primary analysis of the study as defined by protocol, i.e. when 194 IRC assessed PFS events were accrued.		
Descriptive statistics and estimate variability (Primary endpoint)	Treatment group	Treatment Arm A (O+FC)	Treatment Arm B (FC)
	Number of subject	183	182
	median PFS (months) 95% C.I	28.9 (22.8, 35.9)	18.8 (14.4, 25.8)
Descriptive statistics and estimate variability (Secondary endpoints)	Treatment Group	Treatment Arm A (O+FC)	Treatment Arm B (FC)
	Number of subject	183	182
	IRC-assessed Response Rates	84%	68%

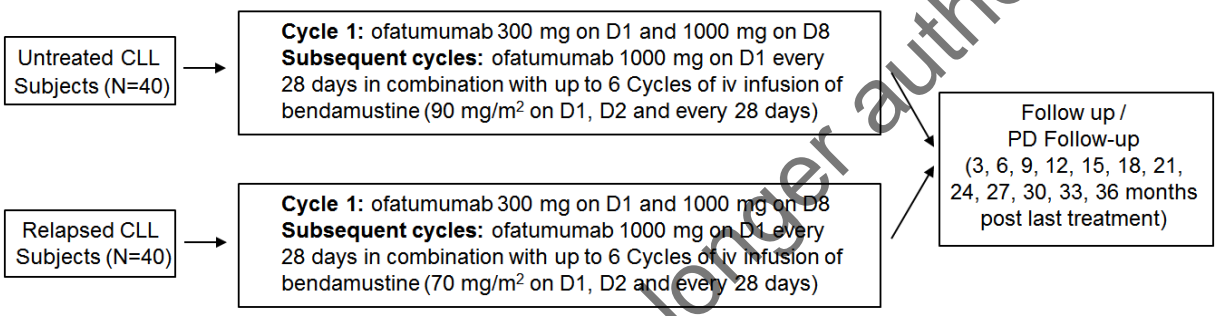
	95% C.I	(77%,89%)	(60%,74%)
	Number of subject	183	182
	Median OS (months) 95% C.I	NE (44.6, NC)	46.3 (37.8,NC)
	Number of subject	183	182
	IRC-assessed Median Time to Progression (months) 95% C.I	42.1 (28.9, 47.7)	26.8 (22.5, 31.9)
	Number of subject	183	182
	Median Time to next therapy (months) 95% C.I	48.1 (40.5, 60.4)	40.1 (32.1, 48.4)
	Number of subject	152	123
	IRC-assessed Median Time to Response (months) 95% C.I	1.0 (1.0, 1.1)	1.0 (1.0,1.2)
	Number of subject	152	123
	IRC-assessed Median Duration of Response (months) 95% C.I	29.6 (25.0, 41.5)	24.9 (19.0, 28.1)
Effect estimate per comparison	IRC-assessed Progression-free survival (PFS)	Comparison groups	Treatment Arm A (O+FC) Treatment Arm B (FC)
		Hazard Ratio	0.67
		95% CI	(0.51, 0.88)
		P-value (stratified log-rank test)	0.0032
	IRC-assessed Overall response rate (ORR)	Comparison groups	Treatment Arm A (O+FC) Treatment Arm B (FC)
		P-value (Chi-square test adjusting for stratification factors)	0.0003
	Overall survival (OS)	Comparison groups	Treatment Arm A (O+FC) Treatment Arm B (FC)
		Hazard Ratio	0.78
		95% CI	(0.56, 1.09)
		P-value (stratified log-rank test)	0.1410
	IRC-assessed Time to Progression (TTP)	Comparison groups	Treatment Arm A (O+FC) Treatment Arm B (FC)
		Hazard Ratio	0.63
		95% CI	(0.45, 0.87)
		P-value (stratified log-rank test)	0.0036
	IRC-assessed Time to next therapy (TTNT)	Comparison groups	Treatment Arm A (O+FC) Treatment Arm B (FC)
		Hazard Ratio	0.73
		95% CI	(0.51, 1.05)

		P-value (stratified log-rank test)	0.0735
Notes	Stratification factors are Binet stages (A vs B vs C) and number of prior therapies (1,2 vs >=3)		

Supportive study

Study OMB991 was a Phase II, multi-centre study investigating the safety and efficacy of ofatumumab and bendamustine combination (O+B) in subjects with untreated or relapsed CLL. A total of 80 subjects were included. Here, only data pertinent to subjects with relapsed CLL is presented from Study OMB991.

Figure 16-2 Study OMB991 design



CLL: chronic lymphocytic leukemia; D: day; PD: progression disease.

Study population

Subjects with previously untreated CLL and subjects with relapsed CLL, all received ofatumumab and bendamustine (O+B). Only data from the relapsed CLL population is included in this document, they had all received at least one prior CLL therapy and the response to the last therapy lasted at least 6 months. Similar to Study OMB913, subjects had to have active disease, and those with refractory CLL were excluded.

Efficacy endpoints

The **primary endpoint** of ORR was assessed for subjects (ATS population) who received at least one dose of both study drugs (O+B). ORR was defined as the percentage of subjects achieving an objective response (i.e. PR or better) at different time points (after 3 cycles, after 6 cycles, and after the last dose, if not after 6 cycles), as per Investigator evaluation, and in accordance with the IWCLL updated NCI-WG guidelines. The primary efficacy evaluation did not include the use of CT scan findings. Response evaluations were also presented for all subjects following their last dose of O+B treatment, to represent the response rates achieved in the full ATS population.

Table *31*: Summary of objective complete response rate across study visits in Study OMB991 (ITT (ISE))

	O+B N=53
Best Response	
Complete response (CR)	6 (11%)
Complete response with incomplete bone marrow recovery (CRi)	2 (4%)

	O+B N=53
Responder	
Yes (CR + CRi)	8 (15%)
No	45 (85%)
(95% CI)	(7%, 28%)

CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide.
[1] OMB110913 Investigator assessed data.
[2] OMB110913 independent review committee-assessed data.
Source: [SCE-Appendix 1-Table 2.1470]

Secondary efficacy endpoints were analyzed using the ATS population and Investigator assessment and included: ORR and complete response rate (CRR) with CT scan assessment.

PFS, defined as the interval of time (in months) between the date of the first administration of study treatment and the earlier of the date of disease progression and the date of death due to any cause.

OS, defined as the interval of time (in months) between the date of the first administration of study treatment and the date of death due to any cause.

TTR, defined as time from date of the first administration of study treatment to the first response (CR/CRi/nPR/PR).

DOR, defined as the time (in months) from the initial response (CR/CRi/nPR/PR) to the first documented sign of disease progression or death due to any cause.

TTP, defined as the time from the date of the first administration of study treatment to the progression of disease.

TTNT, defined as the time from the date of the first administration of study treatment until next anti-CLL therapy.

Changes in B-cell levels, improvement in ECOG performance status and in constitutional symptoms (B-symptoms), reduction in lymph node size and organomegaly, and MRD.

Subgroup analyses were performed for the following subgroups: Gender, age, ethnicity, presence of constitutional symptoms and comorbidities, stage, ECOG performance status and baseline prognostic factors: Cytogenetics, IgVH mutational status, VH3-21 usage, β 2-microglobulin and ZAP-70.

Updated OS data for study OMB110913; Cut off 21 December 2015.

As of cut-off date of 21-Dec-2015, with approximately one year of additional follow-up, there was a modest increase in the number of deaths; an additional 7 patients died in each treatment group (Table 2-12). The median OS was not reached in the O+FC group whereas median OS in the FC group changed slightly to 46.23 months (95% CI: 37.72, NE) from 45.8 months (95% CI: 37.3, NE) (HR=0.79; 95% CI: 0.58, 1.10). However, the censoring rates remain high in the updated analysis, 60% vs 58% in O+FC and FC, respectively and the OS data is still immature

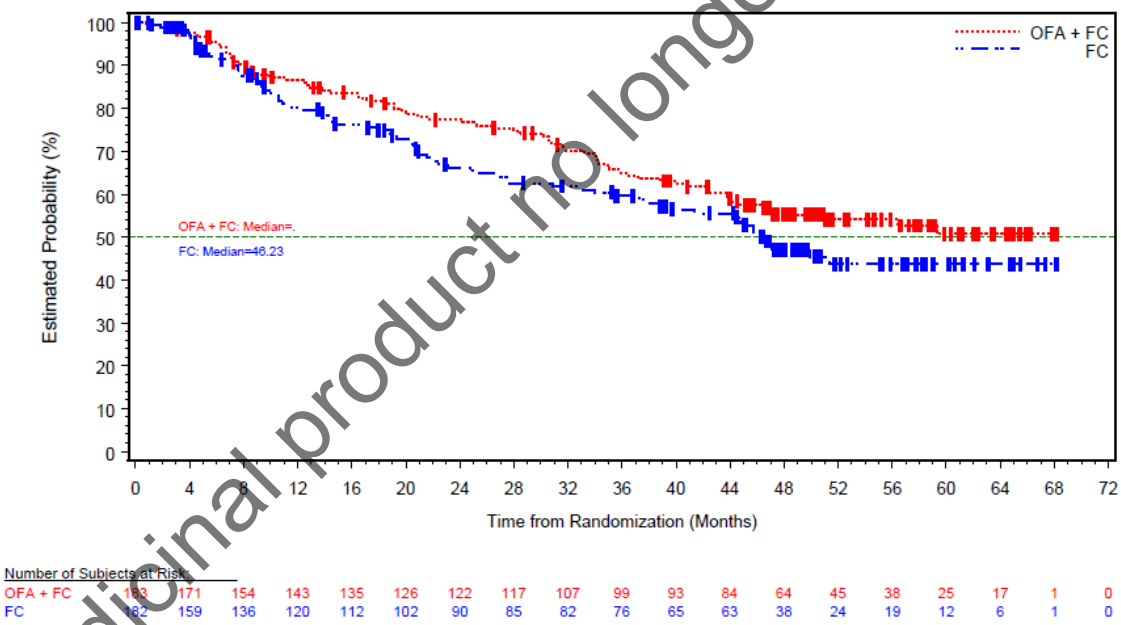
Table *32*: Summary of Kaplan-Meier estimates of OS

	Study OMB110913 17-Dec-2014 cut-off date		Study OMB110913 21-Dec-2015 cut-off date	
	O+FC N=183	FC N=182	O+FC N=183	FC N=182
Number of Subjects, n (%)				
Endpoint (event)	67 (37)	69 (38)	74 (40)	76 (42)
Censored, Last contact date	116 (63)	113 (62)	109 (60)	106 (58)
Event Summary, n (%)				

	Study OMB110913 17-Dec-2014 cut-off date		Study OMB110913 21-Dec-2015 cut-off date	
	O+FC N=183	FC N=182	O+FC N=183	FC N=182
Death	67 (37)	69 (38)	74 (40)	76 (42)
Estimates for Overall Survival (Months)				
1st Quartile	27.99	17.94	27.99	17.94
95% CI	(18.43, 34.07)	(10.58, 22.24)	(18.43, 34.07)	(10.58, 22.24)
Median	56.38	45.77	NE	46.23
95% CI	(44.16, NE)	(37.26, NE)	(44.58, NE)	(37.72, NE)
3rd Quartile				
95% CI	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)
Adjusted Hazard Ratio				
Estimate	0.78		0.79	
95% CI	(0.56, 1.09)		(0.58, 1.10)	
Stratified Log-Rank P-Value	0.1410		0.1543	

Source: [SCE-Appendix 1-Table 2.1688], [Study OMB913 120d update-Table 2.9070]

Figure 2-1 Kaplan-Meier graph of OS



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

Analysis of PFS as assessed by the IRC based on the ITT Analysis Set is summarized in the table and figure below.

Table *33*: Summary of Kaplan-Meier estimates of PFS in Study OMB913 and Study OMB991 (ITT (ISE))

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Number of Subjects					
Endpoint (event)	114 (62%)	103 (56%)	35 (66%)	121 (66%)	105 (58%)
Censored, last adequate assessment	60 (33%)	62 (34%)	14 (26%)	50 (27%)	51 (28%)
Censored, last adequate assessment before death	0	1 (<1%)	0	1 (<1%)	2 (1%)

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Censored, Last adequate assessment before or on anti-cancer therapy	3 (2%)	10 (5%)	3 (6%)	3 (2%)	17 (9%)
Censored, last adequate assessment before progression	0	1 (<1%)	0	0	0
Censored, randomization	6 (3%)	6 (3%)	1 (2%)	7 (4%)	7 (4%)
Event Summary					
Death	29 (16%)	30 (16%)	3 (6%)	27 (15%)	28 (15%)
Progression	85 (46%)	73 (40%)	32 (60%)	94 (52%)	77 (42%)
Estimates for Progression-free survival (Months) [3]					
1st Quartile	13.80	13.80	10.74	7.62	7.89
95% CI	(8.80, 17.05)	(9.95, 17.12)	(8.02, 16.07)	(4.86, 9.33)	(6.28, 9.99)
Median	27.17	28.94	22.54	16.76	18.83
95% CI	(21.78, 32.07)	(22.80, 35.88)	(14.00, 27.33)	(13.77, 23.95)	(14.42, 25.82)
3rd Quartile	48.36	51.06	31.15	34.53	38.54
95% CI	(43.56, NE)	(44.16, NE)	(26.09, NE)	(28.58, 41.82)	(31.87, NE)

CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; NE: not evaluable; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide; PFS: progression-free survival.
[1] OMB110913 Investigator assessed data.
[2] OMB110913 independent review committee-assessed data.
[3] CIs estimated using the Brookmeyer Crowley method.
Source: [SCE-Appendix 1-Table 2.1000]
Source: [Study OMB913-Figure 12.0010]

Key secondary endpoint

Overall response rate

Table *34*: Summary of objective ORR across study visits in Study OMB913 and Study OMB991 (ITT (ISE))

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Best Response					
Complete response (CR)	42 (23%)	49 (27%)	6 (11%)	23 (13%)	13 (7%)
Complete response with incomplete bone marrow recovery (CRi)	12 (7%)	3 (2%)	2 (4%)	5 (3%)	2 (1%)
Nodular partial response (nPR)	2 (1%)	0	8 (15%)	8 (4%)	0
Partial response (PR)	110 (60%)	101 (55%)	23 (43%)	113 (62%)	108 (59%)
Stable disease (SD)	9 (5%)	21 (11%)	5 (9%)	21 (12%)	51 (28%)
Progressive disease (PD)	0	0	8 (15%)	3 (2%)	0
Not evaluable	0	7 (4%)	0	0	4 (2%)
Missing	8 (4%)	2 (1%)	1 (2%)	9 (5%)	4 (2%)
Responder					
Yes (CR + CRi + nPR + PR)	166 (91%)	153 (84%)	39 (74%)	149 (82%)	123 (68%)
No	17 (9%)	30 (16%)	14 (26%)	33 (18%)	59 (32%)
(95% CI)	(86%, 94%)	(77%, 89%)	(60%, 85%)	(75%, 87%)	(60%, 74%)

CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide; ORR: overall response rate.
[1] OMB110913 Investigator assessed data.
[2] OMB110913 independent review committee-assessed data.
Source: [SCE-Appendix 1-Table 2.1250]

Overall survival

At time of submission, Study OMB913, with a median follow-up of 34 months, showed median OS was 56.4 months for O+FC and 45.8 months for FC (HR=0.78; 95% CI: 0.56, 1.09) Table 3-15 & Figure 3-2. The OS data for the study OMB991 was not yet mature as the data cut-off date of 17-Dec-2014.

Table *35*: Summary of Kaplan-Meier estimates of OS in Study OMB913 and Study OMB991 (ITT (ISE))

	O+FC N=183	O+B N=53	FC N=182
Number of Subjects			
Endpoint (event)	67 (37%)	19 (36%)	69 (38%)
Censored, Last contact date	116 (63%)	34 (64%)	113 (62%)
Event Summary			
Death	67 (37%)	19 (36%)	69 (38%)
Estimates for Overall Survival (Months) [1]			
1st Quartile	27.99	22.80	17.94
95% CI	(18.43, 34.07)	(14.00, 30.39)	(10.58, 22.24)
Median	56.38		45.77
95% CI	(44.16, NE)	(29.11, NE)	(37.26, NE)
3rd Quartile			
95% CI	(NE, NE)	(NE, NE)	(NE, NE)

CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; NE: not evaluable; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide; OS: overall survival.
[1] CIs estimated using the Brookmeyer Crowley method.
Source: [SCE-Appendix 1-Table 2.1688]

Time to progression

In Study OMB913, the median IRC assessed TTP was 42.12 months, (95%CI: 28.94, 47.67) in the O+FC arm compared with 26.78 months for the FC arm, (95% CI: 22.51, 31.87) (HR=0.63, 95% CI: 0.45, 0.87; p=0.0036, no multiplicity adjustment applied) (Table 3-16). In study OMB991, the median TTP was 22.67 months (95% CI 16.07, 28.58).

Table *36*: Summary of Kaplan-Meier estimates of time to progression in Study OMB913 and Study OMB991 (ITT (ISE))

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Number of Subjects					
Endpoint (event)	85 (46%)	73 (40%)	32 (60%)	94 (52%)	77 (42%)
Censored, death	29 (16%)	30 (16%)	3 (6%)	27 (15%)	28 (15%)
Censored, Last adequate assessment	60 (33%)	62 (34%)	14 (26%)	50 (27%)	51 (28%)
Censored, Last adequate assessment before death	0	1 (<1%)	0	1 (<1%)	2 (1%)
Censored, Last adequate assessment before or on anti-cancer therapy	3 (2%)	10 (5%)	3 (6%)	3 (2%)	17 (9%)
Censored, Last adequate assessment before progression	0	1 (<1%)	0	0	0
Censored, Randomization	6 (3%)	6 (3%)	1 (2%)	7 (4%)	7 (4%)
Event Summary					
Progression	85 (46%)	73 (40%)	32 (60%)	94 (52%)	77 (42%)
Estimates for Time to Progression (Months) [3]					
1st Quartile	17.87	17.74	13.34	11.99	13.54
95% CI	(15.21, 21.68)	(14.32, 22.80)	(8.18, 17.28)	(7.69, 15.05)	(9.72, 16.49)

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Median	32.26	42.12	22.67	25.79	26.78
95% CI	(27.17, 43.56)	(28.94, 47.67)	(16.07, 28.58)	(17.74, 28.52)	(22.51, 31.87)
3rd Quartile			31.15	38.01	
95% CI	(47.67, NE)	(NE, NE)	(28.29, NE)	(33.38, NE)	(38.01, NE)

CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; NE: not evaluable; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide.
[1] OMB110913 Investigator assessed data.
[2] OMB110913 independent review committee-assessed data.
[3] CIs estimated using the Brookmeyer Crowley method.
Source: [SCE-Appendix 1-Table 2.1920]

Time to next anti-cancer therapy

Table *37*: Summary of Kaplan-Meier estimates of time to next anti-cancer therapy in Study OMB913 and Study OMB991 (ITT (ISE))

	O+FC N=183	O+B N=53	FC N=182
Number of Subjects			
Endpoint (event)	62 (34%)	23 (43%)	59 (32%)
Censored, Last contact date	121 (66%)	30 (57%)	123 (68%)
Event Summary			
Anticancer therapy	62 (34%)	23 (43%)	59 (32%)
Estimates for Time to Next Anti-Cancer Therapy (Months) [1]			
1st Quartile	28.71	12.65	20.47
95% CI	(22.93, 31.93)	(10.18, 24.21)	(16.49, 27.53)
Median	48.13	30.88	40.08
95% CI	(40.54, 60.39)	(24.08, NE)	(32.07, 48.39)
3rd Quartile			
95% CI	(60.39, NE)	(30.88, NE)	(47.67, NE)

CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; NE: not evaluable; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide.
[1] CIs estimated using the Brookmeyer Crowley method.
Source: [SCE-Appendix 1-Table 2.1950]

Time to response

The IRC assessed TTR was approximately 1 month both in the O+FC arm and in the FC arm.

Results were also similar between treatment groups in the analysis of investigator-assessed time to response (approximately 2 months). Median duration of response was approximately 5 months longer with O+FC compared with FC but the result was not statistically significant (HR=0.77, 95% CI: [0.56, 1.05], p=0.09).

It is a bit unexpected that the gain in PFS is not reflected in time to response and duration of response. However, it might be due to the fact that only responders are included in time to response and duration of response.

Duration of response

In Study OMB913, the IRC-assessed median DOR was approximately 5 months longer with O+FC (29.63 months, 95% CI: 25.03, 41.46) compared with FC (24.90 months, 95% CI: 18.99, 28.12). The median DOR was even lower in the OMB991 study, 21.75 months (95% CI: 14.74, 26.41).

Table *38*: Summary of Kaplan-Meier estimates of duration of response in Study OMB913 and Study OMB991 (ITT (ISE))

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Number of Subjects					

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Endpoint (event)	106 (58%)	88 (48%)	31 (58%)	99 (54%)	73 (40%)
Censored, Last adequate assessment	58 (32%)	55 (30%)	14 (26%)	47 (26%)	39 (21%)
Censored, Last adequate assessment before death	0	1 (<1%)	0	1 (<1%)	2 (1%)
Censored, Last adequate assessment before or on anti-cancer therapy	2 (1%)	8 (4%)	2 (4%)	2 (1%)	9 (5%)
Event Summary					
Death	25 (14%)	25 (14%)	2 (4%)	20 (11%)	13 (7%)
Progression	81 (44%)	63 (34%)	29 (55%)	79 (43%)	60 (33%)
Estimates for Duration of Response (Months) [3]					
1st Quartile	11.17	14.19	10.05	7.13	12.25
95% CI	(6.93, 14.98)	(10.25, 16.66)	(7.39, 15.15)	(4.60, 9.07)	(7.49, 14.95)
Median	24.84	29.63	21.75	17.91	24.90
95% CI	(20.96, 30.88)	(25.03, 41.46)	(14.75, 26.41)	(13.11, 23.59)	(18.99, 28.12)
3rd Quartile	46.75		30.16	32.49	42.48
95% CI	(41.95, NE)	(43.79, NE)	(25.56, NE)	(27.66, NE)	(34.56, NE)

CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; NE: not evaluable; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide.
[1] OMB110913 Investigator assessed data.
[2] OMB110913 independent review committee-assessed data.
[3] CIs estimated using the Brookmeyer Crowley method.
Source: [SCE-Appendix 1-Table 2.1942]

Event-free survival

Table 39: Summary of Kaplan-Meier estimates of EFS in Study OMB913 and Study OMB991 (ITT (ISE))

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
Number of subjects					
Endpoint (event)	118 (64%)	113 (62%)	39 (74%)	124 (68%)	118 (65%)
Censored, Last adequate assessment	60 (33%)	62 (34%)	14 (26%)	50 (27%)	51 (28%)
Censored, Last adequate assessment before anticancer therapy	0	1 (<1%)	0	0	4 (2%)
Censored, Last adequate assessment before death	0	1 (<1%)	0	1 (<1%)	2 (1%)
Censored, Last adequate assessment before progression	0	1 (<1%)	0	0	0
Censored, Randomization	5 (3%)	5 (3%)	0	7 (4%)	7 (4%)
Event Summary					
Anticancer therapy	4 (2%)	10 (5%)	4 (8%)	3 (2%)	13 (7%)
Death	29 (16%)	30 (16%)	3 (6%)	27 (15%)	28 (15%)
Progression	85 (46%)	73 (40%)	32 (60%)	94 (52%)	77 (42%)
Estimates for Event-free survival (Months) [3]					
1st Quartile	12.65	12.78	10.32	7.39	7.62
95% CI	(8.25, 16.20)	(9.10, 15.61)	(7.06, 13.60)	(4.83, 9.00)	(5.16, 9.13)
Median	26.74	27.17	19.81	16.72	16.49
95% CI	(20.90, 30.46)	(21.68, 32.07)	(13.34, 25.07)	(13.54, 23.23)	(13.54, 23.23)
3rd Quartile	47.67	47.67	31.15	33.38	34.53
95% CI	(43.50, NE)	(43.56, NE)	(25.07, NE)	(28.12,	(28.52, NE)

	O+FC[1] N=183	O+FC[2] N=183	O+B N=53	FC[1] N=182	FC[2] N=182
				38.31)	

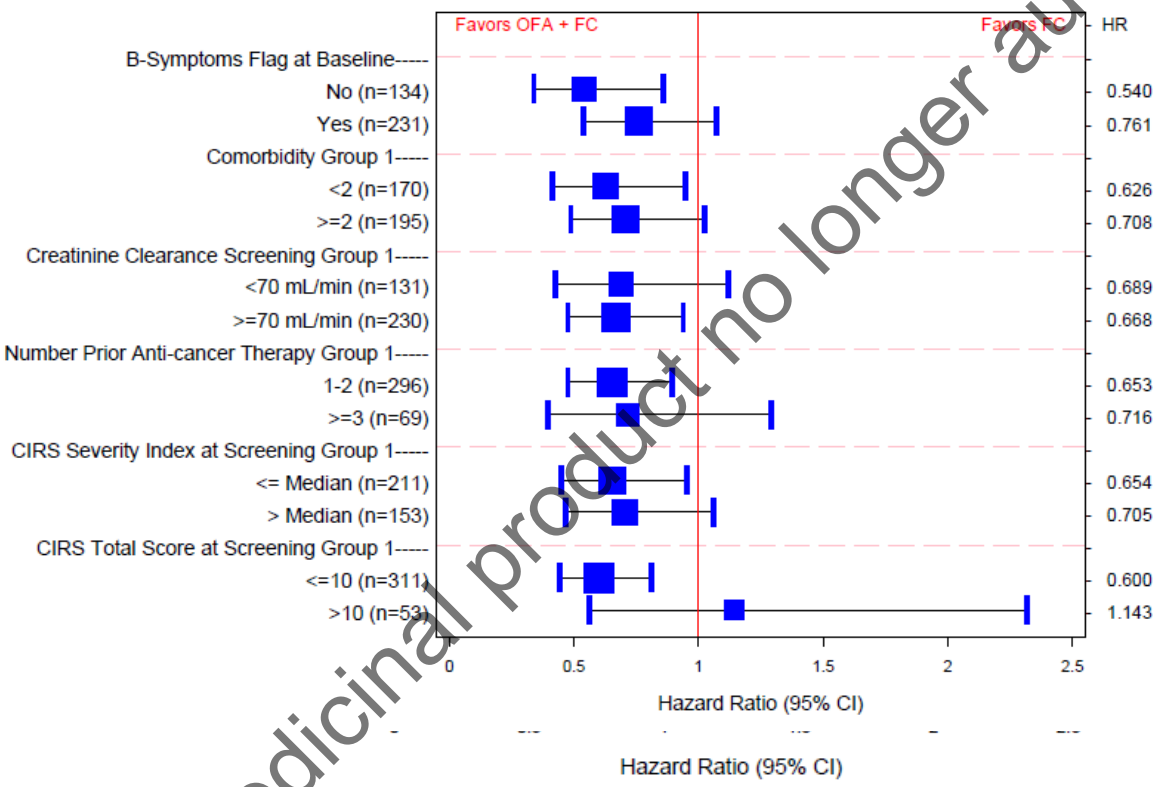
EFS: event-free survival; CI: confidence interval; FC: fludarabine and cyclophosphamide; ITT (ISE): intent-to-treat population defined for integrated summary of efficacy; NE: not evaluable; O+B: ofatumumab plus bendamustine; O+FC: ofatumumab plus fludarabine and cyclophosphamide.
[1] OMB110913 Investigator assessed data.
[2] OMB110913 independent review committee-assessed data.
[3] CIs estimated using the Brookmeyer Crowley method.
Source: [SCE-Appendix 1-Table 2.1970]

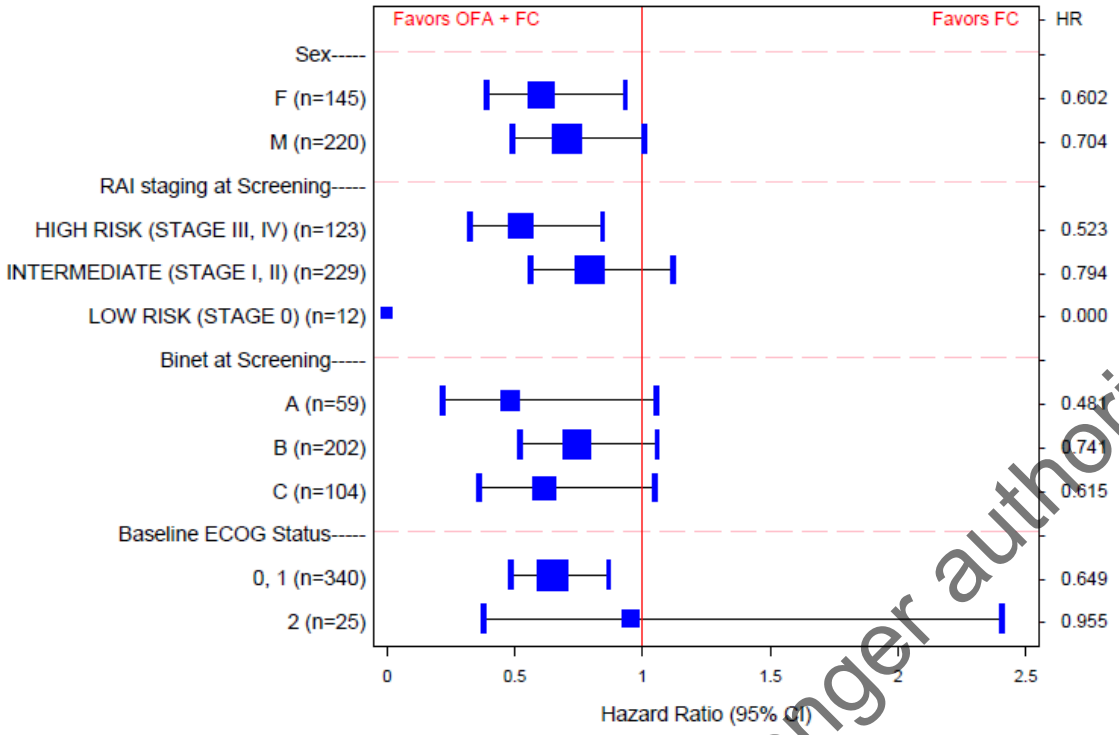
Efficacy results in subpopulations

Exploratory efficacy subgroup analyses were performed for both studies - no multiplicity adjustments were applied. Due to small sample sizes in the subgroups, the results should be interpreted with caution.

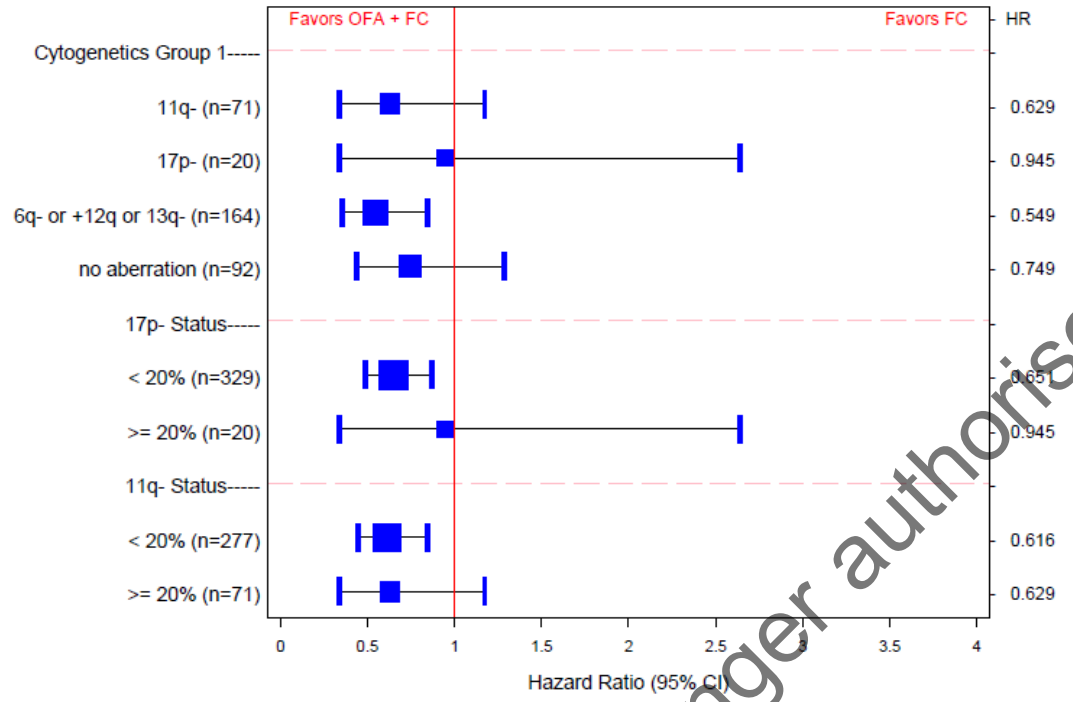
PFS by demographics and Baseline disease characteristics

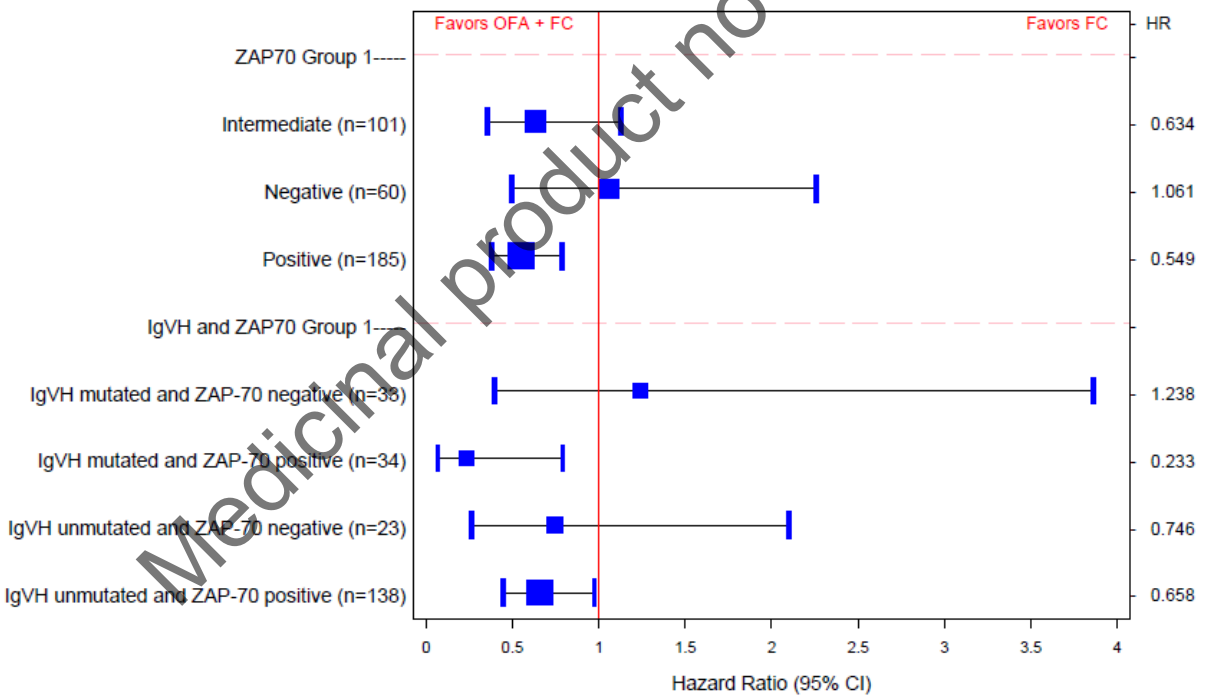
Forest Plot of Hazard Ratios and 95% Confidence Intervals for IRC-assessed PFS by Demographics and Baseline Characteristics





Forest Plot of Hazard Ratios and 95% Confidence Intervals for IRC-assessed PFS by Prognostic Factors





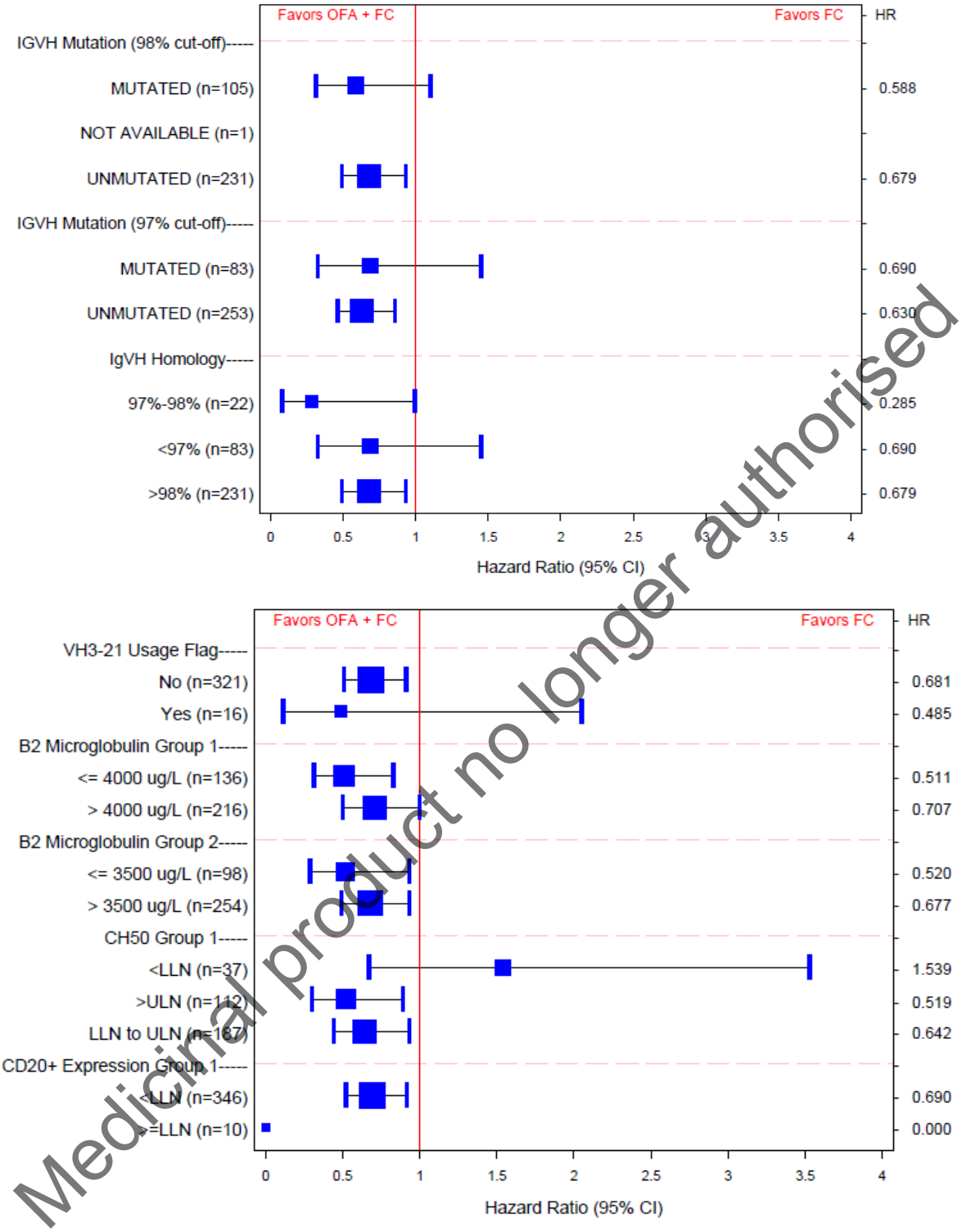


Table 40: Summary of IRC-assessed PFS by number of prior anti-cancer therapies in Study OMB913 (ITT population)

	O+FC N=183	FC N=182
Number of Prior Anti-cancer Therapies: 1-2		
Event (progressed or died), n %	81/149 (54)	82/147 (56)
Kaplan-Meier Estimate for PFS (Months) [a]		
Median (95% CI)	31.6 (26.7, 42.5)	24.0 (15.1, 28.6)
Hazard Ratio Estimate (95% CI) [b]	0.65 (0.48, 0.89)	
Number of Prior Anti-cancer Therapies: ≥ 3		

Event (progressed or died), n %	22/34 (65)	23/35 (66)
Kaplan-Meier Estimate for PFS (Months) [a]		
Median (95% CI)	17.6 (11.8, 19.3)	13.9 (9.3, 16.8)
Hazard Ratio Estimate (95% CI) [b]	0.72 (0.40, 1.29)	

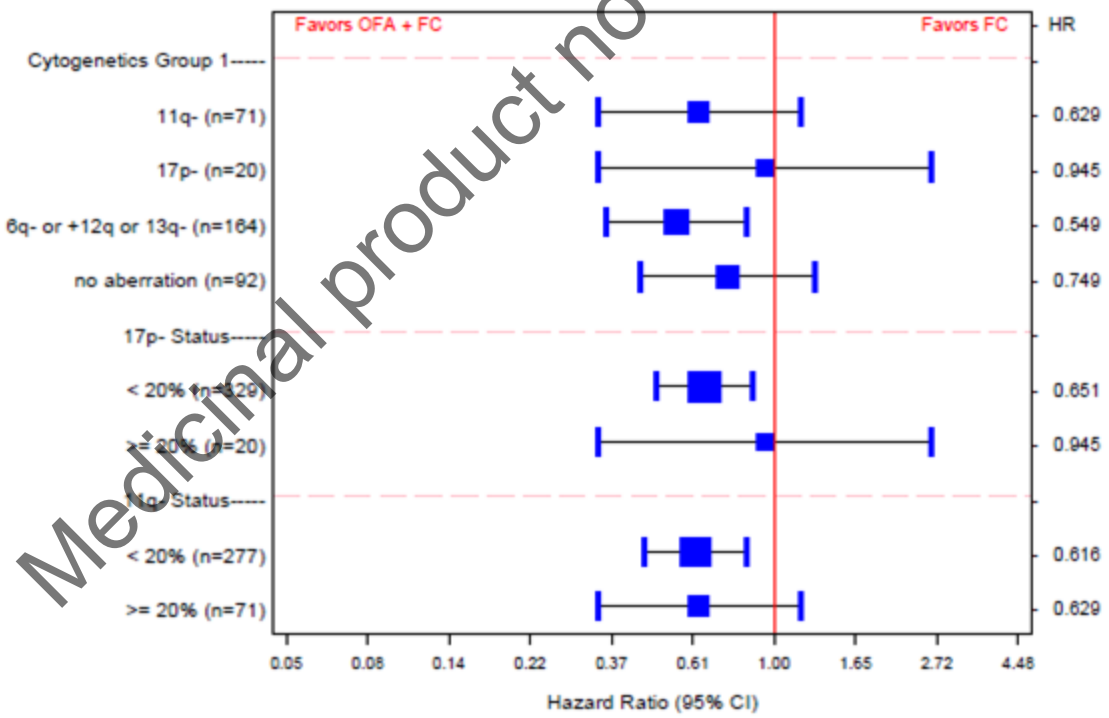
CI: confidence interval; FC: fludarabine and cyclophosphamide; IRC: independent review committee; ITT: intent-to-treat; O+FC: ofatumumab plus fludarabine and cyclophosphamide; PFS: progression-free survival.
[a] CIs estimated using the Brookmeyer Crowley method.
[b] Hazard ratios are estimated using the Pike estimator.
Source: [Study OMB913-Table 2.0078]

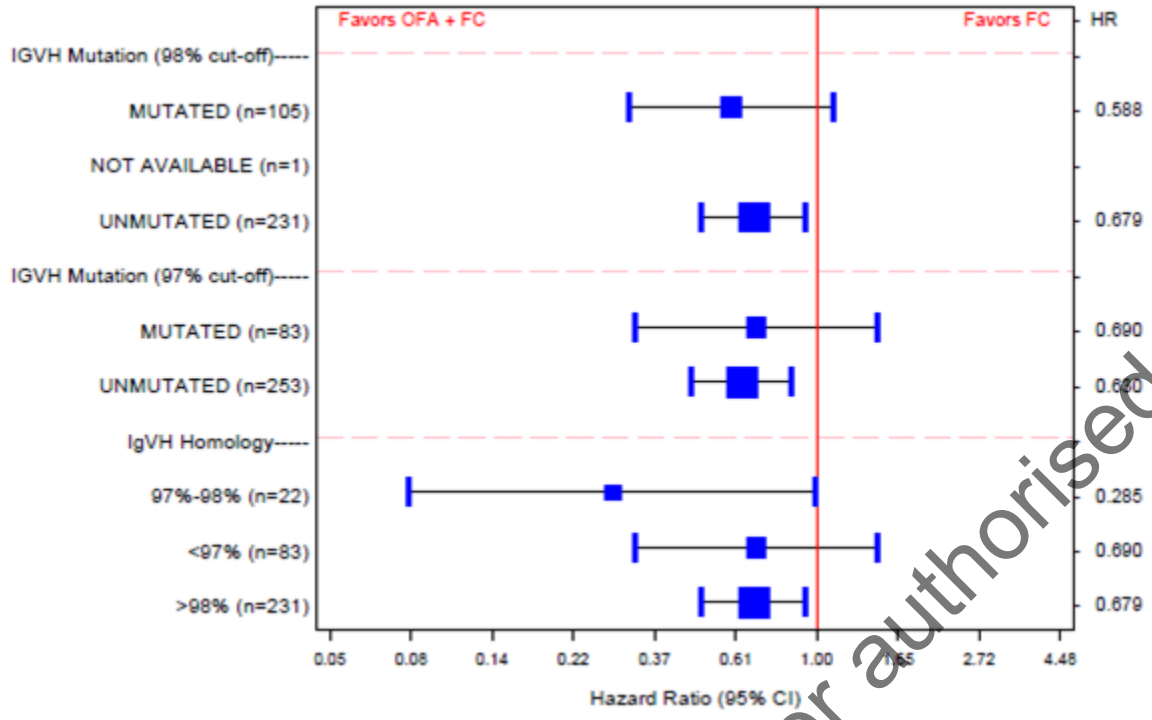
Table 41 Summary of IRC assessed PFS by type of prior rituximab therapy in Study OMB913 (ITT population)

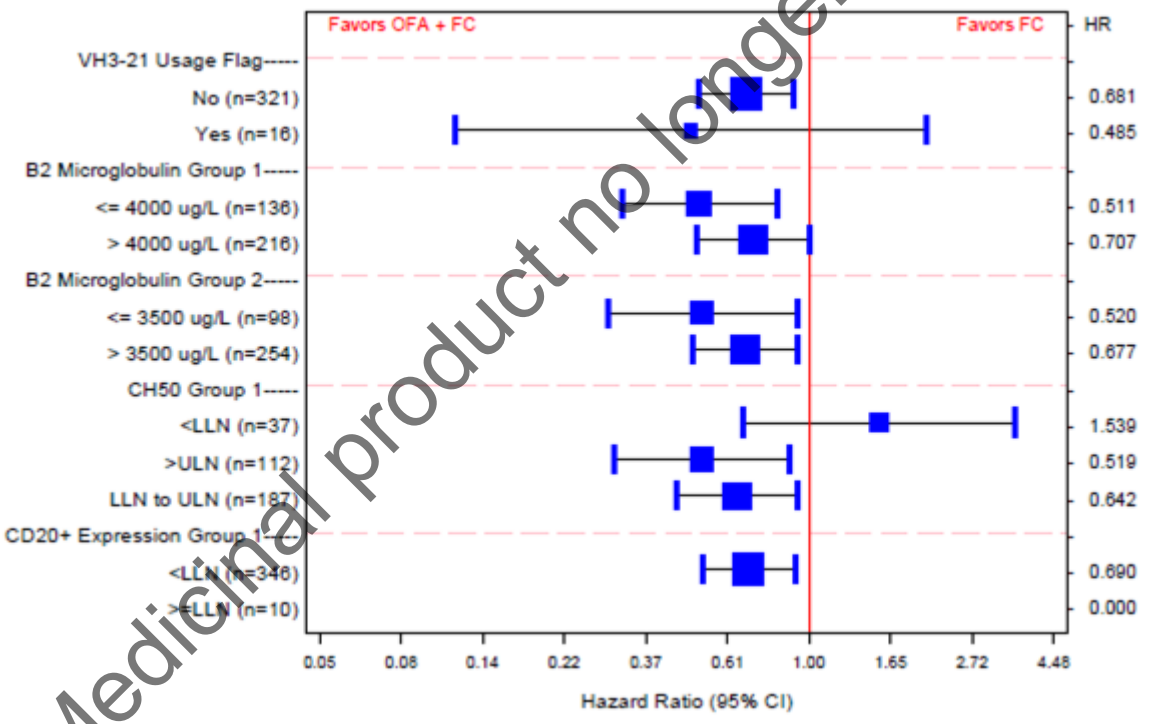
	O+FC N=183	FC N=182
Prior Exposure to Rituximab-based Therapy		
Event (progressed or died), n %	26/43 (60)	17/35 (49)
Kaplan-Meier Estimate for PFS (Months) [1]		
Median (95% CI)	26.8 (16.7, 42.4)	14.4 (6.3, 25.8)
Hazard Ratio Estimate (95% CI) [b]	0.66 (0.34, 1.26)	
No Prior Exposure to Rituximab-based Therapy		
Event (progressed or died), n %	77/140 (55)	88/147 (60)
Kaplan-Meier Estimate for PFS (Months) [a]		
Median (95% CI)	29.7 (22.8, 42.1)	21.0 (14.7, 28.1)
Hazard Ratio Estimate (95% CI) [b]	0.65 (0.47, 0.88)	

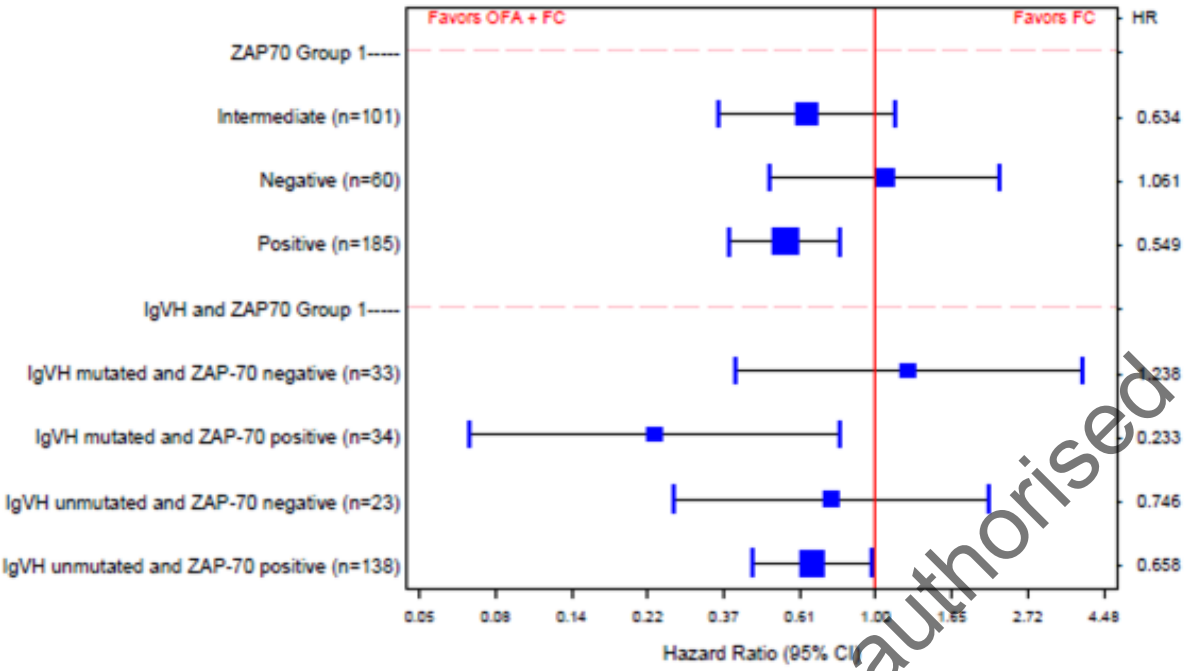
CI: confidence interval; FC: fludarabine and cyclophosphamide; IRC: independent review committee; ITT: intent-to-treat; O+FC: ofatumumab plus fludarabine and cyclophosphamide; PFS: progression-free survival.
[a] CIs estimated using the Brookmeyer Crowley method.
[b] Hazard ratios are estimated using the Pike estimator, adjusted for stratum.
Source: [Study OMB913-Table 2.0082], [Study OMB913-Table 2.0104]

Figure 3-17 Forest plot of HRs and 95% CIs for IRC-assessed PFS by prognostic factors in Study OMB913 (ITT population)









CI: confidence interval; CH50: dose of complement that lyses 50% of a red blood cell suspension; FC: fludarabine and cyclophosphamide; HR: hazard ratio; IgVH: immunoglobulin variable region heavy chain (note that text refers to the more recent nomenclature IGHV); IRC: independent review committee; ITT: intent-to-treat; LLN: lower limit of normal; OFA+FC: ofatumumab plus fludarabine and cyclophosphamide; PFS: progression-free survival; ULN: upper limit of normal; ZAP70: zeta-chain-associated protein kinase 70.
Data Source: [Study OMB913-Figure 12.0130]

Subgroup analyses for prognostic factors

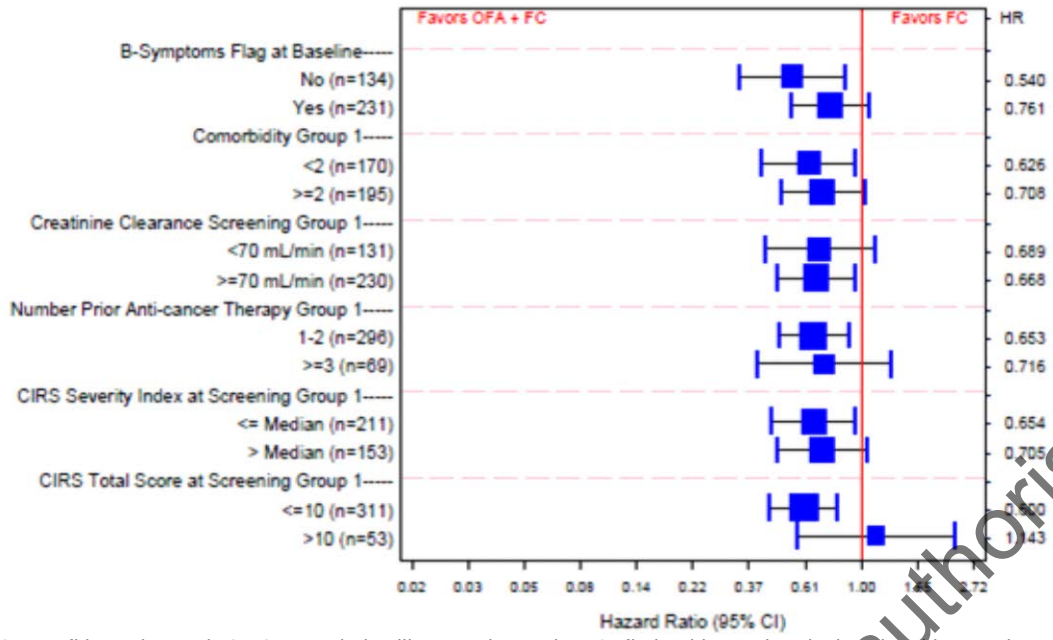
The IRC-assessed PFS HRs favored O+FC (study OMB 913) in subgroups usually associated with favorable prognosis: absence of cytogenetic aberration, aberration of 6q- or +12q or 13q-, mutated IGHV, and low serum B2 microglobulin. The PFS HRs also favored O+FC in subgroups usually associated with poor prognosis: unmutated IGHV, ZAP-70 positive, elevated B2 microglobulin, 11q-, or VH3-21 usage (Figure 3-5). Due to small numbers, no conclusion could be drawn on the ORR data.

In Study OMB913, subjects in O+FC arm had a median OS larger than that of subject in the FC arm irrespective of prognostic factors (except for subjects with 17p-, where due to small numbers, no conclusion could be drawn.

PFS by Baseline comorbid condition burden

In Study OMB913, HRs showed an improvement in PFS (IRC-assessed) with O+FC treatment, consistent with the overall study population, in most subgroups of Baseline fitness or comorbid condition burden, with the exception of the exploratory analysis of CIRS >10 (HR=1.14; 95% CI: 0.56, 2.32; n=30 subjects in the O+FC arm and n=23 subjects in the FC arm); Figure 3-6). In study OMB991, the results were generally consistent. Due to small numbers, no conclusion on ORR data was possible.

Figure 3-18 Forest plot of HRs and 95% CIs for IRC-assessed PFS by Baseline fitness and comorbid condition burden (ITT population)



CI: confidence interval; CIRS: cumulative illness rating scale; FC: fludarabine and cyclophosphamide; HR: hazard ratio; IRC: independent review committee; ITT: intent-to-treat; OFA+FC: ofatumumab plus fludarabine and cyclophosphamide; PFS: progression-free survival.
Source: [Study OMB913-Figure 12.0120]

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The OMB110913 study was a randomized open-label study, the ITT Analysis Set included 365 subjects, and 359 subjects were included in the Safety Analysis Set.

The Patient population included in the OMB110913 study had active disease and indication for treatment was based on modified IWCLL updated NCI-WG guidelines [Hallek, 2008]. Relapsed CLL was defined as a subject who received at least one prior CLL therapy and previously achieved a complete or partial remission/response, but after a period of 6 or more months demonstrated evidence of disease progression [Hallek, 2008]. Patients defined as treatment failure (failure to achieve a CR or PR) or disease progression within 6 months of last anti-leukemic therapy were defined as refractory and excluded from the study. However, as also mentioned in the CHMP scientific advice 2008, the exclusion of patients who progress within 6 months of prior treatment would be most valid for patients receiving FC previously. Patients previously treated with other regimens could have been included in the study, especially as this study does not exclude further than first relapses and therefore may recruit patients who have gone through recurrent treatments (e.g. with chlorambucil) from which they relapse earlier each time. In this respect, the limit of 6 months leads to a selected patient population, as patients relapsing earlier than 6 months probably would also achieve response of new therapy. However, in the case of chlorambucil, only the oldest and most frail patients received this treatment according to current recommendations.

Binet and Rai's staging systems were not used in the inclusion criteria, however, as mentioned by CHMP/SAWP, since the definitions of both staging systems differ e.g. in the Hb cut-off for anaemia, it is considered a better choice to use the definition of disease activity irrespective of stage. Even though a

relatively fit population is enrolled, overall, it can be concluded that the key inclusion and exclusion criteria accurately reflect the target patient population in this variation application of Arzerra.

The method regarding randomisation (IVRS) seems appropriate. Subjects were randomized with a block size of 2 to receive treatment arm A or B in a 1:1 ratio for the duration of the treatment period. Assignment of study drug was stratified according to two stratification factors: the number of prior CLL therapies (1 to 2 vs. ≥3) and Binet stage at Screening (A vs. B vs. C), resulting in six strata in total. However, the applicant has adequately clarified the decision of a block size of 2 and how it might have compromised the randomisation.

The applicant chose to compare the combination of ofatumumab (O) and fludarabine (F) + cyclophosphamide (C) with the combination of FC alone. At the time of CHMP scientific advice (2008) and study start (2009), the combination FC was considered to be acceptable comparators for the eligible patient population. However, currently it is recommended to add the CD20 monoclonal antibody rituximab to FC. While it obviously would have been more in accordance with current guidelines if the comparator arm had consisted of FC + rituximab, it is acknowledged that in 2008 the comparators chosen were adequate. PFS has previously been accepted by CHMP as a primary endpoint in this clinical setting.

At the time of data cut-off, which was the same for both studies, all subjects in both protocols had finished treatment. In study OMB913, 65% in the O+FC arm and 56% in the FC arm had completed the treatment phase. In study OMB991, 89% respectively completed the treatment phase and the majority of subjects (91% and 81%, O+FC and FC respectively) entered the Follow-up Phase. The proportion of subjects who prematurely discontinued in the OMB913 study was 35% and 49% respectively in the O+FC and FC arm, compared to 15% in the O+B study. In both studies the primary reason for withdrawal from study treatment was AEs.

The dose and regimen of ofatumumab in the two studies was based on clinical experience in prior and ongoing clinical studies as well as pharmacokinetics. The dosing regimen with one 300 mg dose the first day in the first cycle to minimize infusion reactions followed by one 1000 mg at day 8 in cycle 1, and then at each subsequent 4-week cycle, achieved steady-state plasma trough concentrations above the target level in > 90% of subjects in Study OMB913.

Overall, demographics and baseline characteristics (age, sex, CLL history and prognostic factors) were generally well balanced between the treatment arms in the O+FC study (OMB913). The median age was 61 years, and 63% of the subjects were < 65 years of age. The median age of the study group was thus a little younger than expected in a relapsed CLL setting. Although more than 90% of subjects in both arms had intermediate/high risk disease and Binet stage B and C, one could suspect that the patients due to a younger age were more fit. The applicant has properly justified this and it is considered not to be an issue. In the Study OMB991, subjects were older (median 68 years) than those in Study OMB913. In the O+B study (OMB991) a higher proportion of subjects received prior rituximab (51%), prior biologic therapy (58%) and prior fludarabine-containing regimens (75%) compared to subjects in Study OMB913 where 23% received rituximab-containing therapies, and 55% prior fludarabine-containing therapies. Subjects in the OMB991 were generally more heavily pretreated compared with those of study OMB913 and median time since diagnosis longer (6.9 years compared with 4.6 years in both O+FC and FC treatment arms. In the O+FC study (OMB913), 32% and 35% respectively in the O+FC arm and FC arm had modified Rai high risk disease (Stage III, IV). While in the supportive OMB991 study, a higher proportion of subjects (57%) had high risk modified RAI stage. Although subjects enrolled in the two studies were representative of the intended target population of relapsed CLL it raises concern, that study design, age of subjects and the fact, that enrollment of subjects to study O+B (OMB913) started 3 years earlier than the OMB991 study. The clinical practice, study design and the populations were not the same in the two studies; the CHMP therefore raised a major objection. The applicant endorsed the objection concerning the combination of ofatumumab and bendamustine for the treatment of relapsed CLL in the OMB991 study and has decided to withdraw this combination from the application.

Efficacy data and additional analyses for pivotal study OMB913

The primary endpoint of study OMB913, PFS, as assessed by the IRC (ITT Analysis Set), showed a statistically significant increase in median PFS by 10 months, with the addition of ofatumumab to FC (O+FC: 28.9 months, FC: 18.8 months, HR=0.67 [95% CI: 0.51, 0.88] p=0.0032). Investigator analysis and sensitivity analysis were consistent with the primary analysis. Start of alternative CLL therapy can confound the median PFS assessment, this was censored for the primary analysis. The analysis of EFS, where the start of alternative CLL therapy was considered an event, and the analysis of PFS without censoring were both consistent with the primary analysis. Exploratory subgroup analysis on IRC-assessed PFS were performed, although no multiplicity adjustments were performed, and the sample sizes were small for some analysis, a PFS prolongation was reported irrespective of age, gender, disease stage, prior therapy and for most prognostic factors. Whether subjects had received prior rituximab or not, they had an equal effect from addition of ofatumumab to FC.

A statistically significantly higher ORR of 84% for O+FC arm vs. 68% for the FC arm was reported, primarily due to a higher proportion of subjects achieving a CR (27% vs. 7% respectively). The PR rate was similar in the treatment arms. Responses occurred equally in both arms, with a median time to response of 1 month.

MRD negativity at 3– and 6– months post-treatment was 21% and 26% respectively in the O+FC arm compared with 8% and 6% respectively in the FC arm, indicating a robust and clinically meaningful response. The median IRC-assessed TTP was increased in the O+FC arm (42.12 months, 95%CI: 28.94, 47.67) compared with the FC arm (26.78 months, 95% CI: 22.51, 31.87) (HR=0.63, 95% CI: 0.45, 0.87; p=0.0036, no multiplicity adjustment applied). Analysis of other secondary endpoints such as DOR and TTNT showed a trend in favour of O+FC.

Median OS data were numerically higher in the O+FC arm, 56.4 months compared with 45.8 months for the FC arm, but not significant. Subjects are continued to be followed for survival. OS data were updated with an additional one year of follow up as of cut-off date of 21 Dec 2015 and were still immature and also confounded by later lines of therapy, median OS in the O+FC group was not reached, while the median OS in the FC group changed from 45.8 months to 46.23 months (95% CI: 37.73,NE). The estimated HR was slightly higher (changed from 0.78 to 0.79). The OS data is. However, as OS data are still not mature, the CHMP recommends that the MAH should submit the mature OS data from this study within the final CSR (see RMP).

Efficacy results for supportive study OMB991

Study OMB991 investigated the safety and efficacy of ofatumumab + bendamustine (n=97). The primary endpoint of this study was ORR. The efficacy results showed an ORR of 74%, and a median investigator-assessed PFS of 22.5 months.

Shortcomings in the study design (i.e. open label, single arm, only 53 previously relapsed CLL patients) raise considerable doubt with respect to the robustness of the provided efficacy data. The adequacy of this study in supporting an indication was therefore questioned by CHMP. Absence of a comparator arm makes it challenging to decide which patients will benefit from this therapy and determine the adequate place of this combination in the hierarchy of treatment options for relapsed CLL. Data to substantiate any clinical relevance of the observed anti-tumour effect of the combination of ofatumumab + bendamustine are also lacking. Although the ORR was 74%, this was not supported by a CR rate of 11%, nor of OS data. The included patient population differs from the population enrolled in the pivotal study, consequently, direct comparisons or extrapolations between these two studies are difficult to make. Due to all these concerns relating to the ofatumumab + bendamustine combination in relapsed CLL, the applicant has decided to withdraw the claim based on this study from the application.

2.4.4. Conclusions on the clinical efficacy

In conclusion, for previously treated patients with relapsed CLL, the difference in PFS and ORR between the 2 arms in the pivotal study OMB913, favouring the O+FC arm, in subjects with both good – and poor risk prognostic factors, is statistically significant and clinically meaningful and seems robust, although no significant effect on overall survival could be demonstrated. The results were supported by the secondary endpoints and delay of time to progression and post-treatment anti-CLL therapy, which seems clinically meaningful in a disease with a relentless pattern of relapses. The efficacy results have been reflected in the SmPC.

In the study OMB991 combining ofatumumab and bendamustine, the benefit of ORR stands alone, there were several critical issues and the data seemed not robust for an approval. The applicant has therefore decided to withdraw the claim for this combination for the treatment of relapsed CLL.

2.5. Clinical safety

Introduction

In this submission, safety data from two clinical studies (the phase III registration study OMB110913 and the supportive phase II study OMB115991) in subjects with relapsed CLL are presented, data were pooled in order to characterize the safety profile of ofatumumab combination therapy. All safety summaries and analyses were performed using the safety population, defined as subjects who received at least one dose of study drug, in accordance with the study-specific statistical analysis plan (SAP) as documented within the CSR.

Table 42: Sources of safety data for combination of ofatumumab and chemotherapy in subjects with relapsed CLL

Study	Phase, Study Design, Study population	No. of subjects randomized	Treatment duration	Treatment dose/day
OMB913[1]	Phase III, open-label, parallel-group, randomized, multi-center O+FC vs. FC in subjects with relapsed CLL	N=365 O+FC=183 FC=182	Up to 6 cycles of 28 days	**Ofatumumab IV infusion** - Cycle 1: 300 mg Day 1 and 1000 mg Day 8 Subsequent Cycles: 1000 mg at Day 1 **Fludarabine IV infusion** - 25 mg/m^2 starting dose, Day 1 to Day 3 of each cycle **Cyclophosphamide IV infusion** - 250 mg/m^2 starting dose, Day 1 to Day 3 of each cycle
OMB991[2]	Phase 2, single group, multi-center O+B in subjects with untreated or relapsed CLL	N=97 O+B (untreated CLL): 44 O+B (relapsed CLL) = 53	Up to 6 cycles of 28 days	**For subjects with Relapsed CLL**: 1) Ofatumumab (IV infusions): Cycle 1: 300 mg Day 1 and 1000 mg Day 8 Subsequent Cycles: 1000 mg at Day 1 2) Bendamustine (IV infusions) - 70 mg/m^2, Days 1 and 2; every 28 Days.

[1] In Study OMB913, six out of 359 subjects were randomized but not treated
[2] Study OMB991 also enrolled untreated subjects, but only the data from cohort of subjects with relapsed CLL is included in this submission
Source: [Synopses of Individual Studies], [Tabular Listing of All Clinical Studies]

Table 43 Number of relapsed CLL subjects in safety population

Treatment Group	Source study	No of subjects in safety analysis
Total number of subjects		412
Ofatumumab + fludarabine + cyclophosphamide (O + FC)	Study OMB913	181
Ofatumumab + bendamustine (O+B)	Study OMB991 relapsed population	53
Fludarabine + cyclophosphamide (FC)	Study OMB913	178
Pooled data from all groups containing ofatumumab (O + Chemo)	Study OMB913 + relapsed population data from Study OMB991	234[a]

[a] All subjects with relapsed CLL who received ofatumumab in combination with chemotherapy
Source: [SCS Appendix 1-Table 1.1100]

Patient exposure

Of the 412 subjects randomized, 234 subjects received ofatumumab in combination with chemotherapy (FC or bendamustine), and 178 subjects received FC. In the O+FC group, 90% received 3 to 6 cycles of treatment and 92% in the O+B group. In both the O+FC and O+B groups, the dose of ofatumumab received was close to the planned dose, with a median dose received equal to 100% of the planned dose during each cycle. The median dose of ofatumumab in the O+Chemo group was 1300 mg for Cycle 1 (300 mg initial dose and 1000 mg subsequent dose for Cycle 1) and 1000 mg for all subsequent cycles.

Table 44 Summary of study treatment status and reasons for study treatment discontinuation (Safety Population)

	O+FC (N=181) n (%)	O+B (N=53) n (%)	FC (N=178) n (%)	O+Chemo (N=234) n (%)
Completion Status				
Completed treatment	119 (66)	45 (85)	93 (52)	164 (70)
Prematurely discontinued	62 (34)	8 (15)	85 (48)	70 (30)
Primary[a] reason for study Treatment withdrawal				
Adverse Event	50 (28)	5 (9)	52 (29)	55 (24)
Protocol Deviation	1 (<1)	0	0	1 (<1)
Study Closed/Terminated	0	0	0	0
Lost to Follow-Up	1 (<1)	0	1 (<1)	1 (<1)
Disease Progression	0	2 (4)	9 (5)	2 (<1)
Physician Decision	4 (2)	1 (2)	10 (6)	5 (2)
Withdrawal by subject	6 (3)	0	13 (7)	6 (3)

[a] Subjects may have only one primary reason for withdrawal
Source: [SCS Appendix 1-Table 1.1200]

Table 45 Summary of subject status and reason for study withdrawal (Safety Population)

	O+FC (N=181)	O+B (N=53)	FC (N=178)	O+Chemo (N=234)
Subject Status				
Completed protocol scheduled visits[1]	70 (39)	19 (36)	69 (39)	89 (38)
Ongoing	82 (45)	33 (62)	57 (32)	115 (49)
Withdrawn from study	29 (16)	1 (2)	52 (29)	30 (13)
Primary[2] reason for study withdrawal				
Lost to follow-up	7 (4)	1 (2)	9 (5)	8 (3)
Physician decision	4 (2)	0	5 (3)	4 (2)
Withdrawal by subject	18 (10)	0	38 (21)	18 (8)

[1]Completed 3 years of follow-up for study OMB991 and 5 years of follow-up for study OMB913
[2] Subjects may have only one primary reason for withdrawal.
Source: [SCS Appendix 1-Table 1.1120]

Adverse events

Table 46 Adverse Event Overview

	O+FC (N=181)	FC (N=178)
Any AE, n (%)	**170 (94)**	**153 (86)**
AE related to study treatment	160 (88)	127 (71)
AE leading to permanent discontinuation of study treatment[a]	49 (27)	49 (28)
AE leading to infusion reduction	40 (22)	32 (18)
AE leading to infusion interruption/delay	99 (55)	39 (22)
AE ≥Grade 3	144 (80)	128 (72)
Any SAE, n (%)	**107 (59)**	**86 (48)**
SAE related to study treatment	60 (33)	51 (29)
Fatal SAE	36 (20)	39 (22)
Fatal SAE related to study treatment	11 (6)	9 (5)

Data Source: Table 3.1010
Abbreviations: AE=adverse event; eCRF=electronic case report form; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SAE=serious adverse event.
a. Includes subjects with 'action taken' recorded as 'study treatment discontinued' in AE log. Four additional subjects were noted to have discontinued study treatment due to an AE based on the study treatment discontinuation details provided in the eCRF (results shown in Table 6). This discrepancy is due to 2 subjects with AEs leading to drug discontinuation, but the primary reason for study drug discontinuation was provided as 'investigator decision' (O+FC: Subject 785, Subject 2082), and 6 subjects who discontinued study drug due to AEs, but had fatal SAEs for which 'action taken' was recorded as 'not applicable' (O+FC: Subject 291, Subject 835, Subject 1880; FC: Subject 821, Subject 837, Subject 1750).

Adverse events

The majority of subjects had 1 or more AEs, with a higher incidence of subjects in the O+FC arm compared with the FC arm. A higher proportion of subjects in the O+FC arm had AEs that were Grade ⩾ 3, related to study treatment, or to an infusion interruption/delay. The proportion of subjects who discontinued due to AEs was similar in both treatment arms (Table 36). The proportion of subjects with fatal SAEs and deaths, was similar between treatment arms, although subjects in the O+FC arm had more SAEs than those in the FC arm.

Common Adverse Events

The most common AEs were consistent with wellknown AEs related to chemotherapy and ofatumumab, and included neutropenia, thrombocytopenia, nausea, and anaemia (reported by ≥15% of subjects in either arm) (Table 38). Neutropenia was reported more frequently in the O+FC arm (O+FC: 55%, FC: 38%); while thrombocytopenia and anaemia were reported more frequently in the FC arm (O+FC: 20%, FC: 31%) and (O+FC: 13%, FC: 24%) respectively. Nausea was reported equally in both treatment arms (19%). AEs related to infusion reactions (e.g., rash, urticaria, pyrexia/chills, pruritus, dyspnea, hypotension, and flushing) were more frequently reported in the O+FC arm.

Table 47 Adverse events reported in at least 5% of subject in either treatment arm

Preferred Term	O+FC (N=181)	FC (N=178)
Any event, n (%)	**170 (94)**	**153 (86)**
Neutropenia	102 (56)	70 (39)
Nausea	46 (25)	36 (20)
Thrombocytopenia	44 (24)	63 (35)
Anaemia	34 (19)	48 (27)
Pyrexia	33 (18)	19 (11)
Leukopenia	27 (15)	11 (6)
Pneumonia	26 (14)	30 (17)
Febrile neutropenia	23 (13)	17 (10)
Rash	21 (12)	8 (4)
Vomiting	20 (11)	23 (13)
Pruritus	19 (10)	2 (1)
Diarrhoea	17 (9)	20 (11)
Dyspnoea	17 (9)	5 (3)
Fatigue	16 (9)	11 (6)
Headache	16 (9)	6 (3)
Upper respiratory tract infection	16 (9)	13 (7)
Cough	15 (8)	10 (6)
Chills	14 (8)	3 (2)
Decreased appetite	14 (8)	8 (4)
Asthenia	13 (7)	16 (9)
Hypotension	13 (7)	4 (2)
Infusion-related reaction (not further specified)	13 (7)	0
Platelet count decreased	13 (7)	5 (3)
Bronchitis	11 (6)	8 (4)
Constipation	10 (6)	11 (6)
Dizziness	9 (5)	1 (<1)
Urinary tract infection	9 (5)	11 (6)
Urticaria	9 (5)	3 (2)
Weight decreased	9 (5)	1 (<1)

Data Source: Table 3.1060

Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

The subgroup analysis of AEs (by age, race, sex, and geographical location) were generally consistent with the overall analysis of AEs.

Table 48 Treatment-Related Adverse Events Reported in at Least 5% of Subjects in Either Treatment Arm

Preferred Term	O+FC (N=181)	FC (N=178)
Any related AE, n (%)	**160 (88)**	**127 (71)**
Neutropenia	99 (55)	68 (38)
Thrombocytopenia	37 (20)	55 (31)
Nausea	34 (19)	33 (19)
Leukopenia	26 (14)	11 (6)
Anaemia	23 (13)	43 (24)
Pyrexia	18 (10)	5 (3)
Rash	19 (10)	3 (2)
Febrile neutropenia	17 (9)	12 (7)
Pruritus	14 (8)	2 (1)
Infusion related reaction	13 (7)	0
Pneumonia	13 (7)	8 (4)
Vomiting	13 (7)	18 (10)
Decreased appetite	11 (6)	5 (3)
Dyspnoea	11 (6)	2 (1)
Fatigue	11 (6)	8 (4)
Platelet count decreased	11 (6)	5 (3)
Chills	10 (6)	0
Hypotension	9 (5)	1 (<1)
Diarrhoea	6 (3)	11 (6)
Asthenia	5 (3)	9 (5)

Data Source: Table 3.1140
Abbreviations: AE=adverse event; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

Adverse Events by Severity

Overall, 76% of subjects (O+FC: 80%, FC: 72%) had Grade ⩾3 AEs, with 64% of subjects reporting a treatment-related Grade ⩾3 AE (O+FC: 69%, FC: 58%). The incidence of fatal AEs (i.e., Grade 5) was similar in the O+FC arm (20%) compared with the FC arm (22%). The incidence of deaths overall was also comparable between arms (O+FC: 37%, FC: 39%).

Table 49 Adverse Events with Maximum Severity of Grade 3 or Higher Reported in at Least 5% of Subjects in Either Treatment Arm

Preferred Term	O+FC (N=181)	FC (N=178)
Any Grade ≥3 AE, n (%)	**144 (80)**	**128 (72)**
Neutropenia	92 (51)	65 (37)
Thrombocytopenia	27 (15)	44 (25)
Pneumonia	21 (12)	25 (14)
Febrile neutropenia	23 (13)	17 (10)
Anaemia	17 (9)	20 (11)
Leukopenia	21 (12)	6 (3)
Treatment-related Grade ≥3 AEs, n (%)	**125 (69)**	**104 (58)**

Data Source: Table 3.1070, Table 3.1150
Abbreviations: AE=adverse event; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide

Adverse Events Leading to Dose Delay, Dose Reduction, or Permanent Discontinuation of Study Drug

AEs leading to dose interruptions/delays were reported more frequently in the O+FC arm (55%) than the FC arm (22%), whereas the incidence of AEs leading to dose reduction was lower and similar in both arms (Table 50). With the exception of neutropenia, the AEs that led to dose delays, interruptions, or reductions in the O+FC arm were events typically associated with infusion reactions, few of which led to permanent discontinuation of study treatment. Haematologic events were the most common type of AE leading to discontinuation of study treatment and the proportion of subjects who discontinued due to AEs was similar in both treatment arms.

Table 50 Adverse events leading to dose interruption / delay or reduction occurring in 4% or more of subjects

Preferred Term	O+FC (N=181)	FC (N=178)
Any AE leading to dose interruption or delay, n (%)	**99 (55)**	**39 (22)**
Neutropenia	24 (13)	7 (4)
Rash	13 (7)	2 (1)
Infusion-related reaction	12 (7)	0
Pruritus	12 (7)	0
Dyspnoea	10 (6)	0
Leukopenia	7 (4)	2 (1)
Pyrexia	7 (4)	2 (1)
Hypersensitivity	7 (4)	0
Thrombocytopenia	2 (1)	8 (4)
Any AE leading to dose reduction, n (%)	40 (22)	32 (18)
Neutropenia	23 (13)	16 (9)
Thrombocytopenia	7 (4)	9 (5)

Data Source: Table 3.1120, Table 3.1110
Abbreviations: AE=adverse event; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

Serious adverse event / deaths / other significant events

Serious adverse events are listed in Table 42 and 43.

Table 51 Overview of Serious Adverse Events

	O+FC (N=181)	FC (N=178)
Any SAE, n (%)	**107 (59)**	**86 (48)**
SAEs related to study treatment	60 (33)	51 (29)
SAEs reported up to 60 days after last dose	67 (37)	58 (33)
SAEs reported up to 60 days after last dose excluding alternative anti-cancer therapy[a]	20 (11)	15 (8)

Data Source: Table 3.1170, Table 3.1180, Table 3.1200, Table 3.1210
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SAE=serious adverse event.
a. Excluding SAEs that occurred after starting alternative anti-cancer therapy.

Table 52 Serious Adverse Events Reported in at Least 2% of Subjects in Either Treatment Arm

Preferred Term	O+FC (N=181)	FC (N=178)
Any SAE, n (%)	**107 (59)**	**86 (48)**
Pneumonia	25 (14)	27 (15)
Febrile neutropenia	18 (10)	15 (8)
Neutropenia	17 (9)	14 (8)
Anaemia	11 (6)	12 (7)
Pyrexia	9 (5)	5 (3)
Thrombocytopenia	7 (4)	10 (6)
Lower respiratory tract infection	6 (3)	2 (1)
Urinary tract infection	6 (3)	6 (3)
Pancytopenia	5 (3)	5 (3)
Renal failure acute	5 (3)	2 (1)
Sepsis	4 (2)	7 (4)
Neutropenic sepsis	4 (2)	5 (3)
Upper respiratory tract infection	4 (2)	5 (3)
Bronchitis	3 (2)	2 (1)
Diarrhoea	3 (2)	2 (1)
Myelodysplastic syndrome	3 (2)	2 (1)
Hypotension	3 (2)	0
Respiratory failure	3 (2)	2 (1)
Death	3 (2)	1 (<1)
Dyspnoea	3 (2)	1 (<1)
Gastrointestinal haemorrhage	3 (2)	1 (<1)
Atrial fibrillation	2 (1)	3 (2)
Bronchopneumonia	2 (1)	3 (2)
Septic shock	1 (<1)	3 (2)
Cardiac failure acute	0	4 (2)

Data Source: Table 3.1170
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SAE=serious adverse event

Table 53 Treatment-related Serious Adverse Events Reported in at Least 2% of Subjects in Either Treatment Arm

Preferred Term	O+FC (N=181)	FC (N=178)
Any related SAE, n (%)	**60 (33)**	**51 (29)**
Neutropenia	13 (7)	11 (6)
Febrile neutropenia	12 (7)	11 (6)
Pneumonia	12 (7)	7 (4)
Pancytopenia	4 (2)	3 (2)
Pyrexia	4 (2)	2 (1)
Myelodysplastic syndrome	3 (2)	2 (1)
Thrombocytopenia	3 (2)	7 (4)
Neutropenic sepsis	3 (2)	2 (1)
Anaemia	2 (1)	9 (5)

Data Source: Table 3.1210
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SAE=serious adverse event.

Deaths

Table 54 Summary of Deaths

	O+FC (N=181)	FC (N=178)
All Deaths, n (%)	**67 (37)**	**69 (39)**
Primary Cause of Death, n (%)		
Disease under study	31 (17)	31 (17)
Other[a]	36 (20)	38 (21)
Time to Death, n (%)		
On treatment and up to 30 days post treatment	3 (2)	4 (2)
>30 days to ≤60 days after last dosing	2 (1)	6 (3)
>60 days after last dosing	60 (33)	58 (33)
Unknown	2 (1)	1 (<1)
Fatal SAEs, n (%)		
All Fatal SAEs	36 (20)	39 (22)
Fatal SAEs ≤60 days after last dose	13 (7)	13 (7)

Data Source: Table 3.1630, Table 3.3140, and Table 3.3150
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SAE=serious adverse event.
a. Other causes of death included adverse events and unknown cause. Fatal SAEs are further discussed in Section 7.2.2.

Fatal Serious Adverse Events

The incidence of fatal serious AE was similar between treatment arms, the most frequently reported fatal SAEs being infections SOC (Table 47) especially pneumonia. Fatal SAEs considered related to study treatment by the investigator were reported in a similar proportion of subjects in both treatment arms (O+FC: 6%, FC: 5%).

Table 55 Fatal SAEs by System Organ Class

System Organ Class	O+FC (N=181)	FC (N=178)
Any Fatal SAE	**36 (20)**	**39 (22)**
Infections and infestations	14 (8)	20 (11)
Cardiac disorders	4 (2)	6 (3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (4)	3 (2)
Respiratory, thoracic and mediastinal disorders	4 (2)	4 (2)
Blood and lymphatic system disorders	3 (2)	3 (2)
General disorders and administration site conditions	3 (2)	2 (1)
Gastrointestinal disorders	3 (2)	0
Vascular disorders	0	3 (2)
Nervous system disorders	2 (1)	0
Hepatobiliary disorders	1 (<1)	0
Renal and urinary disorders	1 (<1)	0

Data Source: Table 3.3140
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide; SAE=serious adverse event.

Adverse events leading to dose interruption / delay or adjustment

The incidence of AEs requiring dose interruption or delay was lower in the FC group compared to O+Chemo group (22% in FC vs. 58% in O+Chemo), primarily due to a higher incidence of neutropenia and AEs associated with infusion reactions (including rash, pruritus, and chills) in the O+Chemo group (Table 56, and under discontinuation).

Table 56: Summary of adverse events leading to dose interruptions/delay by preferred term in at least 5% of subjects (Safety Population)

Preferred Term	O + FC (N=181) n (%)	O + B (N=53) n (%)	FC (N=178) n (%)	O+Chemo (N=234) n (%)
Any Event	99 (55)	36 (68)	39 (22)	135 (58)
Neutropenia	24 (13)	16 (30)	7 (4)	40 (17)
Infusion related reaction	12 (7)	8 (15)	0	20 (9)
Rash	13 (7)	3 (6)	2 (1)	16 (7)
Pruritus	12 (7)	1 (2)	0	13 (6)
Pyrexia	7 (4)	5 (9)	2 (1)	12 (5)
Dermatitis allergic	4 (2)	5 (9)	0	9 (4)
Chills	6 (3)	3 (6)	0	9 (4)
Dyspnoea	10 (6)	0	0	10 (4)
Thrombocytopenia	2 (1)	5 (9)	8 (4)	7 (3)
Nausea	2 (1)	3 (6)	0	5 (2)
Flushing	2 (1)	3 (6)	0	5 (2)

The incidence of AEs leading to dose reductions was lower in the FC group compared to O+Chemo group (18% in FC vs. 26% in O+Chemo), primarily due to a higher incidence of neutropenia in the O+Chemo group.

Table 57: Summary of adverse events leading to dose reductions by preferred term in at least 2% subjects (Safety Population)

Preferred Term	O + FC (N=181) n (%)	O + B (N=53) n (%)	FC (N=178) n (%)	O+Chemo (N=234) n (%)
Any Event	**40 (22)**	**20 (38)**	**32 (18)**	**60 (26)**
Neutropenia	23 (13)	16 (30)	16 (9)	39 (17)
Thrombocytopenia	7 (4)	3 (6)	9 (5)	10 (4)
Anaemia	4 (2)	0	4 (2)	4 (2)
Febrile neutropenia	0	1 (2)	1 (<1)	1 (<1)
Bronchitis	0	1 (2)	0	1 (<1)
Infected bites	0	1 (2)	0	1 (<1)
Pyrexia	0	2 (4)	0	2 (<1)
Toxic skin eruption	0	1 (2)	0	1 (<1)

Source: [SCS Appendix 1 Table 3.1.1.1]

Adverse Events of Special Interest and of Clinical Significance

AEs of special interests are cytopenias (including autoimmune haematologic complications), infusion reactions, infections, mucocutaneous reactions, and tumour lysis syndrome.

Other clinically important AEs of special interests are cardiovascular events, neoplasms, liver events, and small bowel obstructions.

Cytopenias

The incidence of AEs associated with decreased neutrophil counts was higher in the O+FC arm (64%) than in the FC arm (48%) as were the incidence of grade 3 and 4 neutropenia. The proportions of subjects with neutropenia SAEs were similar between the treatment arms (Table 48). The incidence of neutropenic sepsis was low (2%) in both treatment arms as were fatal SAEs of febrile neutropenia (1% in both treatment arms. Overall, the incidence of study drug discontinuations due to neutropenia AEs were low (8%), with a higher proportion of subjects discontinuing treatment due to neutropenia in the

O+FC arm (10%) compared with the FC arm (4%).

A higher incidence of overall and drug-related events was reported in the O+FC arm compared with the FC arm (Table 53). This higher incidence overall was influenced by a greater number of cases of leukopenia in the O+FC arm than in the FC arm. The incidence of other cytopenia-related SAEs was low in both treatment arms.

The incidence of AEs and treatment-related AEs associated with decreased haemoglobin count was lower in the O+FC arm (25% and 20%, respectively) compared with the FC arm (35% and 30%, respectively). There was no significant difference between treatment arms with regard to incidence of SAEs and treatment related SAEs.

The incidence of AEs and treatment-related AEs associated with platelet count decreases was lower in the O+FC arm (31% and 28%, respectively) compared with the FC arm (40% and 35%, respectively). No difference was noted between treatment arms with regard to incidence of SAEs and treatment related SAEs or proportion of subjects who permanently discontinued study treatment due to AEs of thrombocytopenia.

Autoimmune Haematologic Complications is a common complication to subjects having CLL. However, no significant difference between the treatment arms with regard to autoimmune haematologic complications was reported.

- **Infusion Reactions (IR)**

Infusion reactions were defined as reactions that occurred after the start time of infusion and within 24hours of infusion end, and resulted in a temporary interruption or prolongation of infusion time or treatment withdrawal. A higher proportion of subjects in the O+FC arm (60%) reported an infusion-related AE compared with subjects in the FC arm (28%). Infusion-related AEs primarily occurred between 1 and 2 hours post-infusion on the first day of infusion during Cycles 1 and 2, and numbers of subjects with IRs declined over the course of the treatment period. IRs were mild to moderate in severity. Few infusion-related AEs led to permanent discontinuation of study treatment and none of them were fatal. The type of IR is noted in table 58, nausea and rash were the most common IRs.

Table 58 Infusion Reaction Adverse Events Occurring in at Least 5% of Subjects in Either Treatment Arm at Any Infusion

Preferred Term	O+FC (N=181)	
	First Infusion	Any Infusion
Any AE	**88 (49)**	**108 (60)**
Nausea	22 (12)	39 (22)
Rash	16 (9)	19 (10)
Anaphylactoid events	11 (6)	13 (7)
Infusion related reaction	11 (6)	13 (7)
Chills/rigors	10 (6)	10 (6)
Fever/pyrexia	10 (6)	13 (7)
Pruritus	10 (6)	13 (7)
Hypotension	9 (5)	11 (6)
Emesis/vomiting	8 (4)	14 (8)
Dyspnoea	7 (4)	14 (8)
Headache	6 (3)	9 (5)

Data Source: Table 3.1380
Abbreviations: AE=adverse event; FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

- **Infections**

The proportion of subjects having infectious AEs during the study was 46% and 49% respectively in the

O+FC arm and the FC arm, with 29% of subjects in both treatment arms having events that were Grade ⩾3. In total, 20% of subjects (O+FC: 23%, FC: 17%) had infections related to treatment, with only 4% leading to permanent discontinuation of treatment. Serious infectious AEs were reported in a similar proportion of subjects in both treatment arms. In total, 34 subjects (9%) had fatal infections with 9 subjects (3%) having fatal infections related to study treatment. The proportion of subjects with fatal infections was 8% in the O+FC arm, compared with 11% in the FC arm. Fatal infections that were considered related to study treatment were similar between treatment arms.

Incidences of serious infections were similar between treatment arms, with respiratory tract infections being the most frequently reported SAE in both O+FC and FC subjects (Table 59).

Table 59 Serious Infections Reported as Adverse Events

	O+FC (N=181)	FC (N=178)
Any infection	**54 (30)**	**56 (31)**
Lower respiratory tract infections	38 (21)	37 (21)
Pneumonia	30 (17)	33 (19)
Lower respiratory tract infections	6 (3)	2 (1)
Bronchitis	3 (2)	2 (1)
Lung infection	2 (1)	2 (1)
Other infections	22 (12)	21 (12)
Sepsis	11 (6)	16 (9)
Upper respiratory tract infections	6 (3)	8 (4)
Opportunistic infections	5 (3)	8 (4)

Data Source: Table 3.1330
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide

Progressive Multifocal Leukoencephalopathy

No cases of PML was reported in this study.

Hepatitis B Infection and Reactivation

Two cases of HBV infection were reported, 1 in each treatment arm, and 1 case of HBV reactivation in the O+FC arm.

- **Mucocutaneous Reactions**

Mucocutaneous reactions included a variety of events affecting mucous membranes and skin, many of which overlapped with infusion reactions (Table 62). In total 24% (87/359 subjects) had AEs identified as mucocutaneous reactions. The incidence was higher in the O+FC arm (33%) compared with the FC arm (15%). Treatment-related mucocutaneous reactions were reported in 26% of subjects in the O+FC arm and 7% of subjects in the FC arm. The incidence of serious mucocutaneous reactions was low, and similar between treatment arms (Table 60). Only 1 subject in the O+FC arm discontinued study treatment due to mucocutaneous reactions. No cases of toxic epidermal necrolysis, Stevens-Johnson Syndrome or fatal events were reported in the study.

Table 60 Serious Mucocutaneous Reactions

Preferred Term	O+FC (N=181)	FC (N=178)
Serious Mucocutaneous Reactions	**6 (3)**	**3 (2)**
Cellulitis	1 (<1)	2 (1)
Erysipelas	1 (<1)	0
Skin ulcer	1 (<1)	1 (<1)
Pruritus	1 (<1)	0
Mouth ulceration	1 (<1)	0
Stomatitis	1 (<1)	0
Epidermolysis	1 (<1)	0
Infected skin ulcer	0	1 (<1)

Data Source: Table 3.1450
Abbreviations: FC=fludarabine and cyclophosphamide; O+FC=ofatumumab plus fludarabine and cyclophosphamide.

- **Tumour Lysis Syndrome**

Tumour lysis syndrome AEs were reported in 1 subject in the O+FC arm and 1 subject in the FC arm.

- **Cardiovascular Events**

Cardiovascular AEs were reported in 36 subjects (10%) during the study. These AEs and SAEs were 8% and 4% respectively in the O+FC arm compared with 12% and 8% in the FC arm. In 2% (4 subjects) in the O+FC arm and 3% (6 subjects) in the FC arm, the SAEs were fatal. Three cardiovascular SAEs were considered related to study treatment, they were all in the FC arm.

- **Neoplasms**

The incidence of second malignancies/neoplasms during the study was low and higher in the O+FC arm compared with the FC arm (O+FC: 15 subjects [8%], FC: 5 subjects [3%]). All events were reported as SAEs. In both treatment arms, the most frequently reported event was myelodysplastic syndrome (O+FC: 3 subjects [2%], FC: 2 subjects [1%]). All remaining events such as acute myeloid leukaemia, colon adenocarcinoma, diffuse large B-cell lymphoma etc., were reported in 1 subject each,

- **Liver Events and Bowel Obstruction**

Per protocol, liver stopping criteria were defined for subjects in either treatment arm while on-treatment as meeting 1 or more of the following conditions:

- Alanine aminotransferase (ALT) >3 times upper limit of normal (ULN) and bilirubin >2 times ULN (>35% direct bilirubin; bilirubin fractionation required [when available]),
- ALT >8 times ULN, and/or
- ALT >5 times ULN for more than 2 weeks.

In total, 8 subjects (O+FC: 5 subjects, FC: 3 subjects) met liver stopping criteria during the study. Half of these subjects had an event while still receiving study treatment.

One subject in each treatment arm reported a non-serious liver event as an AE. In the O+FC arm, the bilirubin increased together with hepatitis B reactivation, and in the FC arm, ALT increased.

Two subjects in the O+FC arm experienced bowel obstructions during the study, the treatment was discontinued.

Laboratory findings

Haematologic Assessment of Myelosuppression

Decreases in neutrophils, haemoglobin, or platelets from Baseline values occurred in similar proportions of subjects in both treatment arms.

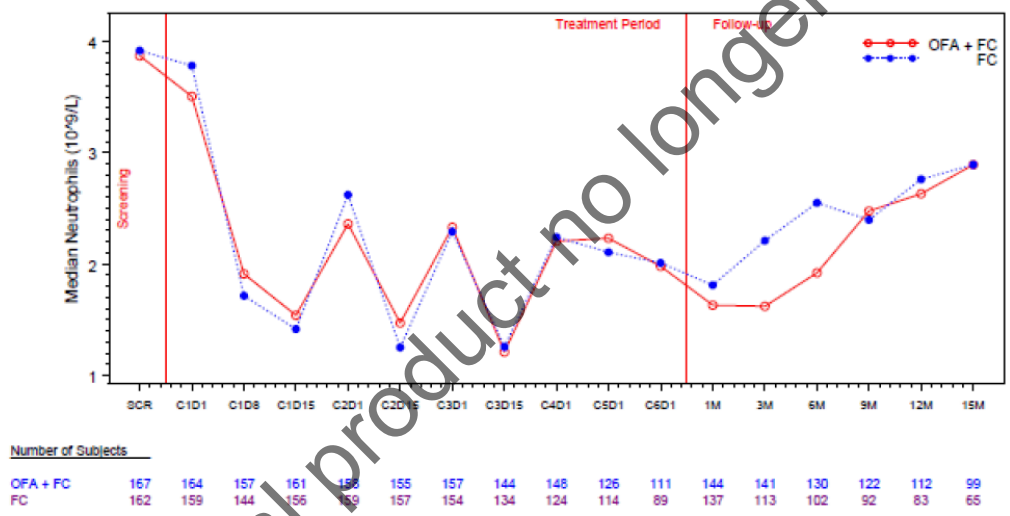
Haemoglobin and platelet worst-case shifts from Baseline to any grade were similar between treatment arms, with no shifts to Grade 3 or Grade 4. The proportion of subjects with neutrophil worst-case shifts from Baseline to any grade was similar (O+FC: 90%, FC: 91%) in both treatment arms; neutrophil shifts to Grade 3 or Grade 4 were also similar between arms. A higher proportion of subjects in the O+FC arm (94%) had decreased leukocytes compared with the FC arm (76%), including events that were Grade 3 or Grade 4 in severity (O+FC: 70%, FC: 43%).

Overall, 50% of subjects received blood supportive care products after the start of study treatment, including a higher proportion of subjects in the O+FC arm (59%) compared with the FC arm (40%). Of the subjects who received blood supportive care products, 48% (O+FC: 56%, FC: 40%) received granulocyte colony-stimulating factor and 6% (O+FC: 7%, FC: 5%) received erythropoietin. The median time to first dose of growth factors was 32.5 days (range: 2 to 173 days) in the O+FC arm and 30.0 days (range: 3 to 164 days) in the FC arm.

Neutrophils

Median neutrophil counts at Baseline were similar between treatment arms (Figure 12). Neutrophil counts decreased during Cycle 1 and remained within a similar range in both treatment arms throughout the study.

Figure 12 Median Neutrophil Counts Over Time



Prolonged Neutropenia

Prolonged and severe neutropenia has been reported with anti-CD20 monoclonal antibody treatment and was therefore analyzed in the study using the definition of 'Grade 3 or Grade 4 neutropenia that occurred while the subject was on study treatment and did not resolve within 42 days after the last dose of study treatment. Prolonged neutropenia occurred in 38 subjects (11%) (O+FC: 18 subjects [10%], FC: 20 subjects [11%]). The median time to first prolonged neutropenia was 70.5 days (range: 7 to 148 days) in the O+FC arm compared with 71.0 days (range: 8 to 162 days) in the FC arm.

Time to recovery from prolonged neutropenia was defined as the time from the first time point when the absolute neutrophil count was <1000 cells/mm3 to the time point when it returned to ≥1500 cells/mm3. Thirteen of the 18 subjects with prolonged neutropenia in the O+FC arm recovered, with a median time to recovery of 253.0 days (range: 70 to 568 days). In the FC arm, 11 of 20 subjects recovered with a median time to recovery of 162.0 days (range: 91 to 323 days).

Late Onset Neutropenia

Although anti-CD20 monoclonal antibodies usually are well tolerated and have an acceptable

haematological toxicity, certain delayed adverse effects have been noted. One of these is late onset neutropenia, defined as "Grade 3 or 4 neutropenia starting at least 42 days after the last treatment dose". In this study, 13 subjects (7%) in the O+FC arm and 5 subjects (3%) in the FC arm had events that met these criteria. The median time since last dose of study drug to the event of late onset neutropenia for O+FC subjects was 113.0 days (range: 75 to 771 days) and 91.0 days (range: 47 to 833 days) for FC subjects.

Haemoglobin

Median haemoglobin counts were similar between the treatment arms at Baseline, but increased in the O+FC arm to levels greater than the FC arm from Cycle 2 to the end of treatment. Haemoglobin counts were similar between treatment arms during follow-up.

Platelets

Median platelet counts were slightly higher in the O+FC arm compared with the FC arm at Baseline, and counts remained higher in subjects receiving O+FC compared with FC throughout treatment and during follow-up (Figure 14).

Figure 14 Median Platelet Counts Over Time

Biochemistry Assessments

The effects of O+FC treatment on clinical chemistry parameters were analyzed, and the majority of subjects did not experience abnormal chemistry values during the study.

Most clinical chemistry parameters had worst-case shifts from Baseline to any grade that were similar between treatment arms. Most of the shifts were to Grade 1 or Grade 2, with few shifts occurring to Grade 3 or Grade 4 values. A higher proportion of subjects in the O+FC arm (38%) had ALT shifts to any grade compared with the FC arm (31%). Few subjects in either treatment arm had shifts to Grade 3 or Grade 4 in any parameter. Bilirubin shifts from Baseline to any grade were similar between treatment arms and included few increases to Grade 3 or Grade 4.

In both treatment arms, the majority of post-baseline shifts in serum chemistry parameters were to a maximum severity of Grade 1 (mild). Shifts to Grade 3 involved high glucose values, liver chemistry parameters (ALT, AST, bilirubin), or electrolytes (sodium, potassium) in subjects in both treatment arms.

In the O+FC arm, post-baseline shifts to Grade 4 (severe) occurred for a small number of subjects for parameters of ALT, AST, glucose, calcium, and creatinine kinase. In the FC arm, post-baseline shifts to Grade 4 occurred only for calcium and potassium, each reported for 1 subject.

Immunoglobulins/immunogenicity

IgG levels were similar in both treatment arms at Baseline, 1-month follow-up, and 6-month follow-up. The current clinical data from studies OMB913 and OMB991 are consistent with immunogenicity data reported in previous submissions.

Safety in special populations

No studies have been conducted in special subject populations in support of this application.

2.5.1. Discussion on clinical safety

The safety profile of ofatumumab as single-agent and in combination has been well characterised in previous trials and in the original marketing application.

Clinical safety data is available from a total of 234 subjects from the supportive and the main study who received ofatumumab (O) in combination with chemotherapy. All subjects received at least one dose ofatumumab. The majority of patients (n=181) were enrolled in the main study and had the combination ofatumumab+fludarabine +cyclophosphamide (O+FC). The number of patients in the supportive study that received ofatumumab+bendamustine (O+B), were limited (n=53), however the number of pooled patients were sufficient to evaluate the safety aspects of ofatumumab in combination with F+C or B. The supportive study was an open- label, single arm Phase II study with limited number of relapsed CLL patients and the efficacy and safety of the combination ofatumumab with bendamustine is not considered sufficiently documented. In their Day 60 response, the MAH decided to withdraw the application regarding the combination of ofatumumab with bendamustine. The unresolved issues associated with study OMB991 is therefore no longer valid.

The combined analysis of safety data from Study OMB913 and Study OMB991 demonstrated an acceptable and manageable safety profile and most subjects were able to receive the planned dose/cycles. No new safety signals were reported, and the safety data were consistent with the known safety profile previously established in the approved indications. The adverse events for ofatumumab + FC arm were combined with the ofatumumab +bendamustine arm, O+Chemo, since the AEs in the two groups were similar.

The combination regimens with chemotherapy (FC or bendamustine) did not reveal any new or unexpected AEs or SAEs, and included subjects with demographic and prognostic factors typical of subjects with relapsed CLL, including subjects with advanced age and multiple comorbid conditions.

The most common AEs in the O+Chemo group were related to infusion reactions (i.e. nausea, rash, pyrexia, pruritus), and cytopenias (neutropenia, thrombocytopenia and anaemia). Monoclonal antibodies has been associated with a risk of infusion-related reactions, however in this study, they were mostly mild to moderate in severity with 8% subjects exhibiting reactions of grade 3 or higher. No fatal infusion related reactions were reported with the addition of ofatumumab.

In the pivotal study (OMB110913) in relapsed CLL patients, prolonged neutropenia was reported in 38 (11%) patients (18 patients [10%] treated with ofatumumab in combination with fludarabine and cyclophosphamide compared to 20 patients [11%] in the fludarabine and cyclophosphamide arm). Thirteen (7%) patients treated with ofatumumab in combination with fludarabine and cyclophosphamide, and 5 (3%) patients treated with fludarabine and cyclophosphamide had late onset neutropenia. This information is reflected in section 4.8 of the SmPC.

The incidence of neutropenia (all grades and grade ≥ 3) was higher in the O+Chemo arm than the FC arm, but this was not associated with an increased risk of infections. In the O+Chemo group, SAE were reported for 56% of the subjects, and 23% had an AE leading to discontinuation. Fatal SAEs were reported in 18% of subjects, and for 6% of subjects, the fatal SAE was considered related to study treatment. The incidence of grade ≥ 3 AE, treatment-related SAEs, and fatal SAEs (including treatment-related fatal SAEs) were similar between the O+Chemo and FC groups.

The incidence of anaemia and thrombocytopenia were slightly less frequent in the O+Chemo arm than in the FC arm, indicating that ofatumumab did not worsen the myelosuppression.

Comparison of the O+Chemo with the FC arm, showed that a higher proportion of subjects in the O+Chemo arm had AEs that required infusion interruption/delay.

The most frequent reason for treatment discontinuation in the O+Chemo group was AE (24%) especially due to neutropenia and thrombocytopenia.

AEs of special interest were identified and analyzed based on data from previous ofatumumab studies and events observed with other anti-CD20 mAbs. Increased neutropenia is well described for anti-CD20 monoclonal antibodies. Incidences of grade ≥3 neutropenia and grade ≥3 infection in the O+Chemo group were comparable with those reported in the FCR (Fludarabine, cyclophosphamide, and rituximab) group.

The overall incidence of death was slightly lower in O+Chemo group compared to FC group (37% vs. 39%) and half of the deaths in both the groups were due to the disease under study. Of the 86 subjects (37%) in the O+Chemo group who died, the majority (77 subjects, 33%) died more than 60 days after last dosing, and only 4 subjects (2%) died while on treatment (i.e. within 30 days of last dose).

Only one subject (in the O+FC arm) had a positive HAHA, at a single time point following treatment with ofatumumab. The presence of HAHA had no effect on safety, pharmacokinetics, or pharmacodynamics of ofatumumab.

2.5.2. Conclusions on clinical safety

In conclusion, ofatumumab in combination with chemotherapy with FC was generally well tolerated with no unexpected AEs or SAEs in subjects with relapsed CLL suggesting a safety profile consistent with previous knowledge of ofatumumab. Adverse events were all manageable.

Section 4.8 of the SmPC has been updated accordingly. The final CSR of study 913 will be provided (see RMP).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP and PRAC considered that the risk management plan version 13.1 is acceptable.

Safety concerns

Table 61 Summary of the safety concerns

Important identified risks	Infusion reactions including Cytokine Release Syndrome Tumour Lysis Syndrome (TLS) Bowel Obstruction Cardiovascular events Hepatitis B Virus (HBV) Infection and Reactivation Neutropenia
Important potential risks	Cytopenias (excluding neutropenia) Risk of Infections Progressive Multifocal Leukoencephalopathy (PML) Severe mucocutaneous reactions Effects on Immunizations, Including Interactions with Live Vaccines Immunogenicity Effect of Concomitant HMG-CoA Reductase Inhibitors on Ofatumumab Response Change in safety profile associated with 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 experience in patients with ECOG 2 Limited long term safety

Pharmacovigilance plan

Table 62. On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date of submission of final study report
OMB112517: A Phase III, open label, randomized, multicenter trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy (3)	Evaluation of safety data from ongoing studies to further characterize known identified and potential risks.	Long te.rm safety data	Ongoing	Second interim analysis CSR: 18-June-2015 Final End of study report: 26-May-2020
OMB110913: A Phase III, open Label, randomized trial of ofatumumab added to fludarabine-cyclophosphamide vs. fludarabine-cyclophosphamide combination in subjects with relapsed CLL (3)	Evaluation of safety data from ongoing studies to further characterize known identified and potential risks	Long term safety data	Ongoing	Primary analysis CSR: 20-Nov-2015 Final CSR (all patients off data): Q4-2017
OMB115991: A Phase II, multi-center study investigating the safety and efficacy of ofatumumab and bendamustine combination in patients with untreated or relapsed CLL (3)	Evaluation of safety data from ongoing studies to further characterize known identified and potential risks	Long term safety data	Ongoing	Primary analysis CSR: 06-Aug-2013 Updated CSR: 21-Dec-2015 (22-month CSR) Final CSR: Q3-2016

Risk minimisation measures

Table 63 Summary table of Risk Minimization Measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Infusion reactions including Cytokine Release Syndrome	Sections 4.4 and 4.8 of the SmPC	The MAH distributed a DHCPL and DIL regarding the potential for infusion reactions to be fatal.
Tumour Lysis Syndrome (TLS)	Sections 4.4 and 4.8 of the SmPC	No additional risk minimization measures.
Bowel obstruction	Sections 4.4 and 4.8 of the SmPC	No additional risk minimization measures.
Cardiovascular events	Sections 4.4 and 4.8 of the SmPC	No additional risk minimization measures.
Hepatitis B Virus infection and reactivation	Sections 4.4 and 4.8 of the SmPC	No additional risk minimization measures.
Neutropenia	Sections 4.4 and 4.8 of the SmPC	No additional risk minimization measures.
Cytopenias (excluding neutropenia)	Sections 4.4 and 4.8 of the SmPC	No additional risk minimization measures.
Risk of infections	Sections 4.4 and 4.8 of the SmPC	No additional risk minimization measures.
Progressive Multifocal Leukoencephalopathy (PML)	Section 4.4 of the SmPC	No additional risk minimization measures.
Severe mucocutaneous reactions	Currently available data do not support the need for risk minimization	No additional risk minimization measures.
Effect on immunizations, Including Interactions with Live Vaccines	Section 4.4 of the SmPC	No additional risk minimization measures.
Immunogenicity	Section 5.1 of the SmPC	No additional risk minimization measures.
Effect of concomitant HMG-Co-A Reductase Inhibitors on Ofatumumab Response	Currently available data do not support the need for risk minimization.	No additional risk minimization measures.
Changes in Safety Profile Following Switch to Acetate Buffer Formulation	Currently available data do not support the need for risk minimization.	No additional risk minimization measures.
Limited data in pregnant and	Section 4.6 of the SmPC	No additional risk minimization

lactating females		measures.
Limited experience in patients with other relevant co-morbidities including cardiac disease, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric diseases	Currently available data do not support the need for risk minimization.	No additional risk minimization measures.
Limited experience in the heterogeneous non-white patient population	Currently available data do not support the need for risk minimization.	No additional risk minimization measures.
Limited experience in patients with ECOG 2	Currently available data do not support the need for risk minimization.	No additional risk minimization measures.
Limited long term safety	Currently available data do not support the need for risk minimization.	No additional risk minimization measures.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 of the SmPC have been updated.

The Package Leaflet has been updated accordingly.

2.7.1. User consultation

N/A

3. Benefit-Risk Balance

Benefits

Beneficial effects

The study OMB913 demonstrated that addition of ofatumumab to FC resulted in an improvement of 10.1 months in IRC-assessed PFS, with a median PFS of 28.9 months in the O+FC arm compared with 18.8 months in the FC arm (HR of 0.67, 95% CI (0.51, 0.88) stratified log-rank p = 0.0032). Investigator assessed analyses were consistent, and sensitivity analysis of PFS confirmed the primary analysis, thus the study met its primary endpoint.

Analyses of secondary endpoints were supportive, indicating a benefit of adding ofatumumab to FC. An improvement of IRC-assessed ORR in the O+FC arm was reported, 84%, compared with 68%in the FC, primarily due to a higher proportion of subjects achieving CR (27% vs. 7% respectively for the O+FC arm vs. the FC arm).

The median IRC-assessed time to progression (TTP) was improved with 15 months in the O+FC arm, (42.12 months compared with 26.78 months in the FC arm, (p=0.0036). Analysis of event free survival (EFS) also

showed an improvement 10 months in the O+FC arm (27.2 months vs.16.5 months for the FC arm, p=0.0012).

Although numbers were small, the IRC-assessed MRD negativity at 3 – and 6 – months post-treatment were 21% and 26% respectively in the O+FC arm compared with 8% and 6% in the FC arm, indicating a clinically meaningful response.

B cell depletion versus tumour response: 39% (O+FC) vs. 4% (FC) for responders demonstrated complete B cell depletion. Median number of CLL cells/µL was 1 vs. 64 (at 1-month follow-up).

Consistent benefit in PFS with O+FC was demonstrated across subgroup analysis, although some were performed with small populations, for patients who had previously received 1-2 prior anti-CLL therapies, high risk RAI stage, un-mutated IGVH and ZAP70 pos. subjects. Whether subjects had received prior rituximab containing therapy or not, they had an equal effect from addition of ofatumumab to FC.

Uncertainty in the knowledge about the beneficial effects

In study OMB913 a numerical trend for benefit in terms of OS was reported with an 11 months prolongation in median OS, median OS was 56.4 months and 45.8 months respectively for the O+FC arm and the FC arm, however the difference did not reach statistical significance.

The MAH will provide the final CSR from study 913 which will include mature data on OS (see RMP).

Risks

Unfavourable effects

Data from the pivotal study OMB913 was presented together with data from the supportive study OMB991. O+Chemo results comprised both O+FC and O+B data. 94% in the O+Chemo group had at least one AE, compared with 86% in the FC group. The most common AEs were related to infusion-reactions, most were mild to moderate, and no fatal infusion related reactions were reported with the addition of ofatumumab. The incidence of grade ≥3AEs was slightly higher in the subgroups of patients ≥ 65 years and lower in the FC arm, compared with the O+FC arm. The most frequent ≥ Grade 3AEs in the O+FC arm was neutropenia, 51% compared with 37% in the FC arm. However, this did not affect the incidence of infections, which was similar in the O+FC and the FC arms, (46% vs 49%). No difference in incidence of serious infections or fatal serious infections was reported between the two treatment arms.

The incidence of AEs leading to infusion interruption/delay was higher in the O+FC arm (55% vs. 22%) or ≥ Grade 3 (80% vs. 72%) compared to the FC arm, however this did not lead to a higher permanent discontinuation of treatment. The most frequent reason for treatment discontinuation in the O+Chemo group was AE (24%), especially due to neutropenia and thrombocytopenia. Interestingly the proportion of subjects who withdrew from the study was higher in the FC group (29%) than the O+Chemo group (13%), primarily due to higher proportion of subjects voluntarily withdrawing from the study in the FC group (21%) compared to O+Chemo group (8%).

No difference was observed in the incidence of treatment-related SAEs between the treatment groups, 31% in the O+Chemo group vs. 29% in the FC group. The incidence of fatal AEs, overall as well as treatment-related, and the incidence of deaths was similar in the two groups. However the incidence of death was higher in patients ≥65, ≥75 vs. age < 65 years. For 6% (n=13) in the O + Chemo group, the fatal events were considered treatment-related.

The safety profile of ofatumumab in both combinations is consistent with the well-known profile of ofatumumab from previous approved indications, as well as the safety profiles of FC and bendamustine.

Uncertainty in the knowledge about the unfavourable effects

No new or unexpected safety events were reported in these studies.

Effects Table

Table 64 Effects Table for study OMB913 (Cut off 21 December 2015)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Progression free survival	months	28.9	18.8	HR 0.67, (95% CI 0.51, 0.88) P=0,0032	See clinical efficacy AR and discussion
TTP	Time to progression	months	42.2	26.8	P=0.0036	
EFS	Event free survival	months	27.2	16.5	P=0.0012	
OS	Overall survival	months	NE	45.3	HR 0.79, CI; 0.58 – 1.10 Not yet mature	
Unfavourable Effects						
Grade ⩾3 AE	treatment-related Grade ⩾3	%	69	58		See clinical safety AR and discussion
Neutropenia		%	51	37		
Incidence of infections		%	46	49		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The addition of ofatumumab to fludarabine and cyclophosphamide demonstrated in the pivotal study OMB913 a statistically significant improvement of PFS and ORR when compared to fludarabine and cyclophosphamide. Although no significant improvement was reported on OS, these data are robust and clinically meaningful.

The efficacy of the combination of ofatumumab and bendamustine in the supportive study is less clear. Although a benefit on ORR was reported, only few subjects achieved CR, data were not supported by other endpoints, further the study revealed some weaknesses, with no control arm, no IRC confirmation of data and the inclusion of few subjects. However, the MAH decided to withdraw the application regarding the combination of ofatumumab with bendamustine and the unresolved issues associated with study OMB991 is therefore no longer valid.

No new safety signals for ofatumumab were reported in these studies, AEs were as expected in this clinical setting with relapsed CLL treated with a combination of a monoclonal antibody and chemotherapy.

Benefit-risk balance

Based on the above discussion, the B/R balance in the indication:

Arzerra is indicated in combination with fludarabine and cyclophosphamide for the treatment of adult patients with relapsed CLL.

is considered positive

Discussion on the Benefit-Risk Balance

Since CLL is a chronic, incurable disease with a history of recurrent relapses, and patients being refractory to previous treatment, there is a need for treatment options to these patients. The combination of ofatumumab and FC demonstrated a robust, clinically meaningful benefit in terms of PFS, which was

supported by other secondary endpoints. AEs were as expected and manageable. The O+FC combination thus represents an alternative to relapse treatment in CLL.

4. Recommendations

Outcome

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

Variations accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the combination of Arzerra with fludarabine and cyclophosphamide for the treatment of adult patients with relapsed Chronic Lymphocytic Leukaemia (CLL); as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 and 9 of the SmPC are updated based on the analysis of the pivotal studies OMB110913 (COMPLEMENT 2). The Package Leaflet and Risk Management Plan (v.13.1) are updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

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.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, 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.