EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/CHMP/77370/2016
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/0041

Marketing authorisation holder (MAH): Novartis Europharm Ltd



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# List of abbreviations

AE – adverse events

CLL – chronic lymphocytic leukemia

CR – complete remission

HAHA - Human anti-human antibodies

HR – hazard ratio

IA – interim analysis

IDMC - independent data monitoring committee

IgHV - Immunoglobulin Heavy Chain Variable Region Genes

ITT – intent-to-treat

MO – major objection

NCI – National Cancer Institute

Obs – observation

Ofa/OFA – ofatumumab

OS – overall survival

PD – pharmacodynamics

PFS – progression-free survival

PFS2 - time to second objective disease progression

PK – pharmacokinetics

PP – per-protocol

PR – partial remission

PRO – patient reported outcomes

SAE – serious adverse events

SOC – system organ class

TTNT – time to next treatment

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 7 July 2015 an application for a variation.

The following variation was requested:

| Variation 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, II and IIIB |

Extension of Indication to include maintenance therapy in Chronic Lymphocytic Leukemia (CLL) for Arzerra; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated based on the interim analysis of the pivotal study OMB112517 (PROLONG). The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 9.1. The MAH is also taking the opportunity of this procedure to combine the SmPCs for 100mg and 1,000mg vials.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and 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.

***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 received Protocol Assistance from the CHMP in October 2009. The Protocol Assistance pertained to clinical aspects of the dossier.

## *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: Sinan B. Sarac Co-Rapporteur: Bjorg Bolstad

| | |
|---|---|
| Rapporteur's preliminary assessment report circulated on: | 29 September 2015 |
| Co-Rapporteur's preliminary assessment report circulated on: | 18 September 2015 |
| Joint Rapporteur's updated assessment report circulated on: | 16 October 2015 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 22 October 2015 |
| MAH's responses submitted to the CHMP on: | 17 December 2015 |
| The CHMP adopted a report on similarity of Arzerra with Imbruvica and Gazyvaro (Appendix 1) | 17 December 2015 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 3 February 2016 |
| Joint Rapporteur's updated assessment report on the MAH's responses circulated on: | 19 February 2016 |
| 2nd Request for supplementary information and extension of timetable adopted by the CHMP on: | 25 February 2016 |
| MAH's responses submitted to the CHMP on: | 28 March 2016 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 13 April 2016 |
| SAG experts meeting to address questions raised by the CHMP (Annex 6) | 14 April 2016 |
| Joint Rapporteur's updated assessment report on the MAH's responses circulated on: | 21 April 2016 |
| 3nd Request for supplementary information and extension of timetable adopted by the CHMP on: | 28 April 2016 |
| MAH's responses submitted to the CHMP on: | 03 May 2016 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 11 May 2016 |
| Joint Rapporteur's updated assessment report on the MAH's responses circulated on: | 19 May 2016 |
| An Oral explanation took place on: | 24 May 2016 |
| 4th Request for supplementary information and extension of timetable adopted by the CHMP on: | 26 May 2016 |
| MAH's responses submitted to the CHMP on: | 01 June 2016 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 16 June 2016 |
| CHMP opinion: | 23 June 2016 |

# 2. Scientific discussion

## *2.1. Introduction*

Chronic lymphocytic leukaemia (also referred to as B-CLL) is the most common type of leukaemia in the western world. The incidence increases with age, is higher in men than in women and higher in Caucasians than in other racial groups. The median age at presentation is 71 years and 11% of patients are diagnosed under the age of 55 years (Howlader, 2014).

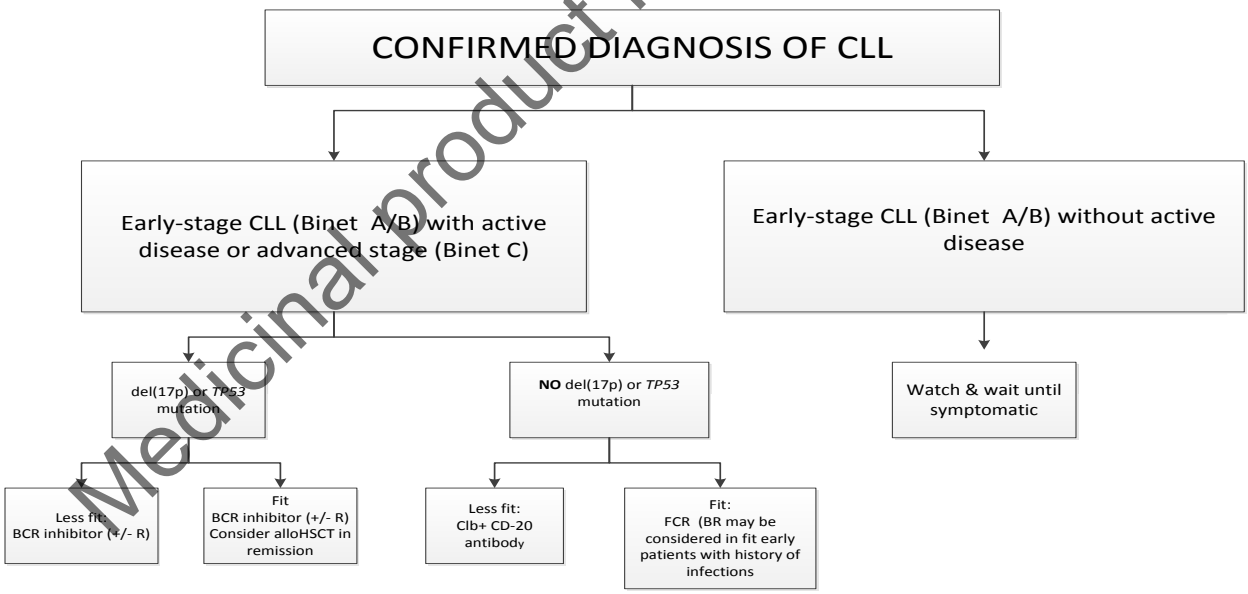
CLL is a haematological neoplasm of unknown aetiology in which peripheral, clonal B-cells progressively accumulate. The disease is characterized by monomorphic, small, round B-lymphocytes in the peripheral blood, bone marrow, and lymph nodes that aberrantly co-express T-cell ($CD5^+$) and B-cell ($CD19^+$, $CD23^+$) cell surface markers, with a low expression of CD20.

CLL follows a variable clinical course with overall survival (OS) times ranging from months to decades. Median survival from diagnosis is approximately 10 years in the overall CLL population, but is only 18 months for patients with advanced disease (Nabhan, 2004) and 9 to 13 months for cases refractory to fludarabine (Byrd, 2004).

Allogeneic stem cell transplantation (SCT) is still the only potentially curative treatment for CLL; however it is feasible in only a small minority of CLL patients.

Current treatment guidelines from the European Society of Medical Oncology (ESMO) indicate the choice of treatment for previously untreated patients with CLL is based on stage of disease, whether a patient is considered "fit" and presence or absence of del17p or *TP53* mutation (Figure 1).

**Figure 1. European Society for Medical Oncology Clinical Practice Guidelines for First-line Treatment of CLL**




Source: Eichorst 2015

A representative summary of first-line treatments approved for patients with CLL in the European Union (EU) is shown in Table 1.

**Table 1. Summary of Approved Treatments for First-line Treatment of CLL in the European Union**

| Treatment /Approval Year | Indication | Monotherapy or combination | Approval based on /comparator | No. of Subjects | Efficacy Endpoints |
|---|---|---|---|---|---|
| Ibrutinib 2014 | CLL with 17p deletion or *TP53* mutation in patients unsuitable for CIT | Monotherapy | Phase 3/ ofatumumab | 391 | PFS, OS, ORR |
| Idelalisib + rituximab 2014 | In combination with rituximab for CLL with 17p deletion or *TP53* mutation in patients unsuitable for CIT | Combination | Phase 3/rituximab | 220 | PFS, OS |
| Ofatumumab with chlorambucil or bendamustine 2014 | In combination with chlorambucil for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy | Combination | Phase 3/ chlorambucil | 444 | PFS, ORR, DOR |
| Obinutuzumab with chlorambucil 2014 | In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy. | Combination | Phase 3/ chlorambucil | 356 | PFS, DOR, OS |
| Rituximab[a] 2010 | CLL (in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia) | Combination | Phase 3/FC | 817 | PFS |
| Bendamustine[a, b] 2008 | CLL in patients for whom fludarabine combination chemotherapy is not appropriate). | Monotherapy | Phase/ chlorambucil | 301 | ORR, PFS |
| Cyclophosphamide[a] 1959 | CLL (unspecified) | Monotherapy | Unknown | Unknown | Unknown |
| Chlorambucil[a] 1957 | CLL (unspecified) | Monotherapy | Unknown | Unknown | Unknown |
| Fludarabine[c] 1994 | CLL (unspecified) | Monotherapy | Phase 3/ chlorambucil | 394 | ORR, DOR, TTP |

CLL: chronic lymphocytic leukemia; DOR: duration of response; EU: European Union; FC: fludarabine + cyclophosphamide; N/A: not available; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTP: time to progression

[a] Efficacy in CLL relative to first-line therapies other than chlorambucil has not been established. [b] Used for first- and second-line treatment of CLL. [c] Information from approved FLUDARA UK SmPC, revision date 14 October 2015

Data from uncontrolled studies using MRD assessment support the concept of maintenance with an anti-CD20 antibody (mainly rituximab) for up to 2 years in responding patients with CLL.

Although maintenance therapy in CLL has not been authorized as such, prolonged therapy (until progression or intolerance) with small molecules such as ibrutinib or idelalisib has been approved in a comparable population.

Ofatumumab is a human monoclonal antibody (IgG1) that binds specifically to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre B to mature B lymphocyte stage and on B cell tumours. The B cell tumours include CLL (generally associated with lower levels of CD20 expression) and non Hodgkin's lymphomas (where >90% tumours have high levels of CD20 expression). The CD20 molecule is not shed from the cell surface and is not internalised following antibody binding.

The binding of ofatumumab to the membrane proximal epitope of the CD20 molecule induces recruitment and activation of the complement pathway at the cell surface, leading to complement dependent cytotoxicity and resultant lysis of tumour cells. Ofatumumab has been shown to induce appreciable lysis of cells with high expression levels of complement defence molecules. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells and in rituximab resistant cells. In addition, the binding of ofatumumab allows the recruitment of natural killer cells allowing the induction of cell death through antibody dependent cell mediated cytotoxicity (SmPC section 5.1).

The current indication for Arzerra is as follows:

Previously untreated chronic lymphocytic leukaemia (CLL):

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

Refractory CLL:

Arzerra is indicated for the treatment of CLL in adult patients who are refractory to fludarabine and alemtuzumab.

The marketing authorisation holder (MAH) applied for the following indication:

Maintenance therapy in CLL

Arzerra is indicated as maintenance treatment for adult patients with CLL who are in complete or partial response after at least two lines of induction therapy.



## *2.2. Non-clinical aspects*

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

## *2.3. Ecotoxicity/environmental risk assessment*

An updated environmental risk assessment, consisting of a justification for not submitting ERA studies, has been provided. This is in accordance with the "Guideline on environmental risk assessment of medicinal products for human use" (EMEA/EHMP/SWP/4447/00 corr 2[1]*), as proteins are unlikely to result in a significant risk to the environment.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

**GCP**

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

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

- **Tabular overview of clinical studies**

An overview of the clinical development program of ofatumumab in CLL is provided in Table 2 below.

**Table 2. Ofatumumab Clinical Development Program in CLL**

| OFA Administration | Previously Untreated CLL | Relapsed CLL | Refractory CLL |
|---|---|---|---|
| Monotherapy | No studies | OMB112517: Phase III, 1000 mg | OMB111773[a]: Phase II, 2000 mg<br>OMB111827[a]: Phase II, 2000 mg<br>OMB114242: Phase III, 2000 mg<br>OMB112855[a]: QTc, 2000 mg |
| | | Hx-CD20-402[a]: Phase I/II, 500 mg, 1000 mg, 2000 mg<br>OMB111148[a] (Japan): Phase I, 500 mg or 1000 mg<br>OMB112758[a] (Japan and Korea): Phase I/II, 2000 mg | |
| Combination Therapy | OMB110911: Phase III O+CHL vs. CHL, 1000 mg<br>OMB111774[a]: Phase II OFC, 500 mg & 1000 mg<br>OMB115601 (Japan): Phase I/II O+CHL, 1000 mg | OMB110913: Phase IIIA OFC vs. FC, 1000 mg | No studies |
| | OMB115991: Phase II O+B, 1000 mg | | |

Abbreviations: B=bendamustine; CHL=chlorambucil; FC=fludarabine/cyclophosphamide; O=ofatumumab; OFC=ofatumumab plus fludarabine/cyclophosphamide; QTc=corrected QT interval.
Note: Information provided for each study includes study phase and OFA dose, not including any initial dose

## 2.4.2. Pharmacokinetics

The MAH did not submit new phase II dose finding PK/PD studies for the current application. The PK data supporting the dose selection is based on clinical experience with the 1000 mg dose in prior and ongoing clinical trials as well as in PK modelling and simulation. The initial dose of 300 mg was used to minimize infusion reactions. A 1000 mg dose was administered 1 week later to increase ofatumumab concentrations further during the first 8-week cycle. Modelling and simulation of the proposed dosing regimen based on early PK data in subjects with CLL indicated that the dosing regimen was expected to achieve prolonged exposure to plasma concentrations above the target level (>10 µg/mL) in a high proportion of patients with CLL who were in response after induction therapy. The target level was based on preclinical studies to identify the OFA concentrations sufficient to suppress peripheral B-cell recovery in cynomolgus monkey as well as suppress tumour cell growth in Daudi tumour-bearing SCID mice (Bleeker, 2008).

In Study OMB112517, subjects with CLL who were in complete response (CR) or partial response (PR) after induction therapy received ofatumumab using the proposed dosing regimen: 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 8-week cycle. The PK parameters estimated in this study are reported in Table 3.

**Table 3: PK parameter estimates from Study OMB112517**

| | Cycle 1 Week 1 | | Cycle 1 Week 2 | | Cycle 4 | |
|---|---|---|---|---|---|---|
| Parameter | n | Geometric Mean (%CVb) | n | Geometric Mean (%CVb) | n | Geometric Mean (%CVb) |
| Cmax (µg/mL) | 219 | 73.8 (65) | 212 | 264 (50) | 157 | 275 (31) |
| Ctrough (µg/mL) | - | - | 218 | 16.3 (254) | 164 | 9.9 (1323) |
| AUC(0-τ)[a] (µg.h/mL) | 190 | 6113 (38) | 173 | 104013 (43) | 124 | 122782 (50) |
| tmax[b] (hr) | 219 | 5.3 (0.5-23.6) | 211 | 4.7 (0.5-9.0) | 156 | 4.7 (0.5-120.1) |
| CLtot (mL/h) | - | - | - | - | 124 | 8.1 (50) |
| Vss[c] (L) | | | | | 224 | 6.0 (27) |
| t½ (days) | - | - | - | - | 124 | 22.6 (48) |

Data Source: Table 5.0010. %CVb = between-subject coefficient of variation

a. AUC(0-τ) = AUC(0-168) for Cycle 1 Week 1, AUC(0-1176) for Cycle 1 Week 2, and AUC(0-1344) for Cycle 4
b. Reported as median (minimum-maximum)
c. Vss calculated as V1+V2 for each subject overall and reported under Cycle 4 in the table

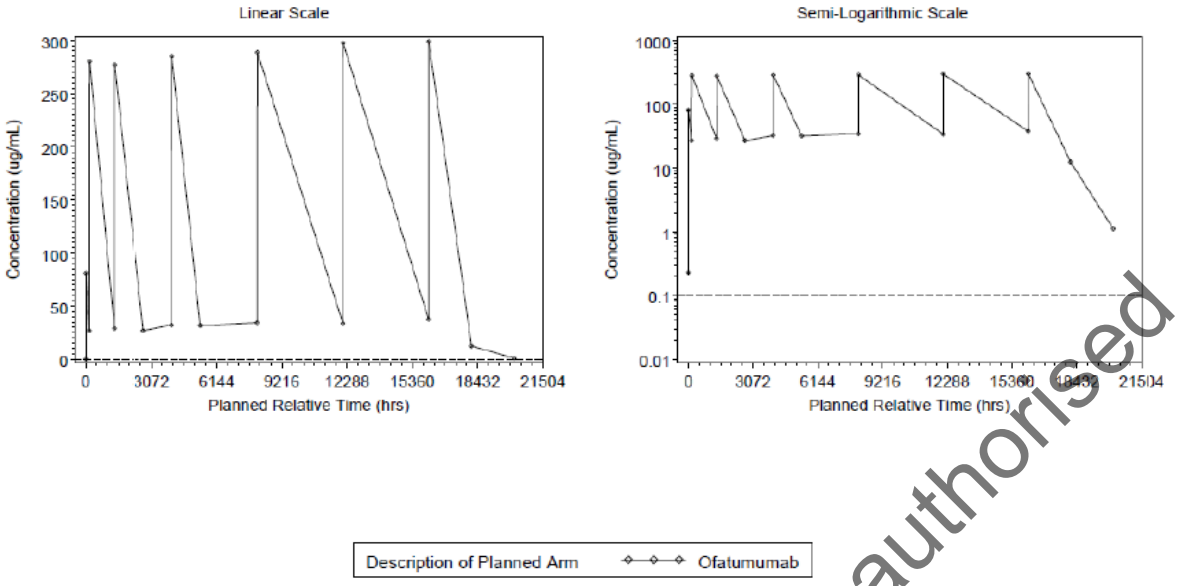
A comparison of PK parameters estimates across groups of patients in partial versus complete response is shown in the table below:

**Table 4: Ofatumumab Pharmacokinetic Parameters by CR and PR Patients (Study OMB112517)**

| Parameter | CR (n) | Geometric Mean (%CV) | PR (n) | Geometric Mean (%CV) |
|---|---|---|---|---|
| **Cycle 1 week 1** | | | | |
| Cmax (ug/mL) | 42 | 85.8 (27) | 177 | 71.17 (72) |
| AUC (ug/mL.hr) | 39 | 7304 (19) | 151 | 5839 (40) |
| Ctrough (ug/mL) | NA | NA | NA | NA |
| **Cycle 1 week 2** | | | | |
| Cmax (ug/mL) | 40 | 297.2 (23) | 172 | 256.4 (55) |
| AUC (ug/mL.hr) | 35 | 121686 (32) | 138 | 99955 (44) |
| Ctrough (ug/mL) | 42 | 29.2 (58) | 176 | 14.2 (303) |
| **Cycle 4** | | | | |
| Cmax (ug/mL) | 36 | 290.9 (24) | 121 | 269.8 (33) |
| AUC (ug/mL.hr) | 31 | 143074(40) | 93 | 116679(52) |
| Ctrough (ug/mL) | 36 | 21.6 (471) | 128 | 8.00 (1600) |

Source: [Appendix to EMA Response-Table 5.0020]
NA – Not applicable

Mean Ofatumumab plasma concentration-time curves are shown in Figure 1.




[Data Source: OMB112517 CSR Figure 15.0010]

**Figure 2. Mean ofatumumab plasma concentration-time curves (Study OMB112517)**

Ofatumumab PK results from a phase I study (OMB112758) in Japanese and South Korean subjects with CLL were consistent with those seen in Western subjects with CLL.

A trend of longer PFS was observed with higher ofatumumab AUC and was also noted with Cmax and Ctrough at certain time points. Univariate analyses found that higher Cmax at Cycle 1 Week 1; AUC at Cycle 1 Week 1, Cycle 1 Week 2, and Cycle 4; and Ctrough at Cycle 1 Week 2 and Cycle 4 were associated with longer PFS. In multivariate analyses, ofatumumab AUC values at Cycle 1 Week 1, Cycle 1 Week 2, and Cycle 4 were significantly associated with PFS after adjustment for disease factors that are known to affect clinical outcome.

Ofatumumab had a small volume of distribution, consistent with distribution largely in the systemic circulation. In Study OMB112517, the geometric mean Vss value was 6.0 L at Cycle 4 (1000 mg), which is consistent with Vss values observed in other studies in CLL.

*Population pharmacokinetics*

A population PK model has been used to characterize the PK of ofatumumab after intravenous infusion in subjects with CLL receiving maintenance ofatumumab every two months after responding to induction therapy. The model was revised based on studies in refractory CLL (Study OMB111773/Hx-CD20-406), rheumatoid arthritis (RA, Study Hx-CD20-403), relapsed/refractory follicular lymphoma (FL, Study Hx-CD20- 001), and relapsed/refractory CLL (Study Hx-CD20-402).

The population PK dataset from Study OMB112517 included 2192 observations from 224 subjects after exclusions. A total of 30 observations out of 2222 results were excluded from the final analysis as anomalous values or due to missing dosing records.

Individual PK parameter values were determined for each subject. Cmax, Ctrough, and tmax values were based on the observed concentration-time data for each dose in each cycle. AUC(0-τ) values were calculated for each subject by integrating the predicted concentrations over the dosing interval until the next dose using NONMEM (planned: AUC(0-168 hr) for Cycle 1 Week 1; AUC(0-1176 hr) for Cycle 1 Week

2; and AUC(0-1344 hr) for Cycle 2 and later). Total clearance (CLtot) for Cycle 4 and later was calculated based on the AUC(0-τ). Steady-state volume of distribution (Vss) was determined by individual post hoc parameters. Half-life (t½) values were determined based on the individual post hoc parameters and CLtot values using standard equations.

*Results and evaluation*

The parameter estimates for the previously developed OFA PPK model is given in Table 5. Individual post hoc parameter estimates are provided in Table 6.

**Table 5. Parameter estimates for the population ofatumumab PK model (Study OMB112517)**

| Parameter | Estimate | %RSE | 95% CI |
|---|---|---|---|
| **Fixed effects** | | | |
| CL [mL/hr] | 7.45 | 3.56 | 6.93 –7.97 |
| $V_1$ [L] | 3.26 | 2.01 | 3.13 – 3.39 |
| Q [mL/hr] | 22.2 | 11.5 | 17.2 – 27.2 |
| $V_2$ [L] | 2.07 | 3.34 | 1.93 – 2.21 |
| DONB [1/(μg/mL•hr)] | 0.186 | 10.3 | 0.149 – 0.223 |
| TVBOND [mL/hr] | 0.335 | 7.1 | 0.288 – 0.382 |
| BONDadj_CLL | 0.0473 | N/A | N/A |
| BOUT [1/hr] | 0.000963 | N/A | N/A |
| BSA effect on CL | 1 | | |
| BSA effect on $V_1$ | 0.814 | 16 | 0.559 – 1.07 |
| BSA effect on $V_2$ | 0.813 | 29.6 | 0.341 – 1.29 |
| GEN effect on $V_1$ | -0.115 | 24.3 | -0.17 – -0.0603 |
| IGG effect on CL [L/g] | 0.0258 | 20.2 | 0.0156 – 0.036 |
| **Inter-individual variability[1]** | | | |
| $\omega^2_{CL}$ | 0.276 (52.5%) | 10.2 | 0.221 – 0.331 |
| $\omega^2_{V1}$ | 0.076 (27.6%) | 16.1 | 0.0521 – 0.0999 |
| $\omega^2_{V2}$ | 0.229 (47.9%) | 17.5 | 0.151 – 0.307 |
| $\omega^2_{BIN}$ | 0.608 (78.0%) | 12.7 | 0.456 – 0.76 |
| **Residual variability** | | | |
| $\sigma^2_{prop}$ | 0.0199 | 6.88 | 0.0172 – 0.0226 |
| $\sigma^2_{add}$ | 14.8 | 41 | 2.9 – 26.7 |

All parameters except BONDadj were fixed to generate post hoc estimates.
%RSE: percent relative standard error (SE) of the estimate = SE/parameter estimate * 100; CI: confidence interval
1. IIV reported as variance estimate (%CV).

**Table 6: Summary of Individual ofatumumab post hoc parameter estimates (Study OMB112517)**

| Parameter | n | Geometric mean (%CVb) | 95% CI |
|---|---|---|---|
| CL (mL/h) – linear | 224 | 7.36 (47) | 6.94, 7.81 |
| V1 (L) | 224 | 3.7 (22) | 3.6, 3.9 |
| V2 (L) | 224 | 2.1 (46) | 2.0, 2.2 |
| BIN (1/h) | 224 | 0.00342 (80) | 0.00312, 0.00375 |

%CVb = between-subject coefficient of variation

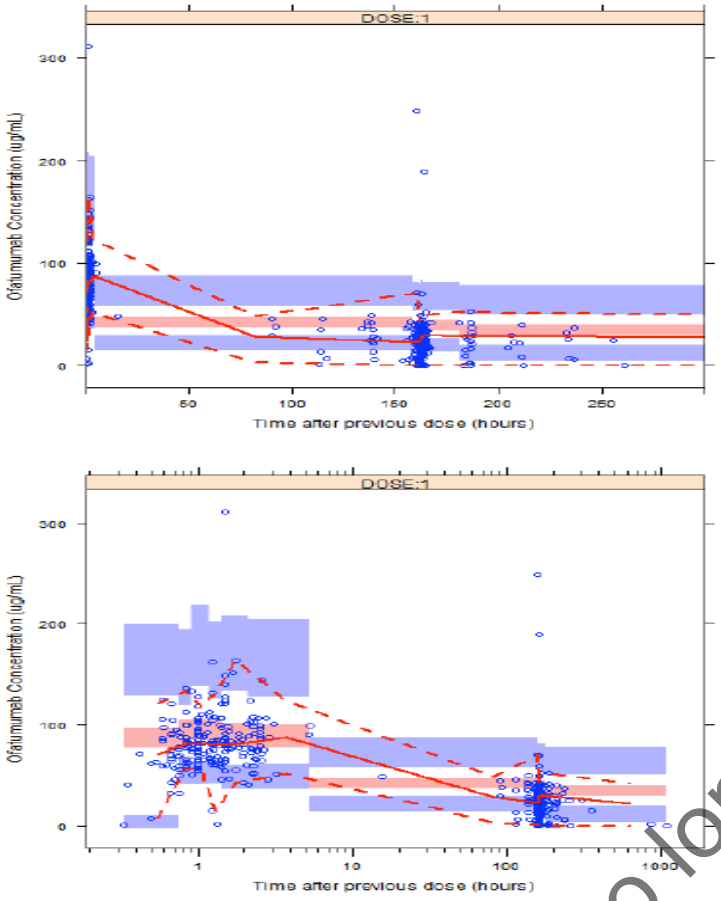



**Figure 3. Visual predictive check for ofatumumab at cycle 1, dose 1 (Study OMB112517)**

Red solid and dotted lines are median, 2.5th, and 97.5th percentiles for observed data. Red area is the 95% CI around the simulated median. Blue areas are the 95% CI around the simulated 2.5th and 97.5th percentiles. Each dose group has two plots: top=linear x-axis and bottom=log scale x-axis.



**Figure 4. CWRES**

## 2.4.3. Pharmacodynamics

***Mechanism of action***

PD has been assessed in terms of CD5+, CD19+, CD20+ and CD23+ counts:

*Study OMB112517:* In subjects receiving ofatumumab maintenance treatment, the median decreases in $CD5^+CD19^+$ cell counts after the first cycle and prior to the sixth eight-week cycle were 61% and 80%; in the observation arm, the median changes in $CD5^+CD19^+$ cell counts at the same time points were increases of 32% and 1328%.

*Study OMB111827/GEN416:* In the total group, the median percent reduction in peripheral blood $CD5^+CD19^+$ cells was 91% one week after the eighth weekly infusion (Week 8) and 90% before the second monthly infusion (Month 4). In the double refractory group, the median percent reduction was 97% and 94% at Week 8 and Month 4, respectively, while, in the bulky fludarabine-refractory group, the median percent reduction was 67% and 73% at the same timepoints.

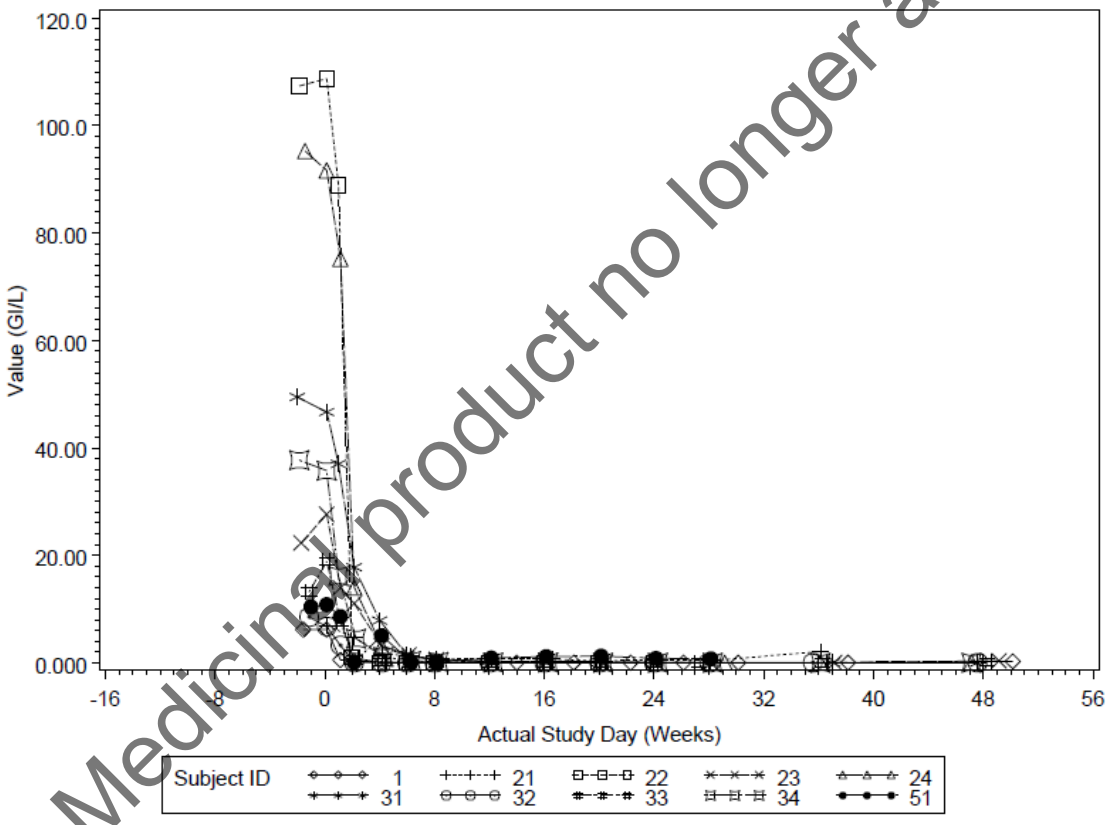





**Figure 5: CD5+CD19+ B-Cell Counts over Time by Subject (Study OMB112758)**

***Primary and secondary pharmacology***

*Immunogenicity*

*Study OMB112517*: In the 205 subjects with post-ofatumumab HAHA results one subject tested positive for HAHA, and 185 subjects had all negative post-ofatumumab HAHA results with at least one ofatumumab plasma concentration low enough (<200 μg/mL) for the negative HAHA results to be

considered conclusive. For the subject tested positive for HAHA, at the six-month follow-up visit (titer = 16); samples at all other time points were negative.

*Study OMB111827/GEN416:* There were no positive results for HAHA in the study using the enzyme-linked immunosorbent assay (ELISA) method. Post-ofatumumab HAHA results were available for 21 subjects. Of these 21 subjects, 3 subjects were negative for HAHA, and 18 were inconclusive due to the presence of ofatumumab.

*Study OMB112758:* There were no detectable anti-ofatumumab antibodies (HAHA) in samples collected from all ten subjects after the administration of ofatumumab using the G2 MSD ECL assay. Ofatumumab concentrations were below the drug tolerance of the assay at the time of HAHA sample collection in seven subjects.

### 2.4.4. PK/PD modelling

Not applicable.

### 2.4.5. Discussion on clinical pharmacology

The sponsor did not submit new phase II dose finding PK/PD studies for the current application. The PK data supporting the dose selection is based on prior and ongoing clinical experience with the proposed doses, preclinical identification of a target level of 10 µg/ml and PK modelling and simulation. Sparse PK data has been collected in the pivotal study OMB112517 to confirm that the expected exposure levels is reached.

The clinical pharmacology of ofatumumab in CLL has been previously well defined. New data presented in this submission do not alter the understanding of ofatumumab PK, PD, or immunogenicity. The PK profile of ofatumumab in CLL patients in partial or complete response after induction treatment is generally in line with what previously reported in other indications. However, the exposures are somewhat higher than expected compared to previous studies in CLL patients, which could be due to reduced contribution of target- mediated clearance, as the subjects entering this study is in complete or partial response after induction treatment. The immunogenicity is reported as low, and potential contribution of ADA to the elimination of ofatumumab is not expected to differ from other indications. The previously developed population PK model reasonable well predict the PK data in the current population (CLL patients in partial of complete response after induction therapy), however some miss specification is present, as the model slightly, but systematically, overestimates the concentrations.

In the submitted PK data from the pivotal trial, some exposure response correlations have been identified, and there is a trend for higher efficacy (PFS) in the quartiles with higher exposure (AUC, Cmax and Ctrough). It is difficult to know the causality, as efficacy of the drug will result in a decreasing level of B-cells, which will cause decreased ofatumumab CL.

The estimated concentration levels show a Cmean above the target exposure of 10µg/ml. Although the probability of attaining a trough concentration of at least 10 µg/mL at steady-state (Cycle 4 and later) was approximately 50%, there does not seem to be a systematic trend for individual patients to consistently fall below the target concentration during the entire study period.

It is of course acknowledged that a higher number of B-cells result in a greater component of target-mediated elimination, faster clearance, and shorter ofatumumab OFA half-life compared to a low B-cell count setting. This makes the relationship between ofatumumab exposure and clinical response complex, and the relationship has not been fully characterized. However, the data available does not allow a clear

identification of a target exposure and a recommendation for dose adjustments at later Cycles or between PR of CR patients cannot be made.

### 2.4.6. Conclusions on clinical pharmacology

The dose selection based on preclinical data with ofatumumab, prior experience with rituximab and ofatumumab as well as population PK modelling and simulation with the existing ofatumumab population-PK model is acceptable.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response studies

No specific dose-finding studies for the maintenance therapy have been conducted (see discussion on clinical pharmacology).

### 2.5.2. Main study

**OMB112517 (PROLONG)**

This was a Phase III, open-label, randomized, multicentre trial of ofatumumab (OFA) maintenance treatment versus no further treatment in subjects with CLL in remission (partial response [PR] or CR) after at least two lines of induction therapy.

***Methods***

***Study participants***

*Inclusion Criteria*

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Adults with documented diagnosis of CLL based on the modified IWCLL updated NCI-WG guidelines [Hallek, 2008]
2. At least PR according to the revised 2008 NCI-WG CLL criteria within 3 months of the response assessment after the last dose of 2nd/3rd line treatment
3. The anti-leukemic treatment before study entry should have been for at least 3 months or 3 cycles
4. ECOG Performance Status of 0-2
5. Signed written informed consent prior to performing any study-specific procedures.

*Exclusion Criteria*

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Known primary or secondary fludarabine-refractory subjects, defined as treatment failure (failure to achieve a CR or PR) or disease progression within 6 months [Hallek, 2008]
2. Prior maintenance therapy
3. Known transformation of CLL (e.g. Richter's transformation), prolymphocytic leukemia (PLL), or CNS involvement of CLL
4. Active Autoimmune Haemolytic Anaemia (AIHA) requiring treatment except if in the opinion of the investigator it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data
5. Previous autologous or allogeneic stem cell transplantation
6. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis B or C (Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HBV DNA test will be performed and if positive the subject will be excluded)
7. Other past or current malignancy (with the exception of basal cell carcinoma of the skin or in situ carcinoma of the cervix or breast) unless the tumour was successfully treated with curative intent at least 2 years prior to trial entry except if in the opinion of the investigator it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data
8. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months prior to screening, congestive heart failure, and arrhythmia requiring therapy, with the exception of extra systoles or minor conduction abnormalities except if in the opinion of the investigator it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data
9. History of significant cerebrovascular disease or event with symptoms or sequelae
10. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator contraindicates participation in this study
11. Other anti-leukemic use of medications including glucocorticoids
12. Known HIV positive
13. Screening laboratory values:
    - Platelets<50 x 109/L
    - Neutrophils<1.0 x 109/L
    - Creatinine > 1.5 times upper normal limit (unless normal creatinine clearance)
    - Total bilirubin > 1.5 times upper normal limit (unless due to liver involvement of CLL or Gilbert's syndrome)
    - Alanine Aminotransferase (ALT) > 2.5 times upper normal limit (unless due to liver involvement of CLL)
    - Alkaline phosphatase >2.5 times upper normal limit
14. Known or suspected hypersensitivity to ofatumumab that in the opinion of the investigator or medical monitor contraindicates study participation

15. Subjects who have received treatment with any non-marketed drug substance or experimental therapy within 5-terminal half-lives or 4 weeks whichever is longer prior to first dose of study medication or currently participating in any other interventional clinical study

    *Note: Participation in any other interventional clinical study after disease progression during post PD follow-up is permitted*

16. Lactating women, women with a positive pregnancy test at Visit 1 or women (of childbearing potential) as well as men with partners of childbearing potential, who are not willing to use adequate contraception from study start through one year following last ofatumumab dose. Adequate contraception is defined as abstinence, oral hormonal birth control, implants of levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device, and male partner sterilization if male partner is sole partner for that subject. For females in the USA, the use of a double barrier method is also considered adequate (condom or occlusive cap plus spermicidal agent).

***Treatments***

The study consisted of screening, a Treatment/Obs Phase, and a Follow-up Phase. Disease status assessments to determine response or disease progression were done approximately every 8 weeks for up to 2 years for both arms (per National Cancer Institute [NCI] criteria) during the Treatment/Obs Phase and to include:

• Physical examination including lymph node examination, spleen and liver measurement, and detection of constitutional symptoms

• Peripheral blood sample evaluation of complete blood count (CBC) and differential (expressed in % and absolutes).

Subjects in the maintenance arm (Arm A) were given ofatumumab by IV infusion as follows: first infusion of 300 mg OFA on Day 1, second infusion of 1000 mg OFA on Day 8, followed by infusions of 1000 mg OFA every 8 weeks for up to 2 years. Prior to the start of each ofatumumab infusion, subjects received acetaminophen, antihistamine, and glucocorticoids for premedication. Dose reductions or modifications of ofatumumab were not permitted unless for subject safety (i.e., due to infusion reactions). If a dose delay was required for ofatumumab for safety (including AEs), dosing may have resumed at physician discretion and the subject was still considered to be in remission. Subjects in the control Obs arm (Arm B) received no further treatment, which is the current standard of care. The visit schedule was identical for the ofatumumab maintenance and Obs arms.

Subjects were randomized to treatment arms A or B as follows:

**Arm A:**

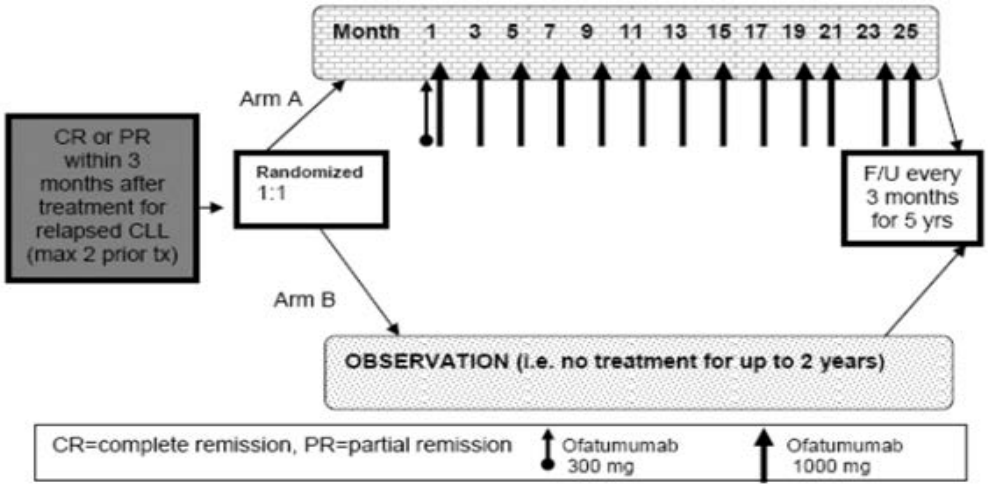
Ofatumumab:

- 300mg IV Week 1 followed by 1000mg IV on Week 2
- 1000mg IV (1 dose every 8 weeks for up to 2 years following the first 1000 mg dose)

OR

**Arm B:**

- No further treatment (observation and assessments as per arm A)




Abbreviations: CLL=chronic lymphocytic leukemia; F/U = follow-up; tx=therapy(ies).

**Figure 6: Design of Study OMB112517**

*Follow-up phase*

Survival and disease status assessments (physical examination and evaluation of peripheral blood samples) was planned to be performed post treatment every 3 months for 5 years after last treatment.

A bone marrow examination is required to confirm CR at least 2 months after completion of therapy and when a subject fulfils the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-Sponsored Working Group (NCI-WG) requirements for CR. Previous results may be used or if not available, a bone marrow exam may be done at screening. If a subject's response improves to a CR while on study, then a bone marrow examination is required to confirm CR at least 2 months after response as per the updated IWCLL NCI-WG requirements for CR.

Additionally, CT Scans were required yearly while on study, including during follow-up, and at disease progression, whenever that may occur.

Subjects demonstrating disease progression were supposed to be followed for survival status until study completion. Follow-up assessment after disease progression on treatment was planned to assess survival status, date of next CLL therapy, type of therapy and response to therapy.

**Objectives**

The primary objective was to evaluate progression free survival (PFS) of subjects treated with ofatumumab maintenance treatment compared to no further treatment after remission induction in subjects with relapsed chronic CLL.

Secondary objectives included the following:

To evaluate the improvement in response, improvement in response time to next CLL treatment and overall survival in subjects receiving ofatumumab maintenance compared to no further treatment.

To evaluate the PFS after next-line therapy and the time to progression after next line therapy.

To evaluate the safety and tolerability in subjects with CLL receiving ofatumumab maintenance compared to no further treatment.

To evaluate the health-related quality of life in subjects with CLL receiving ofatumumab maintenance compared to no further treatment as assessed by changes in patient reported outcome (PRO) measures relative to baseline.

To evaluate prognostic marker correlation with clinical response in subjects with CLL receiving ofatumumab maintenance compared to no further treatment.

To evaluate ofatumumab PK parameters in subjects with CLL receiving maintenance ofatumumab every 2 months.

**Outcomes / endpoints**

**Table 7: Study Objectives and Endpoints of Study OMB112517**

| Objectives | Endpoints |
|---|---|
| **Primary Efficacy** | |
| To evaluate PFS of subjects treated with OFA maintenance treatment compared to no further treatment after remission induction in subjects with relapsed chronic CLL | PFS: defined as the interval between the date of randomization and the earliest date of disease progression or death due to any cause |
| **Secondary Efficacy** | |
| To evaluate the improvement in response, time to next CLL treatment and overall survival in subjects receiving OFA maintenance compared to no further treatment<br><br>To evaluate PFS after next-line therapy and time to progression after next-line therapy | Improvement in response, time to next treatment and overall survival<br><br>PFS after next-line therapy and time to progression after next-line therapy |
| **Safety** | |
| To evaluate the safety and tolerability in subjects with CLL receiving OFA maintenance compared to no further treatment | Incidence of and number of subjects with grade 3 and 4 infections; incidence, severity of adverse events, serious adverse events and other safety parameters; evaluation of myelosuppression (anemia, neutropenia, thrombocytopenia); frequency of transfusions; incidence of autoimmune hemolytic anemia (AIHA); human anti-human antibodies (HAHA); IgG, IgA, IgM serum levels |
| **Health Related Quality of Life** | |
| To evaluate the health related quality of life in subjects with CLL receiving OFA maintenance compared to no further treatment as assessed by changes in patient reported outcome (PRO) measures relative to baseline | Changes in PRO measures; changes in PRO scores; improvement of Eastern Cooperative Oncology Group (ECOG) performance status |
| **Biomarkers** | |
| To evaluate prognostic marker correlation with clinical response in subjects with CLL receiving OFA maintenance compared to no further treatment | Cytogenetics by fluorescent in-situ hybridization (FISH); immunoglobulin heavy chain variable region (IGHV) mutational status; β2 microglobulin; changes in complement levels |
| **Pharmacokinetics** | |
| To evaluate OFA pharmacokinetic (PK) parameters in subjects with CLL receiving maintenance OFA every 2 months | Plasma OFA concentrations |



**Sample size**

The sample size calculation is based on the primary endpoint, PFS, using the following assumptions:

- Exponential survival curves where the ratio of the hazard rates is constant over time
- Median PFS for the no further treatment group is 28 months

- Median PFS for the ofatumumab maintenance treatment group is 39.2 months
- A 1:1 stratified randomization scheme
- A 5% two-sided risk of erroneously claiming a difference in the presence of no true underlying difference (alpha level)
- An 80% chance of successfully declaring a difference in the presence of a true underlying difference (power)
- Accrual rate of 12 subjects per month
- Stratified Log-rank test for hypothesis testing

Using the above assumptions, approximately 280 total events from both treatment arms are needed for the study to attain 80% power. With a total sample size of 478 evaluable subjects, the total duration of the study will be approximately 63.5 months in order to obtain the 280 total events. Assuming a drop-out rate of 10%, the total sample size for both arms combined will be about 532 and the total duration of the study will be approximately 68 months.

**Randomisation**

Subjects were randomized to ofatumumab maintenance versus Obs arms in a 1:1 ratio. Randomization was stratified based on the following factors: 1) CR or PR at study entry, 2) number of previous induction treatments (two vs. three) and 3) type of prior treatment (chemo immunotherapy, only alkylating monotherapy, or other treatment).

**Blinding (masking)**

The design was an open-label study.

**Statistical methods**

*Hypotheses*

The null and alternative hypotheses were designed with the goal of demonstrating the superiority of ofatumumab maintenance treatment over no further treatment after remission induction in subjects with relapsed chronic CLL. The following hypotheses were to be evaluated:

H0: Distribution of PFS curves for the ofatumumab maintenance treatment and for the no further treatment groups are the same (HR is equal to 1).

H1: Distribution of the PFS curves for the ofatumumab maintenance treatment and for the no further treatment groups are not the same (HR is not equal to 1).

*Analysis Populations*

The following analysis populations were defined for this study:

- *Intent-to-Treat (ITT) population:* all subjects randomized in the study; subjects were grouped based on randomized arm regardless of which treatment they received
- *Safety population:* all randomized subjects; used for safety analyses; subjects were grouped based on treatment received regardless of how they were randomized

- *Per Protocol (PP) population:* all randomized subjects excluding those with major protocol deviations that impacted efficacy
- *PK population:* of all subjects in the ITT population for whom a PK sample was obtained and analysed.

*Planned Analyses*

The analysis of the primary endpoint was planned when the total number of events (280 PFS events/deaths) was reached in the study. An additional analysis was planned to be performed after all patients had completed follow-up or had been withdrawn.

The final analysis of PFS was planned to be tested based on a two-sided test with a significance level of 0.0498. The survival distributions should be estimated using Kaplan-Meier survival curves and compared using a stratified log-rank test. In addition to the stratified log-rank test based on the Kaplan-Meier procedure, a Cox regression model should be used and include covariates for treatment, stratification factors, and other baseline data deemed appropriate (*i.e.* cytogenetics at baseline, IgVH mutational status at baseline, β2-microglobulin at baseline, baseline CD20 and baseline complement level).

*Subgroup analyses*

Summary tables for PFS would be provided by the baseline stratification factors. Other subgroups of interest include age (<70 vs ≥70), gender, race, RAI/Binet Stage, ECOG (0-1 vs 2), baseline cytogenetics, cytogenetics at relapse, prognostic factors (Beta-2 microglobulin, IgVh status), baseline lymphocyte count and MRD status.

*Sensitivity analyses*

Three sensitivity analyses of PFS were planned:

- Using the IRC response data as opposed to using investigator assessment of response.
- Using the investigator response data where events of progression determined by CT scan will be included in the analysis.
- Using sensitivity data generated by the IRC where CT scan data was used to determine progression.

*Efficacy Analyses*

Assessments of disease status were based on IWCLL updated NCI-WG CLL criteria, with primary assessments based on investigator assessment and IRC assessments used for sensitivity analyses. The ITT population was used for all efficacy endpoint analyses.

The investigator assessment of response was used for the primary analysis of PFS, defined as the interval from randomization until disease progression or death. The length of the PFS interval was calculated from the date of randomization to the date of death or PD, whichever occurred first. Events of disease progression determined by CT scan were excluded from the primary analysis (but were included in a sensitivity analysis of PFS). The algorithm for whether or not a subject was classified as progressed or censored is presented in OMB112517 RAP Section 11.1. PFS was estimated using Kaplan-Meier survival curves and compared between arms with a stratified log-rank test using pre-specified baseline stratification factors: 1) CR or PR at study entry, 2) number of previous induction treatments (two vs. three) and 3) type of prior treatment (chemoimmunotherapy, only alkylating monotherapy, or other). The Pike estimator of the treatment hazard ratio (HR) and 95% confidence intervals (CI) for the HR were also provided. Kaplan-Meier plots, median times to PFS, and first and third quartiles were presented along with 95% CIs and associated probabilities for the effect of treatment, stratification factors, and the

covariates. The HR for treatment expressed the risk of experiencing disease progression or death for the OFA maintenance arm versus Obs.

A PP sensitivity analysis of PFS was not done as PP and ITT populations differed by <10%. Three other planned sensitivity analyses of PFS were performed. Concordance between investigator and IRC assessments of progression was evaluated for both arms based on percent agreement. The number and percentage of subjects with investigator-assessed progression during the Treatment/Obs Phase and follow-up was summarized for both arms.

Subgroup analyses of investigator-assessed PFS were conducted using a log-rank test: Response at entry (CR, PR); Number of previous induction therapies (two, three); Type of prior treatment (chemoimmunotherapy, only alkylating therapy, other); Age (<70, ≥70); Gender (male, female); Race (White, non-White); Modified Rai stage at screening (low risk, intermediate risk, high risk); Binet Stage at screening (A, B, C); Baseline cytogenetics with 20% cut-off (17p-, 11q-, 6q- or 12q or 13q-, no aberration); Baseline cytogenetics with 12% cut-off; Cytogenetics at relapse with 20% cut-off; Cytogenetics at relapse with 12% cut-off; Baseline MRD status (negative, positive).

***Results***

**Participant flow**

**Table 8 : Subject Disposition (ITT Population) for Study OMB112517**

| Phase/Status | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| Treatment/Obs Phase Status, n (%) | | | |
| Ongoing | 77 (32) | 71 (30) | 148 (31) |
| Completed | 128 (54) | 150 (64) | 278 (59) |
| Discontinued Treatment/Obs[a] | 33 (14) | 15 (6) | 48 (10) |
| Primary[b] Reason for Discontinuation During Treatment/Obs Phase[c], n (%) | | | |
| Adverse Event | 20 (8) | 3 (1) | 23 (5) |
| Protocol Deviation | 1 (<1)[g] | 0 | 1 (<1) |
| Lost to Follow-Up | 0 | 1 (<1) | 1 (<1) |
| Physician Decision | 5 (2) | 5 (2) | 10 (2) |
| Withdrawal by Subject | 7 (3) | 6 (3) | 13 (3) |
| Follow-up Status, n (%) | | | |
| Ongoing | 189 (79) | 182 (77) | 371 (78) |
| Follow-up | 42 (18) | 23 (10) | 65 (14) |
| Survival Follow-up[d] | 70 (29) | 88 (37) | 158 (33) |
| Completed[e] | 32 (13) | 34 (14) | 66 (14) |
| Withdrawn from study | 17 (7) | 20 (8) | 37 (8) |
| Primary[b] Reason for Study Withdrawal[f], n (%) | | | |
| Adverse event | 0 | 0 | 0 |
| Lost to follow-up | 2 (<1) | 1 (<1) | 3 (<1) |
| Physician decision | 4 (2) | 2 (<1) | 6 (1) |
| Withdrawn consent by subject | 11 (5) | 17 (7) | 28 (6) |

a. Subjects discontinued prior to completing 24 months in the Treatment/Obs Phase.
b. Subjects may have only one primary reason for study withdrawal and treatment discontinuation.
c. No subjects discontinued treatment due to disease progression as the primary reason.
d. Survival follow-up for subjects after disease progression or after start of subsequent CLL therapy.
e. All subjects in the "completed" category had died.
f. Subjects may have only primary reason for withdrawal.
g. Subject 679 had a protocol deviation of not meeting inclusion criterion of at least PR per revised 2008 NCI-WG CLL criteria within 3 months of the response assessment after the last dose of second- or third-line treatment.

***Recruitment***

The study was conducted in 130 sites within 24 counties. The 474 subjects were enrolled at 130 centres in 24 countries. Countries that enrolled the greatest number of subjects included Poland (42 subjects), Israel (39 subjects), Russia (39 subjects), the Netherlands (37 subjects), and the US (35 subjects).

The initiation date of the trial was 6 May 2010 and the data cut-off date was 19 June 2014. The MAH also submitted an update with a data cut-off date of 28 February 2015.

***Conduct of the study***

The original protocol, finalized on 14 July 2009, was amended 5 times. None of the amendments were implemented for safety concerns and recruitment was not held between amendments.

**Table 9: Protocol amendments for study OMB112517**

| Amendment # | Date | Summary of Amendment |
|---|---|---|
| NA | 14-JUL-2009 | Original |
| 1 | 11-NOV-2009 | Amendment No. 01: Addition of baseline minimal residual disease (MRD), exploratory endpoints, post-progressive disease PRO questionnaires and clarifications |
| 1 (Republished) | 20-NOV-2009 | Amendment No. 01 (Republished): Addition of baseline MRD, exploratory endpoints, post- progressive disease Patient Reported Outcomes (PRO) questionnaires and clarifications |
| 2 | 21-MAY-2010 | Amendment No. 02: Added study name and clarifications, modified inclusion/exclusion criteria |
| 3 | 07-FEB-2013 | Amendment No. 03: Country specific amendment: At the request of the French regulatory agency related information from the Study Procedures Manual was added into Section 6.4.6 |
| 4 | 17-DEC-2013 | Amendment No. 04: Food and Drug Administration request for additional Hepatitis B Virus information and protocol clarifications |
| 5 | 26-AUG-2014 | Amendment No. 05: As the significance level was met at the interim analysis of efficacy, further enrollment in the study will be discontinued |

a. This version of the protocol was not sent to study sites and was republished prior to sending to study sites

**Table 10: Protocol Deviations (ITT Population - Study OMB112517)**

| Devation Category | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| **Any Deviation, n (%)** | **193 (81)** | **174 (73)** | **367 (77)** |
| **Deviations which did not require exclusion from PP population, n (%)** | **192 (81)** | **173 (73)** | **365 (77)** |
| Eligibility criteria not met | 6 (3) | 6 (3) | 12 (3) |
| Assessments and/or procedures | 176 (74) | 161 (68) | 337 (71) |
| Received wrong treatment or incorrect dose | 12 (5) | 0 | 12 (3) |
| Visit, assessment or time point window | 102 (43) | 94 (40) | 196 (41) |
| Other protocol deviation category | 31 (13) | 19 (8) | 50 (11) |
| **Deviations which required exclusion from PP population, n (%)** | 5 (2)[a] | 8 (3) | 13 (3)[a] |
| Eligibility criteria not met | 3 (1) | 0 | 3 (<1) |
| Other protocol deviation category | 4 (2) | 8 (3) | 12 (3) |

Data Source: Table 1.1310

Note: Subjects with multiple protocol deviations were counted in more than one row.

a. Some subjects had >1 PP deviation and are listed in more than one category

***Baseline data***

**Demographics**

**Table 11: Demographic Characteristics (ITT Population - Study OMB112517)**

| | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| Age, years[a] | | | |
| Median (min-max) | 64.0 (33-86) | 65.0 (39-87) | 64.5 (33-87) |
| <70, n (%) | 168 (71) | 162 (69) | 330 (70) |
| ≥70, n (%) | 70 (29) | 74 (31) | 144 (30) |
| ≥75, n (%) | 40 (17) | 35 (15) | 75 (16) |
| Sex, n (%) | | | |
| Female | 77 (32) | 77 (33) | 154 (32) |
| Male | 161 (68) | 159 (67) | 320 (68) |
| Ethnicity, n (%) | | | |
| Hispanic/Latino | 14 (6) | 18 (8) | 32 (7) |
| Not Hispanic/Latino | 224 (94) | 217 (92) | 441 (93) |
| Missing[b] | 0 | 1 (<1) | 1 (<1) |
| Race, n (%) | | | |
| African American/African Heritage | 3 (1) | 2 (<1) | 5 (1) |
| American Indian or Alaska Native | 0 | 1 (<1) | 1 (<1) |
| Asian | 8 (3) | 4 (2) | 12 (3) |
| Central/South Asian Heritage | 4 (2) | 2 (<1) | 6 (1) |
| Japanese/East Asian Heritage/South East Asian Heritage | 4 (2) | 2 (<1) | 6 (1) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (<1) | 1 (<1) |
| White | 226 (95) | 227 (96) | 453 (96) |
| African American/African Heritage & White | 1 (<1) | 0 | 1 (<1) |
| Missing[b] | 0 | 1 (<1) | 1 (<1) |

Abbreviations: max=maximum; min=minimum.

a. Age was calculated from birth date to screening date in years.

b. Subject 1484 was enrolled in The Netherlands.

**Table 12: Actual Stratification Factors (ITT Population - Study OMB112517)**

| | OFA (N=238) | Obs[a] (N=236) | Total (N=474) |
|---|---|---|---|
| Response at Entry, n (%) | | | |
| CR | 45 (19) | 46 (19) | 91 (19) |
| PR | 193 (81) | 189 (80) | 382 (81) |
| Missing | 0 | 1 (<1) | 1 (<1) |
| Number of Previous Induction Treatments, n (%) | | | |
| 1 | 0 | 1 (<1)[b] | 1 (<1) |
| 2 | 168 (71) | 166 (70) | 334 (70) |
| 3 | 66 (28) | 62 (26) | 128 (27) |
| 4 | 3 (1)[b] | 7 (3)[b] | 10 (2) |
| 5 | 1 (<1)[b] | 0 | 1 (<1) |
| Type of Most Recent Prior Treatment, n (%) | | | |
| Chemoimmunotherapy | 191 (80) | 189 (80) | 380 (80) |
| Only Alkylating Monotherapy | 14 (6) | 9 (4) | 23 (5) |
| Other Prior Treatment | 33 (14) | 38 (16) | 71 (15) |

Abbreviations: CR=complete response; PR=partial response.

a. One subject in the Obs arm did not have data available for all of the covariates.

b. Subjects that had received 1, 4, or 5 prior induction treatments met criteria for major protocol deviations.

**Table 13: Disease Characteristics at Screening (ITT Population- Study OMB112517)**

| | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| **Modified Rai Stage, n (%)** | | | |
| Low Risk (Stage 0) | 68 (29) | 85 (36) | 153 (32) |
| Intermediate (Stage I, II) | 80 (34) | 70 (30) | 150 (32) |
| High Risk (Stage III, IV) | 36 (15) | 36 (15) | 72 (15) |
| Unknown | 46 (19) | 40 (17) | 86 (18) |
| Missing | 8 (3) | 5 (2) | 13 (3) |
| **Binet Stage, n (%)** | | | |
| A | 123 (52) | 134 (57) | 257 (54) |
| B | 54 (23) | 38 (16) | 92 (19) |
| C | 33 (14) | 42 (18) | 75 (16) |
| Unknown | 20 (8) | 16 (7) | 36 (8) |
| Missing | 8 (3) | 6 (3) | 14 (3) |
| **Lymphocytes, $10^9$/L** | | | |
| n | 236 | 231 | 467 |
| Median (min-max) | 1.1 (0-43) | 0.9 (0-46) | 1.0 (0-46) |
| **Neutrophils, $10^9$/L** | | | |
| n | 236 | 231 | 467 |
| Median (min-max) | 2.4 (0-11) | 2.5 (0-11) | 2.5 (0-11) |
| **B-Symptoms[a]** | | | |
| n | 238 | 236 | 474 |
| With No B-symptoms, n (%) | 223 (94) | 222 (94) | 445 (94) |
| With ≥1 B-symptoms, n (%) | 15 (6) | 14 (6) | 29 (6) |

[Data Source: OMB112517 CSR Table 1.4120], [OMB112517 CSR Table 1.4130], [OMB112517 CSR Table 2.2040]
Note: n=number of subjects with values at the specified analysis visit.
Abbreviations: max=maximum; min=minimum.
a. B-symptoms include fever, night sweats, weight loss, and extreme fatigue.

*Baseline Prognostic Markers*

**Table 15: Prognostic Markers at Baseline (ITT Population - Study OMB112517)**

| | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| Baseline Cytogenetics (20% Cut-Off), n (%) | | | |
| 11q Deletion | 11 (5) | 9 (4) | 20 (4) |
| 17p Deletion | 7 (3) | 4 (2) | 11 (2) |
| 6q Deletion or 12q Trisomy or 13q Deletion | 33 (14) | 12 (5) | 45 (9) |
| No Aberration | 165 (69) | 178 (75) | 343 (72) |
| Missing | 22 (9) | 33 (14) | 55 (12) |
| Baseline Cytogenetics (12% Cut-Off), n (%) | | | |
| 11q Deletion | 15 (6) | 12 (5) | 27 (6) |
| 17p Deletion | 7 (3) | 4 (2) | 11 (2) |
| 6q Deletion or 12q Trisomy or 13q Deletion | 44 (18) | 16 (7) | 60 (13) |
| No Aberration | 150 (63) | 171 (72) | 321 (68) |
| Missing | 22 (9) | 33 (14) | 55 (12) |
| **β2 Microglobulin Group, n (%)** | | | |
| ≤3500 µg/L | 157 (66) | 163 (69) | 320 (68) |
| >3500 µg/L | 79 (33) | 68 (29) | 147 (31) |
| Missing | 2 (<1) | 5 (2) | 7 (1) |
| IGHV Mutational Status, n (%) | | | |
| Mutated <98% | 47 (20) | 66 (28) | 113 (24) |
| Unmutated ≥98% | 129 (54) | 108 (46) | 237 (50) |
| Not available[a] | 3 (1) | 1 (<1) | 4 (<1) |
| Missing | 59 (25) | 61 (26) | 120 (25) |
| IGHV Homology, n (%) | | | |
| 97%-98% | 9 (4) | 5 (2) | 14 (3) |
| <97% | 38 (16) | 60 (25) | 98 (21) |
| >98% | 129 (54) | 108 (46) | 237 (50) |
| Missing | 62 (26) | 63 (27) | 125 (26) |
| $V_H$3-21 Usage, n (%) | | | |
| Yes | 5 (2) | 7 (3) | 12 (3) |
| No | 233 (98) | 229 (97) | 462 (97) |

Abbreviations: IGHV=immunoglobulin heavy chain variable region.

a. The electronic case report form (eCRF) indicated that the value was "not available".

*Prior Anti-Cancer Therapy*

**Table 14: Prior Anti-Cancer Therapy (ITT Population - Study OMB112517)**

| | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| Alemtuzumab-Based Therapy, n (%) | | | |
| Monotherapy | 1 (<1) | 3 (1) | 4 (<1) |
| Alkylator-Based Therapy, n (%) | | | |
| Any Therapy | 51 (21) | 40 (17) | 91 (19) |
| Monotherapy | 13 (5) | 7 (3) | 20 (4) |
| Combination Therapy – Other | 6 (3) | 5 (2) | 11 (2) |
| Combination Therapy with Monoclonal Antibody but No Purine Analog | 32 (13) | 28 (12) | 60 (13) |
| Bendamustine-Based Therapy, n (%) | | | |
| Any Therapy | 47 (20) | 50 (21) | 97 (20) |
| Monotherapy | 1 (<1) | 2 (<1) | 3 (<1) |
| Combination Therapy | 46 (19) | 48 (20) | 94 (20) |
| Fludarabine-Based Therapy, n (%) | | | |
| Any Therapy | 127 (53) | 136 (58) | 263 (55) |

| | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| Monotherapy | 4 (2) | 5 (2) | 9 (2) |
| Combination Therapy | 123 (52) | 131 (56) | 254 (54) |
| Other Therapeutic Agents, n (%) | | | |
| Monotherapy | 0 | 1 (<1) | 1 (<1) |
| Rituximab-Based Therapy[a], n (%) | | | |
| Any Therapy | 11 (5) | 6 (3) | 17 (4) |
| Monotherapy | 2 (<1) | 1 (<1) | 3 (<1) |
| Combination Therapy | 9 (4) | 5 (2) | 14 (3) |
| Investigational Agents, n (%) | | | |
| Monotherapy | 1 (<1) | 0 | 1 (<1) |

a. Subjects who received fludarabine, cyclophosphamide, rituximab (FCR) are not necessarily counted under rituximab-based therapy.

**Table 15: Types of Most Recent Prior Chemoimmunotherapy (ITT Population - Study OMB112517)**

| Most Recent Type of Prior Chemoimmunotherapy<br>Best Response (PR or CR) | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| Any Chemoimmunotherapy | 191 | 189 | 380 |
| BR | | | |
| n (%) | 46 (24) | 47 (25) | 93 (24) |
| CR, n/N (%) | 12/46 (26) | 13/47 (28) | 25/93 (27) |
| PR, n/N (%) | 34/46 (74) | 34/47 (72) | 68/93 (73) |
| Missing | 0 | 0 | 0 |
| FCR | | | |
| n (%) | 100 (52) | 103 (54) | 203 (53) |
| CR, n/N (%) | 27/100 (27) | 23/103 (22) | 50/203 (25) |
| PR, n/N (%) | 73/100 (73) | 79/103 (77) | 152/203 (75) |
| Missing | 0 | 1 (<1) | 1 (<1) |
| FR | | | |
| n (%) | 4 (2) | 5 (3) | 9 (2) |
| CR, n/N (%) | 1/4 (25) | 2/5 (40) | 3/9 (33) |
| PR, n/N (%) | 3/4 (75) | 3/5 (60) | 6/9 (67) |
| Missing | 0 | 0 | 0 |
| Other | | | |
| n (%) | 28 (15) | 23 (12) | 51 (13) |
| CR, n/N (%) | 1/28 (4) | 4/23 (17) | 5/51 (10) |
| PR, n/N (%) | 27/28 (96) | 19/23 (83) | 46/51 (90) |
| Missing | 0 | 0 | 0 |
| R-CVP | | | |
| n (%) | 13 (7) | 11 (6) | 24 (6) |
| CR, n/N (%) | 3/13 (23) | 1/11 (9) | 4/24 (17) |
| PR, n/N (%) | 10/13 (77) | 10/11 (91) | 20/24 (83) |
| Missing | 0 | 0 | 0 |

Abbreviations: BR=bendamustine and rituximab; CR=complete response; FCR= fludarabine, cyclophosphamide, rituximab; FR=fludarabine and rituximab; n/N=number of subjects that received the type of chemoimmunotherapy with PR or CR; PR=partial response; R-CVP=rituximab, cyclophosphamide, vincristine and prednisolone.



***Numbers analysed***

**Table 16: Study Populations Study OMB112517 (Randomized Population - Study OMB112517)**

| Study Populations | OFA (N=238) | Obs (N=236) | Total (N=474) |
|---|---|---|---|
| Intent-to-treat (ITT) population[a] | 238 | 236 | 474 |
| Safety population[b] | 237 | 237 | 474 |
| Per-protocol population[c] | 233 | 228 | 461 |
| OFA PK population[d] | 225 | NA | 225 |

Data Source: Table 1.0010

a. Includes all randomized subjects. Subjects were grouped based on the randomized treatment regardless of which treatment was actually received.
b. Includes all randomized subjects but subjects were grouped based on the actual treatment received
c. Includes all randomized subjects excluding those with major protocol deviations
d. Subjects in the ITT population for whom a PK sample was obtained and analyzed.

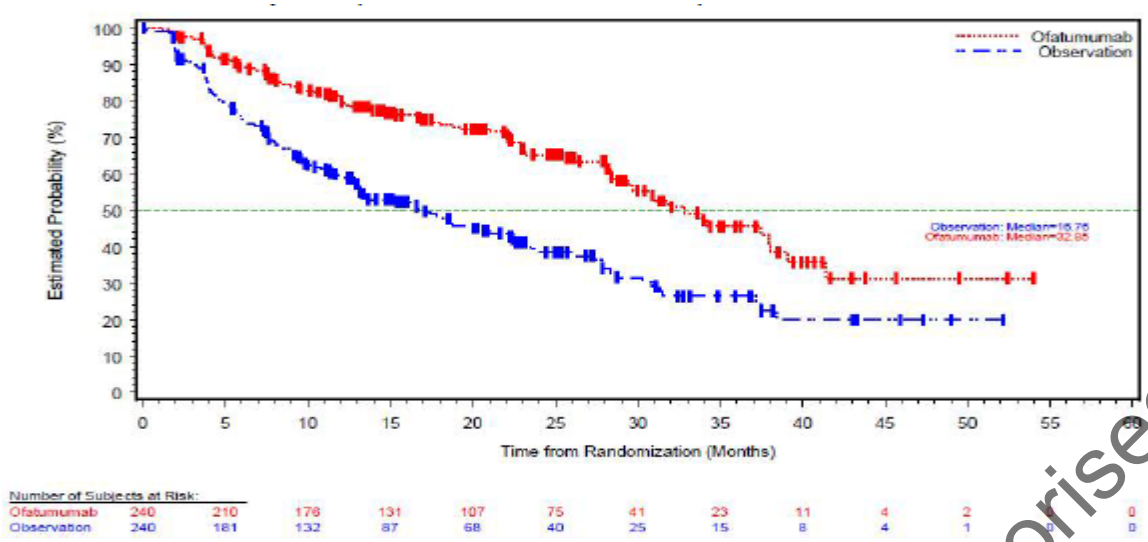
***Outcomes and estimation***

*Primary endpoint - Progression-Free Survival Assessed by Investigator*

**Table 17: Kaplan-Meier Estimates of Investigator-assessed PFS (ITT Population – Study OMB112517) – (Original: data cut-off of 19 June 2014- Update: Data cut-off 28 February 2015)**

| | Original submission | | Efficacy update | |
|---|---|---|---|---|
| | OFA (N=238) | Obs (N=236) | OFA (N=240) | Obs (N=240) |
| **Subject Classification, n (%)** | | | | |
| Progressed or died (event) | 78 (33) | 120 (51) | 87 (36) | 137 (57) |
| Death | 4 (2) | 4 (2) | 4 (2) | 6 (3) |
| Progression | 74 (31) | 116 (49) | 83 (35) | 131 (55) |
| Censored, last adequate assessment (LAA) [a] | 140 (59) | 109 (46) | 122 (51) | 85 (35) |
| Censored, LAA before or on anti-cancer therapy [b] | 18 (8) | 4 (2) | 27 (11) | 14 (6) |
| Censored, LAA before progression [c] | 1 (<1) | 0 | 1 (<1) | 0 |
| Censored, randomization [d] | 1 (<1) | 3 (1) | 1 (<1) | 4 (2) |
| **Estimates for PFS (Months) [e]** | | | | |
| 1st Quartile (95% CI) | 15.24 (10.91, 22.11) | 5.98 (4.37, 7.66) | 16.82 (11.96, 22.34) | 5.98 (4.50, 7.69) |
| **Median (95% CI)** | **29.44 (26.18, 34.17)** | **15.24 (11.79, 18.76)** | **32.85 (28.58, 38.08)** | **16.76 (13.01, 22.28)** |
| 3rd Quartile (95% CI) | 38.08 (34.17, NE) | 31.47 (27.86, NE) | NR (39.10, NE) | 37.16 (28.35, NE) |
| Adjusted HR Estimate [f] (95% CI) | 0.50 (0.38,0.66) | | 0.49 (0.37, 0.63) | |
| Stratified Log-Rank P-Value | <0.0001 | | <0.0001 | |

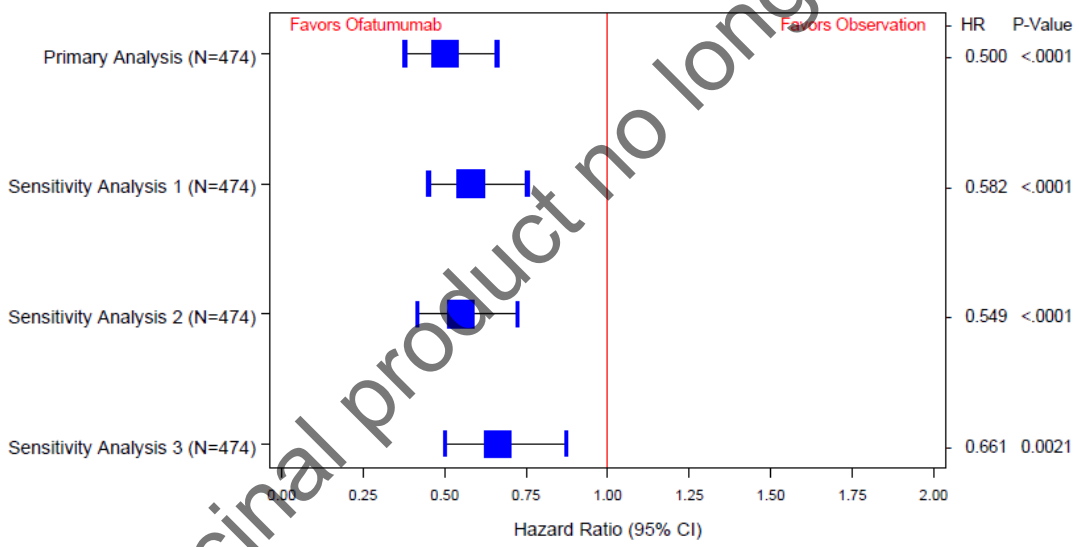
Source: [Appendix to EMA Response-Table 2.0010]
Abbreviations: LAA=last adequate assessment; CI=confidence interval; NE=not estimable; NR=not reached
Subjects alive and progression-free, censored at LAA.
Subjects took alternative therapy prior to documented progression, censored at LAA.
Event (PD or death) occurred after 2 or more missed visits, censored at LAA.
No disease assessment after randomization.
Confidence intervals estimated using the Brookmeyer Crowley method.
Hazard ratios are obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with OFA maintenance compared with Obs.




Source: [Appendix to EMA Response-Figure 12.0010 ]

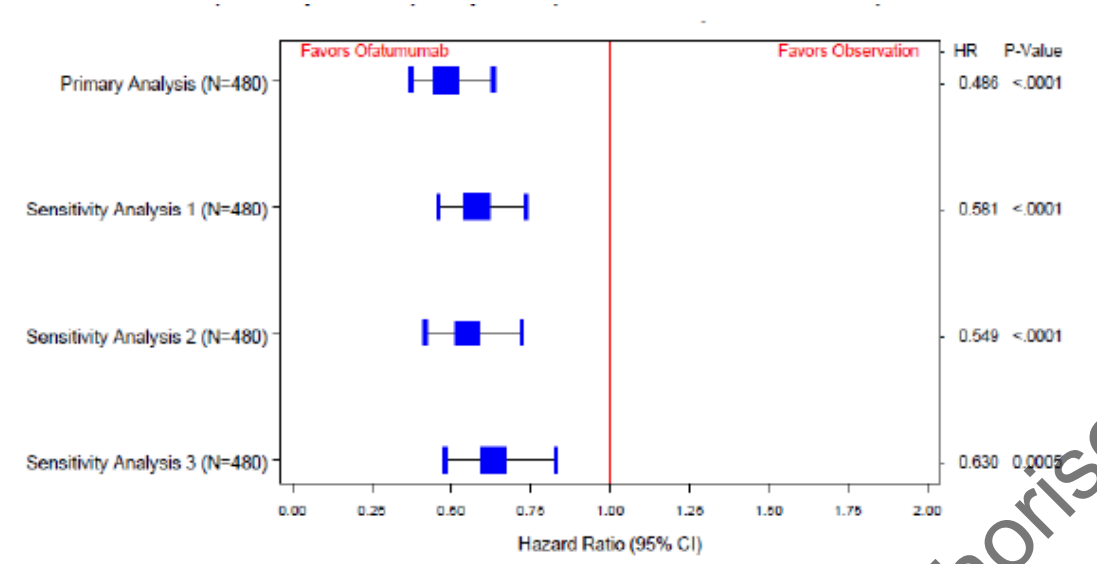
**Figure 8: Kaplan-Meier Estimates of Investigator-assessed PFS (ITT Population - Study OMB112517) – Update (Data cut-off 28 February 2015)**

### *Sensitivity Analyses of PFS*




[Data Source: OMB112517 CSR Figure 12.0100].
Abbreviations: CI=confidence interval; HR=hazard ratio; IRC=Independent Review Committee; progression-free survival (PFS).
Note: For sensitivity analyses of PFS, the censoring rules used for both treatment arms were the same as those used for the primary endpoint analysis of PFS.
Primary Analysis: Investigator-Assessed PFS
Sensitivity Analysis 1: Investigator-assessed PFS including events determined by CT scan IRC-assessed PFS
Sensitivity Analysis 2: IRC-assessed PFS
Sensitivity Analysis 3: IRC sensitivity analysis with CT scan assessed PFS
Note: HRs obtained using the Pike estimator. HR <1 indicates a lower risk with OFA maintenance compared with Obs.

**Figure 9: Forest Plot of Hazard Ratios from Sensitivity Analyses of PFS (ITT Population - Study OMB112517)**

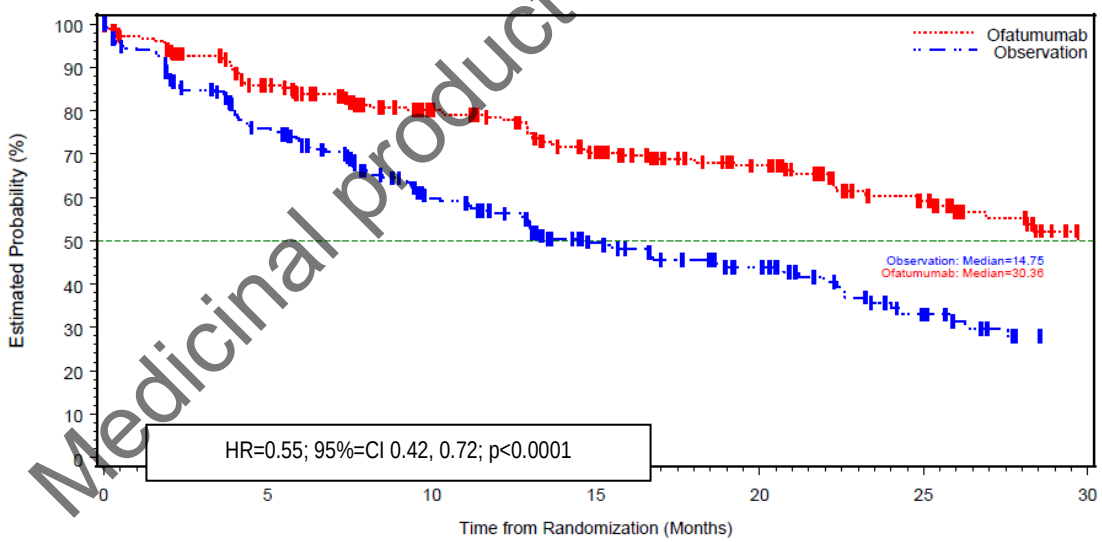



Source: [Appendix to EMA Response-Figure 12.0100]
Primary Analysis: Investigator-Assessed PFS
Sensitivity Analysis 1: Investigator-Assessed PFS including events determined by CT scan/IRC-Assessed PFS
Sensitivity Analysis 2: Independent review committee (IRC)-Assessed PFS
Sensitivity Analysis 3: IRC sensitivity analysis with CT scan assessed PFS
HRs are obtained using the Pike estimator. HR<1 indicates a lower risk with OFA maintenance vs. Obs.

**Figure 10: Forest Plot of Hazard Ratios and 95% CIs for PFS Sensitivity Analyses (ITT Population - Study OMB112517) – Update (Data cut-off 28 February 2015)**

**PFS Assessed by IRC**

Median PFS based on IRC assessment of progression (OFA maintenance: 30.36 months, Obs: 14.75 months, p<0.001) was consistent with the investigator-assessed analysis of PFS. The HR for the updated sensitivity analysis (data cut-off 28 February 2015) of 0.55 (95% CI=0.42, 0.72; p<0.001) was comparable with the primary analysis and was statistically significant.




| Number of Subjects at Risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ofatumumab | 238 | 181 | 140 | 106 | 79 | 51 | 26 |
| Observation | 236 | 154 | 100 | 65 | 45 | 23 | 12 |

[Data Source: OMB112517 CSR Figure 12.0040].
Abbreviations: CI=confidence interval; HR=hazard ratio.

**Figure 11: Kaplan-Meier Estimates of IRC-Assessed PFS (ITT Population - Study OMB112517)**

**Table 18: IRC-Assessed Kaplan-Meier Estimates of PFS (ITT Population - Study OMB112517) – Update (Original: data cut-off of 19 June 2014- Update: Data cut-off 28 February 2015)**

| | Original submission | | Efficacy update | |
|---|---|---|---|---|
| | OFA (N=238) | Obs (N=236) | OFA (N=240) | Obs (N=240) |
| **Subject Classification, n (%)** | | | | |
| Progressed or died (event) | 85 (36) | 119 (50) | 86 (36) | 121 (50) |
| Death | 4 (2) | 4 (2) | 4 (2) | 6 (3) |
| Progression | 81 (34) | 115 (49) | 82 (34) | 115 (48) |
| Censored, LAA[a] | 138 (58) | 106 (45) | 124 (52) | 94 (39) |
| Censored, LAA before or on anti-cancer therapy[b] | 13 (5) | 8 (3) | 26 (11) | 21 (9) |
| Censored, LAA before progression[c] | 1 (<1) | 0 | 1 (<1) | 0 |
| Censored, randomization[d] | 1 (<1) | 3 (1) | 1 (<1) | 4 (2) |
| **Estimates for PFS (Months)[e]** | | | | |
| 1st Quartile (95% CI) | 12.91 (8.11, 18.00) | 5.98 (4.37, 7.66) | 13.63 (10.35, 21.03) | 5.95 (4.01, 7.82) |
| **Median (95% CI)** | **30.36 (25.30, 35.58)** | **14.75 (11.30, 21.19)** | **35.58 (29.70, NE)** | **18.69 (13.01,24.02)** |
| 3rd Quartile (95% CI) | 38.08 (35.58, NE) | 37.45 (24.28, NE) | NE (NE, NE) | NE (37.16, NE,) |
| Adjusted HR Estimate[f] (95% CI) | 0.55 (0.42,0.72) | | 0.55 (0.42, 0.72) | |
| Stratified Log-Rank P-Value | <0.0001 | | <0.0001 | |

Source: [Appendix to EMA Response-Table 2.1010]

Abbreviations: LAA=last adequate assessment; CI=confidence interval; NE=not estimable; Obs=Observational; OFA=Ofatumumab

[a] Subjects alive and progression-free, censored at LAA.
[b] Subjects took alternative therapy prior to documented progression, censored at LAA.
[c] Event (PD or death) occurred after 2 or more missed visits, censored at LAA
[d] No disease assessment after randomization.
[e] Confidence Intervals estimated using the Brookmeyer Crowley method.
[f] Hazard ratios are obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with OFA maintenance compared with Obs.

**Table 19: Comparison of Investigator-Assessed and IRC PFS Timings (ITT Population - Study OMB112517)**

| Assessment, n (%) | OFA (N=238) | Obs (N=236) |
|---|---|---|
| PFS Events (Progression or Death) by IRC | 85 (36) | 119 (50) |
| PFS Events (Progression or Death) by Investigator | 78 (33) | 120 (51) |
| PFS Events by Both IRC and Investigator | 67 (28) | 111 (47) |
| IRC PFS Events Complete Agreement with Investigator | 33 (14) | 59 (25) |
| IRC PFS Events Earlier by Investigator | 26 (11) | 44 (19) |
| IRC PFS Events Later by Investigator | 8 (3) | 8 (3) |
| PFS Censored by IRC | 153 (64) | 117 (50) |
| PFS Censored by Investigator | 160 (67) | 116 (49) |
| PFS Censored by Both IRC and Investigator | 142 (60) | 108 (46) |
| IRC PFS Censored Complete Agreement with Investigator | 142 (60) | 108 (46) |
| IRC PFS Censored Earlier by Investigator | 0 | 0 |
| IRC PFS Censored Later by Investigator | 0 | 0 |

Abbreviations: CT=computed tomography; IRC=Independent Review Committee, PFS=progression-free survival.

Note: Investigator-assessed PFS without CT scan (primary analysis) was compared to IRC without CT scan (sensitivity analysis).



*PFS with Events Based on CT Scans Included*

Investigator-assessed PFS replacing palpated measurements of lymph nodes and organs with CT scan measurements (ofatumumab maintenance: 24.54 months, observation: 12.98 months) resulted in marginally shorter PFS than the primary endpoint of investigator-assessed PFS. The HR for the updated sensitivity analysis of 0.58 (95% CI=0.45, 0.75; p<0.0001).

*PFS with IRC Sensitivity Scans*

This sensitivity analysis was conducted using data generated by the IRC, where palpitation was replaced with CT scans to determine progression. The updated analysis resulted in a shorter PFS than the primary endpoint (ofatumumab maintenance: 23.69 months, observation: 13.54 months). The HR for this sensitivity analysis of 0.66 (95% CI=0.50, 0.87; p=0.0021)

*PFS During Follow-Up*

At the time of the data cut-off of 19 June 2014, 99 subjects had completed 2 years in the Treatment/Obs Phase, and the proportion of subjects that had progression at that time was similar between arms (ofatumumab maintenance: 32%, observation: 33%). The number of subjects included in this analysis was based on exposure data for the ofatumumab maintenance arm and based on visit data for the observation arm.

*PFS at One Year*

Two subjects had only 1 year of dosing, therefore, comparison of PFS with subjects completing the protocol-defined 2 years of dosing is not meaningful.

***Secondary Efficacy Results***

*Response rate*

All subjects were in remission at study entry; therefore, improvement in response during the study could only occur in those subjects who were in PR at baseline (ofatumumab maintenance: 193 subjects, observation: 189 subjects). At the time of the data cut-off, only a small proportion of subjects in either arm had an improvement in response from PR to CR during the course of the study (ofatumumab maintenance: 6% [11/193], observation: 1% [2/189]). However, confirmatory bone marrow biopsy after screening was obtained in only 7% of the subjects.

*Overall Survival*

**Table 20: Kaplan-Meier Estimates of Overall Survival (ITT Population - Study OMB112517) – Update (Original: data cut-off of 19 June 2014- Update: Data cut-off 28 February 2015)**

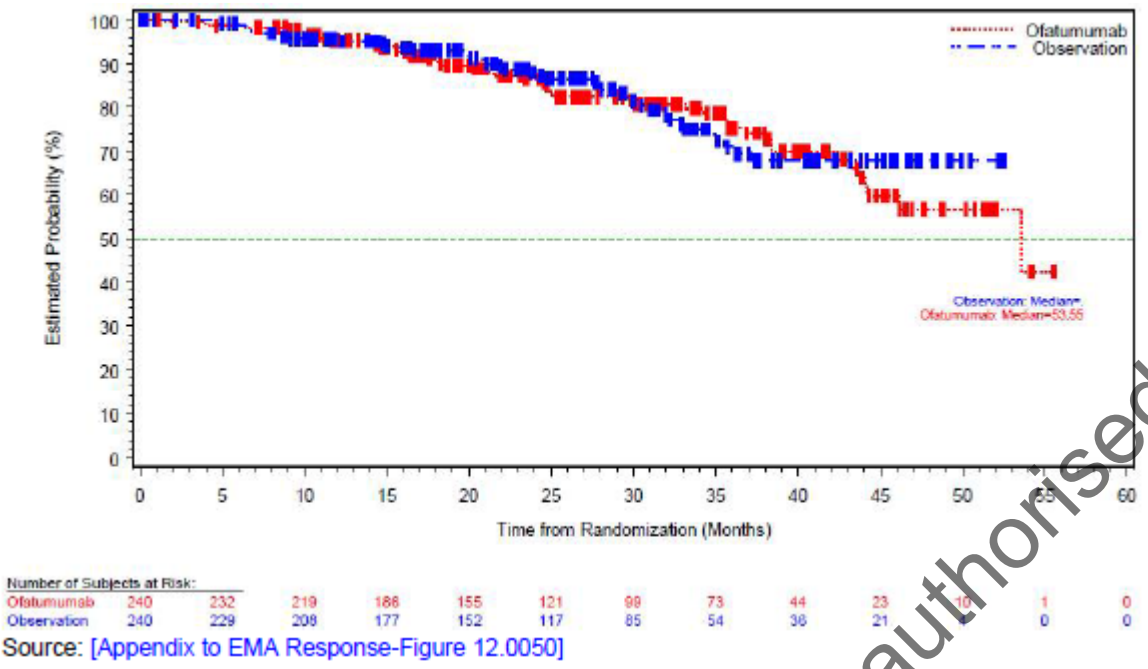
| | Original submission | | Efficacy update | |
|---|---|---|---|---|
| | OFA (N=238) | Obs (N=236) | OFA (N=240) | Obs (N=240) |
| Subject Classification, n (%) | | | | |
| Event | 32 (13) | 34 (14) | 51 (21) | 42 (18) |
| Death | 32 (13) | 34 (14) | 51 (21) | 42 (18) |
| Censored, last contact date | 206 (87) | 202 (86) | 189 (79) | 198 (83) |
| Estimates for OS (Months) [a] | | | | |
| 1st Quartile (95% CI) | 38.37 (25.07, NE) | 31.61 (28.02, 35.55) | 36.86 (29.67, 43.27) | 33.02 (29.80, NE) |
| **Median (95% CI)** | **NR** | **NR (35.55, NE)** | **53.55 (44.16, NE)** | **NR** |
| 3rd Quartile (95% CI) | NR | NR | NR (53.55, NE) | NR |
| Adjusted HR Estimate (95% CI) [b] | 0.85 (0.52, 1.37) | | 1.08 (0.72, 1.62) | |
| Stratified Log-Rank P-Value | 0.4877 | | 0.7205 | |

Source: [Appendix to EMA Response-Table 2.1110]

Abbreviations: CI=confidence interval; NE=not estimable; NR=Not reached

a. Confidence Intervals estimated using the Brookmeyer Crowley method.

b. Hazard ratios are obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with OFA maintenance compared with Obs.




Source: [Appendix to EMA Response-Figure 12.0050]

**Figure 13: Kaplan-Meier Overall Survival Curve (ITT Population - Study OMB112517) – Update (Data cut-off 28 February 2015)**

**Table 21: Kaplan-Meier Estimates of Overall Survival by IgVH Mutational Status (ITT Population - Study OMB112517) – Update: Data cut-off 28 February 2015**

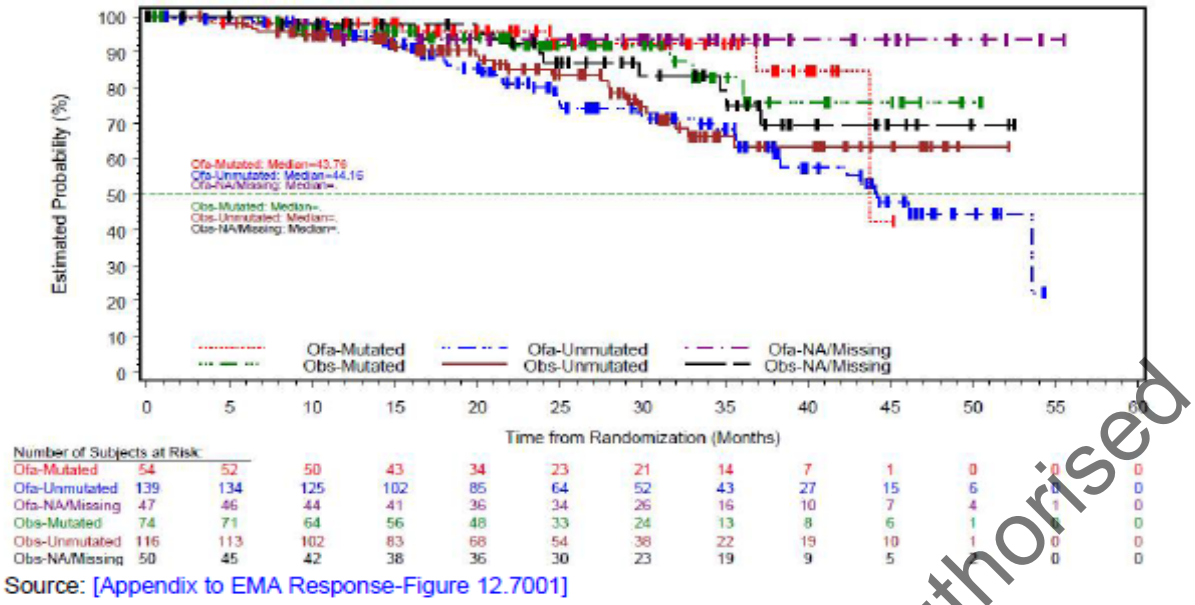
| | Efficacy update | |
|---|---|---|
| | OFA (N=240) | Obs (N=240) |
| **Subjects with Mutated IgVH** | **54 (23)** | **74 (31)** |
| Subject Classification, n (%) | | |
| Event | 5 (9) | 8 (11) |
| Death | 5 (9) | 8 (11) |
| Censored, last contact date | 49 (91) | 66 (89) |
| Estimates for OS (Months)[a] | | |
| 1st Quartile (95% CI) | 43.76 (36.86, NE) | NR (31.61, NE) |
| **Median (95% CI)** | **43.76 (43.76, NE)** | **NR** |
| 3rd Quartile (95% CI) | NR (43.76, NE) | NR |
| Adjusted HR Estimate (95% CI)[b] | 0.78 (0.26, 2.34) | |
| **Subjects with Unknown IgVH Status** | **47 (20)** | **50 (21)** |
| Subject Classification, n (%) | | |
| Event | 3 (6) | 9 (18) |
| Death | 3 (6) | 9 (18) |
| Censored, last contact date | 44 (94) | 41 (82) |
| Estimates for OS (Months)[a] | | |
| 1st Quartile (95% CI) | NR | 35.06 (23.75, NE) |
| **Median (95% CI)** | **NR** | **NR (37.16, NE)** |
| 3rd Quartile (95% CI) | NR (43.76, NE) | NR |
| Adjusted HR Estimate (95% CI)[b] | 0.53 (0.17, 1.71) | |
| **Subjects with UnMutated IgVH** | **139 (58)** | **116 (48)** |
| Subject Classification, n (%) | | |
| Event | 43 (31) | 25 (22) |
| Death | 43 (31) | 25 (22) |
| Censored, last contact date | 96 (69) | 91 (78) |
| Estimates for OS (Months)[a] | | |
| 1st Quartile (95% CI) | 24.07 (21.26, 35.68) | 29.73 (24.51, 35.55) |
| **Median (95% CI)** | **44.16 (37.98, NE)** | **NR (35.55, NE)** |
| 3rd Quartile (95% CI) | 53.55 (53.55, NE) | NR |
| Adjusted HR Estimate (95% CI)[b] | 1.16 (0.71, 1.88) | |

Source: [Appendix to EMA Response-Table 2.4412]

Abbreviations: CI=confidence interval; NE=not estimable; NR=Not reached

a. Confidence Intervals estimated using the Brookmeyer Crowley method.

b. Hazard ratios are obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with OFA maintenance compared with Obs.




Source: [Appendix to EMA Response-Figure 12.7001]

**Figure 14: Summary of Kaplan-Meier Estimates of Overall Survival by IgVH Mutational Status (ITT Population - Study OMB112517) – Update (Data cut-off 28 February 2015)**



*Time and Response to Next-Line Therapy*

**Table 22: Kaplan-Meier Estimates of Time to Next Therapy (ITT Population - Study OMB112517)**

| | OFA (N=238) | Obs (N=236) |
|---|---|---|
| Subject Classification, n (%)<br>Progression<br>Events (Anti-Cancer Therapy) | <br>74 (31)<br>62 (26) | <br>116 (49)<br>80 (34) |
| Median Time to Progression, months (95% CI)[a] | 29.44 (26.18, 34.17) | 16.59 (12.88, 20.63) |
| Median Time to Next Anti-Cancer Therapy, months (95% CI)[a, b] | 37.98 (28.29, NE) | 31.11 (21.62, NE) |
| Hazard Ratio Estimated[b] (95% CI)<br>Stratified Log-Rank P-Value | 0.66 (0.47, 0.92)<br>0.0108 | |

Abbreviations: CI=confidence interval; NE=not estimable.

a. Confidence intervals estimated using the Brookmeyer Crowley method.
b. Median for each treatment arm based on all subjects in that treatment arm from randomization to the date of receiving the next CLL treatment.
c. Hazard ratios (HRs) obtained using the Pike estimator. HR <1 indicates a lower risk with OFA maintenance compared with Obs.

**Table 23: Sensitivity Analyses of Time to Next Treatment (ITT Population - Study OMB112517)**

| | Original submission | |
|---|---|---|
| | OFA (N=238) | Obs (N=236) |
| **KM Estimate of TTNT for Subjects who Took NTX or Died** | | |
| Subject Classification, n (%) | | |
| Event | 74 (31) | 88 (37) |
| NTX | 62 (26) | 80 (34) |
| Death | 12 (5) | 8 (3) |
| Censored, last contact date | 164 (69) | 148 (63) |
| Median TTNT (Months) (95% CI) [a] | 35.42 (27.43,NE) | 24.94 (20.37,NE) |
| Adjusted HR Estimate [b] (95% CI) | 0.71 (0.52,0.97) | |
| Stratified Log-Rank P-Value | 0.0279 | |
| **KM Estimate of TTNT excluding Subjects who Took NTX without Progression** | | |
| Subject Classification, n (%) | | |
| Event | 43 (18) | 76 (32) |
| NTX | 43 (18) | 76 (32) |
| Censored, last contact date | 176 (74) | 156 (66) |
| Median TTNT (Months) (95% CI) [a] | NR (35.42,NE) | 31.11 (22.28,NE) |
| Adjusted HR Estimate [b] (95% CI) | 0.53 (0.37,0.75) | |
| Stratified Log-Rank P-Value | 0.0005 | |
| **KM Estimate of Time from Investigator-assessed PD to NTX for Subjects who Progressed and Took NTX** | | |
| Subject Classification, n (%) | | |
| Event | 43 (18) | 76 (32) |
| Progression and NTX | 43 (18) | 76 (32) |
| Median Time from investigator-assessed PD to NTX (Months) (95% CI) [a] | 2.66 (1.18,4.01) | 2.61 (2.14,3.68) |
| **KM Estimate of Time from Investigator-assessed PD To NTX for Subjects who Progressed** | | |
| Subject Classification, n (%) | | |
| Event | 43 (18) | 76 (32) |
| Progression and NTX | 43 (18) | 76 (32) |
| Censored, last contact date (Progression and no NTX) | 35 (15) | 44 (19) |
| Median Time from investigator-assessed PD to NTX (Months) (95% CI) [a] | 4.21 (2.99,7.10) | 4.27 (3.25,7.39) |

Source: [Appendix to EMA Response-Table 2.7002], [Appendix to EMA Response-Table 2.7004], [Appendix to EMA Response-Table 2.7007], [Appendix to EMA Response-Table 2.7015]

Abbreviations: TTNT=time to next treamtnet; NTX=Next Treatment; CI=confidence interval; NE=not estimable; NR=Not Reached

a. Confidence Intervals estimated using the Brookmeyer Crowley method.
b. Hazard ratios are obtained using the Pike estimator. A hazard ratio <1 indicates a lower risk with OFA maintenance compared with Obs.



*Post-Treatment Anti-Cancer Therapy*

**Table 24: Summary of Type of Follow-up Anti-Cancer Therapy (ITT Population - Study OMB112517)**

| | Ofatumumab (N=238) | Observation (N=236) | Total (N=474) |
|---|---|---|---|
| Any Anti-Cancer Therapy | | | |
| Yes | 61 (26%) | 81 (34%) | 142 (30%) |
| No | 177 (74%) | 155 (66%) | 332 (70%) |
| Type of Anti-Cancer Therapy | | | |
| BIOLOGIC THERAPY (ANTIBODIES, CYTOKINES) | 38 (16%) | 57 (24%) | 95 (20%) |
| CHEMOTHERAPY (CYTOTOXICS, NON-CYTOTOXICS) | 55 (23%) | 66 (28%) | 121 (26%) |
| HORMONAL THERAPY | 8 (3%) | 10 (4%) | 18 (4%) |
| IMMUNOTHERAPY | 14 (6%) | 7 (3%) | 21 (4%) |
| SMALL MOLECULE TARGETED THERAPY | 7 (3%) | 7 (3%) | 14 (3%) |
| UNKNOWN | 5 (2%) | 12 (5%) | 17 (4%) |
| Time from Study Treatment Discontinuation to Start of Subsequent Anti-Cancer Therapy (days) | | | |
| n | 58 | 80 | 138 |
| Min. | 5 | 1 | 1 |
| 1st Quartile | 91.0 | 16.5 | 50.0 |
| Median | 142.5 | 68.5 | 99.0 |
| 3rd Quartile | 195.0 | 156.5 | 189.0 |
| Max. | 534 | 596 | 596 |

**Table 25: Summary of Investigator-Assessed Kaplan-Meier Estimates of PFS after Next Line Therapy (ITT Population- Study OMB112517)**

| | Ofatumumab (N=74) | Observation (N=88) |
|---|---|---|
| Number of Subjects | | |
| Endpoint (event) | 14 (19%) | 15 (17%) |
| Censored, LAST ADEQUATE ASSESSMENT BEFORE DEATH | 20 (27%) | 19 (22%) |
| Censored, LAST CONTACT DATE | 40 (54%) | 54 (61%) |
| Event Summary | | |
| DEATH | 11 (15%) | 15 (17%) |
| PROGRESSION | 3 (4%) | 0 |
| Estimates for Progression-free Survival (Months) [1] | | |
| 1st Quartile | 36.76 | 32.79 |
| 95% CI | (14.13,) | (19.88,) |
| Median | | |
| 95% CI | (,) | (,) |
| 3rd Quartile | | |
| 95% CI | (,) | (,) |
| Hazard Ratio [2] | | |
| Estimate | 1.00 | |
| 95% CI | (0.48,2.07) | |
| Log-Rank P-Value | 0.9977 | |

The median PFS after next-line therapy has not yet been met.

**Exploratory Efficacy Results**

*B-Symptoms*

The majority of subjects (OFA maintenance: 94%, Obs: 94%) had no B-symptoms at baseline because subjects were required to be in remission at study entry. Up to the data cut-off date, most subjects continued to have no B-symptoms during the course of the study.

*Minimal Residual Disease*

Overall, 316 subjects were assessed for MRD at baseline (56/91 subjects in CR and 260/382 subjects in PR). Of 28 subjects in CR randomized to OFA maintenance with a baseline MRD sample, 39% (11 subjects) were MRD-negative at baseline and 42% (13 subjects) were MRD-negative at any visit.

*B Cell Monitoring*

**Table 26: Subjects with Complete and Near-Complete B Cell Depletion (ITT Population - Study OMB112517)**

| Visit, n/N (%) | Complete B cell Depletion | | Near-Complete B cell Depletion | |
|---|---|---|---|---|
| | OFA (N=238) | Obs (N=236) | OFA (N=238) | Obs (N=236) |
| Any Visit | 60/233 (26) | 25/234 (11) | 123/233 (53) | 93/234 (40) |
| Baseline | 15/222 (7) | 11/219 (5) | 63/222 (28) | 74/219 (34) |
| Cycle 2 Week 9 / Month 3 | 14/191 (7) | 9/163 (6) | 72/191 (38) | 51/163 (31) |
| Cycle 3 Week 17 / Month 5 | 13/176 (7) | 7/159 (4) | 74/176 (42) | 34/159 (21) |
| Cycle 4 Week 25 / Month 7 | 17/162 (10) | 3/141 (2) | 73/162 (45) | 20/141 (14) |
| Cycle 5 Week 33 / Month 9 | 13/151 (9) | 1/135 (<1) | 65/151 (43) | 8/135 (6) |
| Cycle 6 Week 41 / Month 11 | 14/133 (11) | 0/108 | 59/133 (44) | 6/108 (6) |
| Cycle 7 Week 49 / Month 13 | 15/126 (12) | 1/97 (1) | 53/126 (42) | 4/97 (4) |
| Cycle 8 Week 57 / Month 15 | 6/111 (5) | 0/83 | 45/111 (41) | 1/83 (1) |
| Cycle 9 Week 65 / Month 17 | 10/97 (10) | 0/62 | 41/97 (42) | 2/62 (3) |
| Cycle 10 Week 73 / Month 19 | 6/87 (7) | 0/59 | 40/87 (46) | 1/59 (2) |
| Cycle 11 Week 81 / Month 21 | 9/78 (12) | 0/56 | 29/78 (37) | 1/56 (2) |
| Cycle 12 Week 89 / Month 23 | 6/71 (8) | 0/42 | 30/71 (42) | 1/42 (2) |
| Cycle 13 Week 97 / Month25 | 8/60 (13) | 0/34 | 21/60 (35) | 0/34 |
| 3 Month Follow-up | 1/49 (2) | 0/24 | 15/49 (31) | 0/24 |
| 6 Month Follow-up | 4/36 (11) | 0/19 | 12/36 (33) | 1/19 (5) |
| 9 Month Follow-up | 0/26 | 0/11 | 6/26 (23) | 0/11 |
| 12 Month Follow-up | 1/16 (6) | 1/8 (13) | 3/16 (19) | 1/8 (13) |
| 15 Month Follow-up | 0/8 | 0/5 | 2/8 (25) | 0/5 |
| 18 Month Follow-up | 0/4 | 0/3 | 0/4 | 0/3 |
| 21 Month Follow-up | 0/3 | 0/1 | 0/3 | 0/1 |
| Withdrawal | 1/57 (2) | 0/69 | 8/57 (14) | 4/69 (6) |

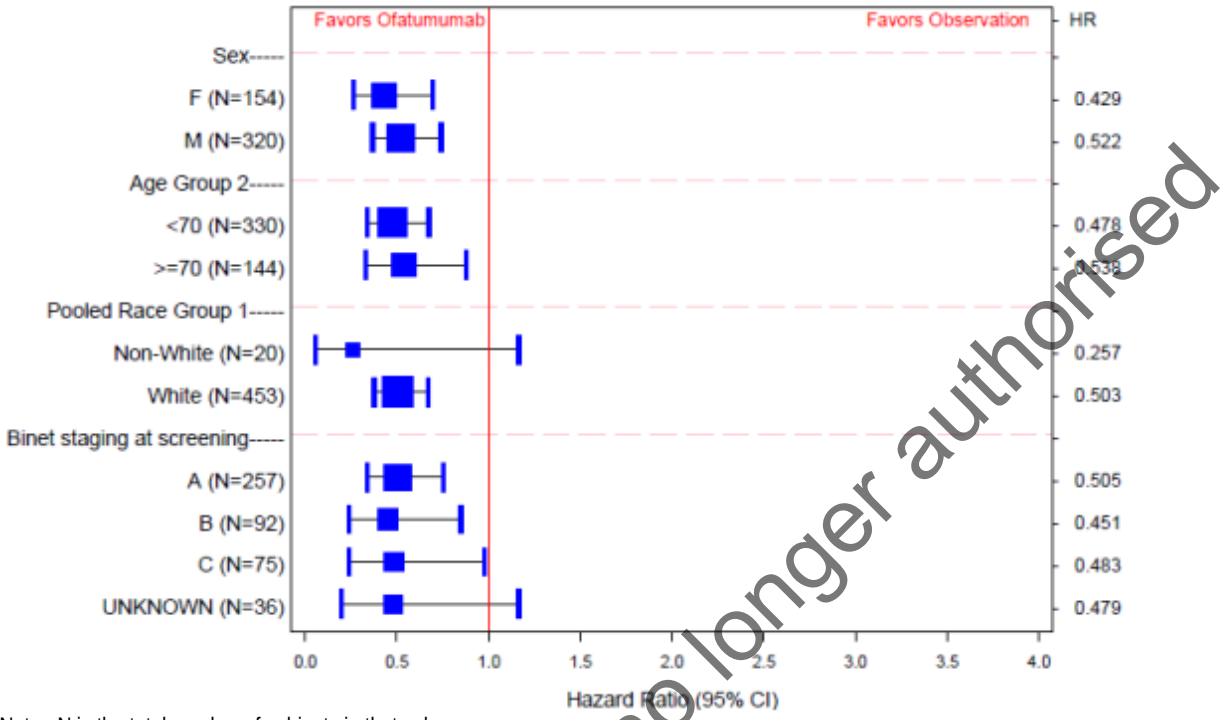
**Table 27: Median $CD5^+CD19^+$ Count Over Time (ITT Population - Study OMB112517)**

| Visit | OFA (N=238) | | Obs (N=236) | |
|---|---|---|---|---|
| | n | Median (cells/μL) | n | Median (cells/μL) |
| Baseline | 222 | 44.0 | 219 | 13.0 |
| Cycle 2 Week 9 / Month 3 | 191 | 4.0 | 163 | 29.0 |
| Cycle 3 Week 17 / Month 5 | 176 | 5.0 | 159 | 66.0 |
| Cycle 4 Week 25 / Month 7 | 162 | 5.0 | 141 | 100.0 |
| Cycle 5 Week 33 / Month 9 | 151 | 3.0 | 135 | 117.0 |
| Cycle 6 Week 41 / Month 11 | 133 | 3.0 | 108 | 107.5 |
| Cycle 7 Week 49 / Month 13 | 126 | 4.0 | 97 | 121.0 |
| Cycle 8 Week 57 / Month 15 | 111 | 4.0 | 83 | 102.0 |
| Cycle 9 Week 65 / Month 17 | 97 | 4.0 | 62 | 118.0 |
| Cycle 10 Week 73 / Month 19 | 87 | 4.0 | 59 | 188.0 |
| Cycle 11 Week 81 / Month 21 | 78 | 5.0 | 56 | 304.5 |
| Cycle 12 Week 89 / Month 23 | 71 | 10.0 | 42 | 398.0 |
| Cycle 13 Week 97 / Month 25 | 60 | 6.5 | 34 | 466.0 |
| 3 Month Follow-up | 49 | 46.0 | 24 | 595.5 |
| 6 Month Follow-up | 36 | 156.0 | 19 | 132.0 |
| 9 Month Follow-up | 26 | 115.0 | 11 | 114.0 |
| 12 Month Follow-up | 16 | 87.0 | 8 | 89.0 |
| 15 Month Follow-up | 8 | 206.5 | 5 | 146.0 |
| 18 Month Follow-up | 4 | 330.0 | 3 | 180.0 |
| 21 Month Follow-up | 3 | 1399.0 | 1 | 231.0 |
| Withdrawal (any time) | 57 | 882.0 | 69 | 6403.0 |

***Comparison of Results in Sub-Populations***

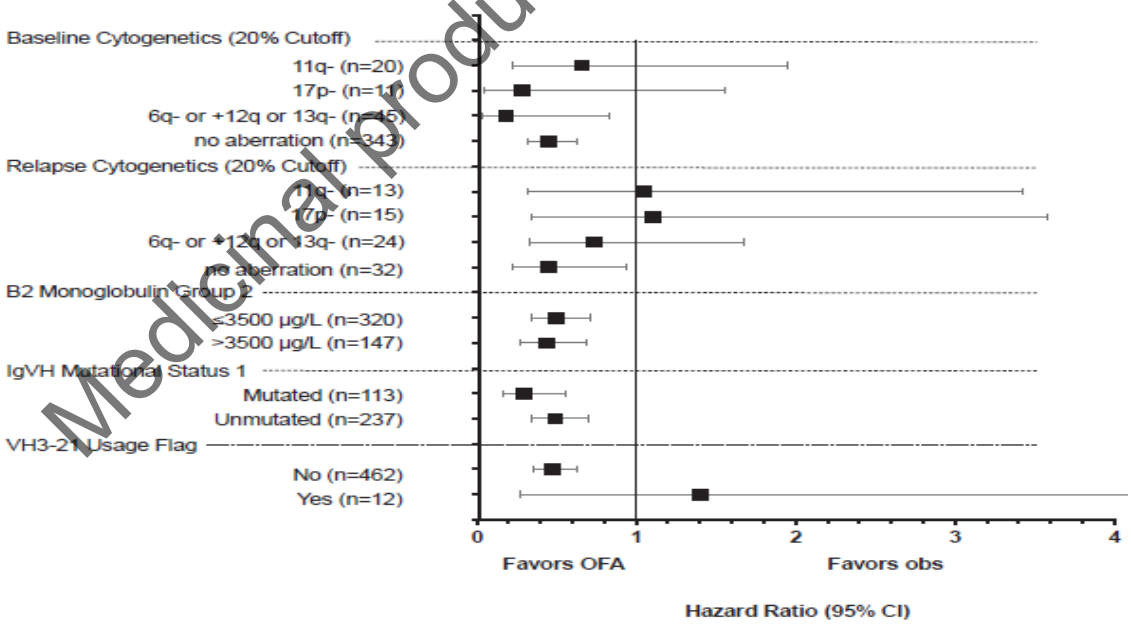
**Progression-Free Survival Subgroup Analysis**

*Investigator-Assessed PFS by Demographics and Prognostic Factors*



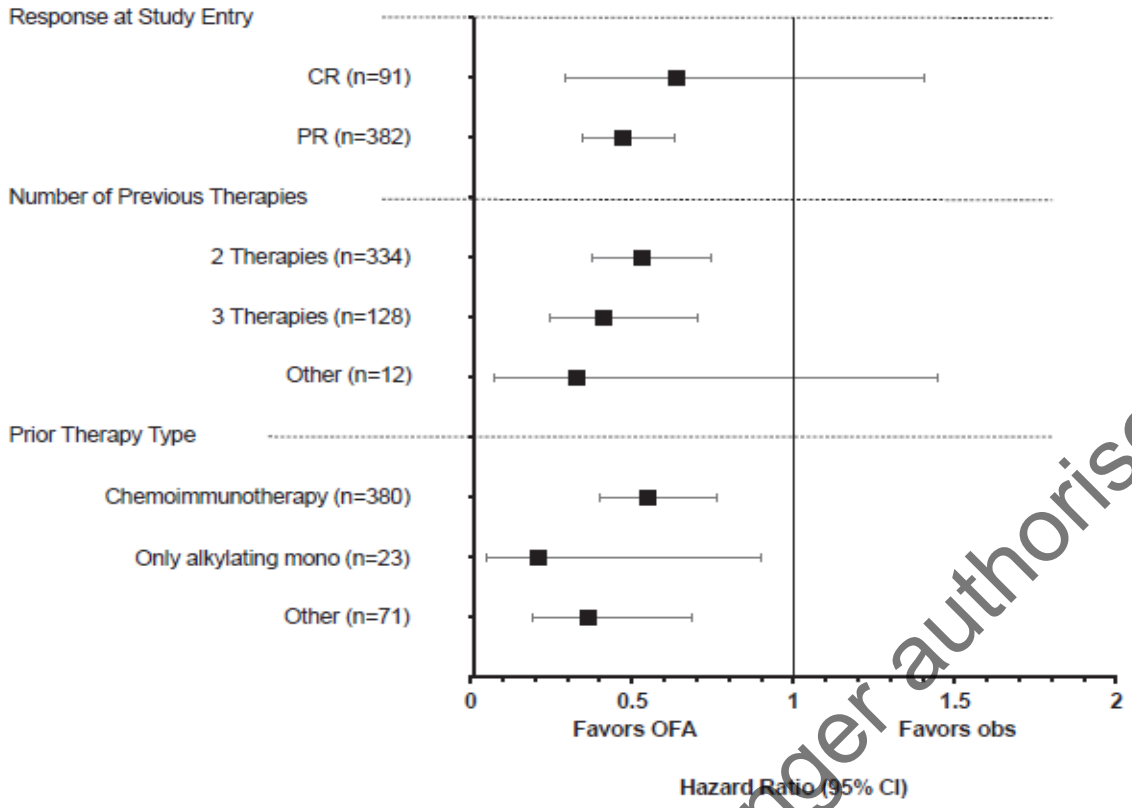

Note: N is the total number of subjects in that subgroup.
Abbreviations: CI=confidence interval; F=female; HR=hazard ratio; M=male; PFS=progression-free survival.

**Figure 15: Investigator-Assessed PFS by Demographics (ITT Population - Study OMB112517)**



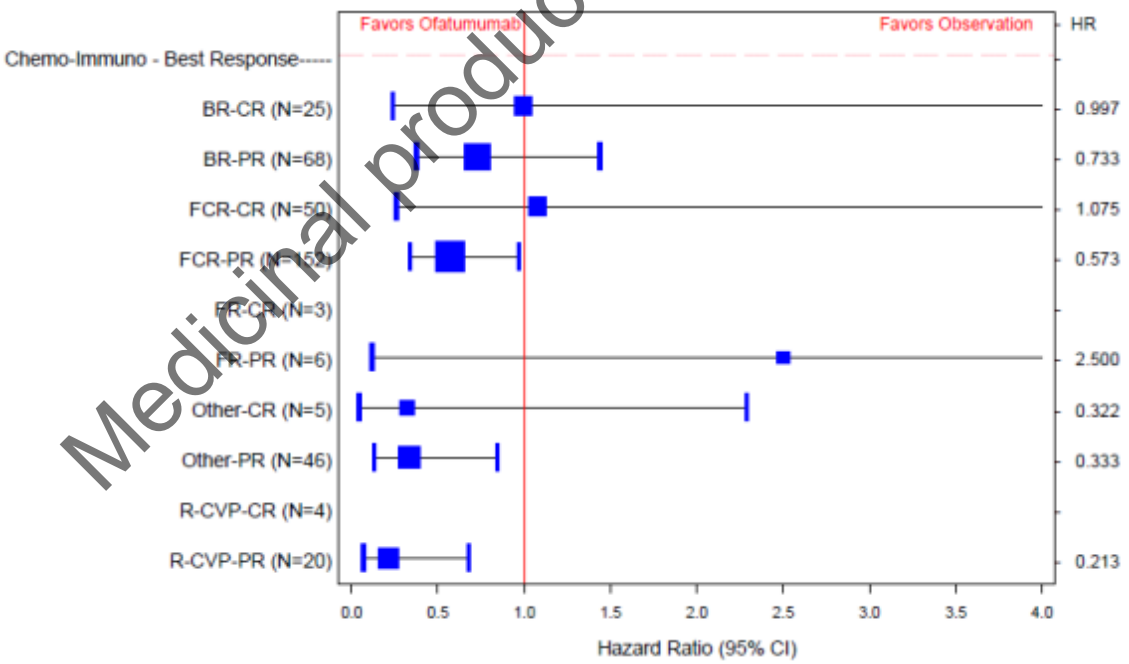

Note: n is the total number of subjects in that subgroup.
Abbreviations: CI=confidence interval; IGVH=immunoglobulin heavy chain variable region.

**Figure 16: Investigator-Assessed PFS by Baseline Prognostic Factors (ITT Population - Study OMB112517)Investigator-Assessed PFS by Stratification Factors**




Note: n is the total number of subjects in that subgroup.
Abbreviations: CR=complete response; PR=partial response; mono=monotherapy.

**Figure 17: Investigator-Assessed PFS by Stratification Factors (ITT Population - Study OMB112517)**




Note: N is the total number of subjects in that subgroup.
Abbreviation: BR=bendamustine and rituximab; CR=complete response, FCR=fludarabine, cyclophosphamide, rituximab; FR=fludarabine and rituximab; PR=partial response; R-CVP=rituximab, cyclophosphamide, vincristine, and prednisolone.

**Figure 18: Investigator-Assessed Kaplan-Meier Estimates of PFS by Most Recent Type of Prior Chemo immunotherapy and Best Response of CR or PR (ITT Population - Study OMB112517)**

*Patient Reported Outcome (PRO)*

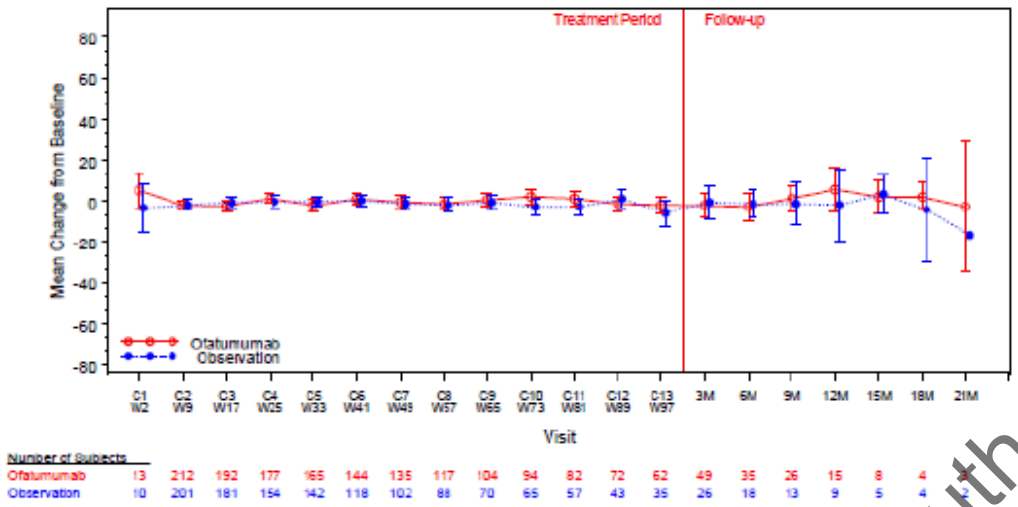



**Figure 19: Mean Change from Baseline of EORTC QLQ-CLL 30 with 95% CI – C30 Global Health Score / HRQoL (ITT Population - Study OMB112517)**



***Ancillary analyses***

Efficacy results in patients at high risk for relapse

To identify high risk patients, the following parameters were considered: duration of remission to first induction therapy, response to therapy prior to study entry, and the international Prognostic Index for patients with CLL (CLL-IPI).

The CLL-IPI has been proposed by Kutsch, et al (2015) because the clinical staging systems (Rai/Binet) do not accurately discriminate between prognostic groups given the availability of new and more effective treatments for CLL. While there are several new prognostic markers, there is no system that integrates the major clinical, biological and genetic variables into one widely accepted score. The authors performed a comprehensive meta-analysis of 26 prognostic factors to develop an internationally applicable prognostic index for CLL patients. The full analysis set (FAS) was collected from 8 phase 3 trials (3472 treatment–naive patients at early and advanced stage with a median age of 61 years (range 27 - 86) and a median observation time of 80 months. The FAS was randomly divided into training and internal validation datasets [TD, 2308 (67%); IVD, 1164 (33%)]. Methods of multivariable statistics were applied; the main endpoint was OS and the model was externally validated in a third dataset comprised of 845 newly diagnosed CLL patients from the Mayo Clinic with a median age of 62 years (range 25 - 89) and a median observation time of 63 months. Based on 1192 (52%) patients from the training dataset, five independent predictors for OS were identified:

- age;
- del(17p) and/or TP53 mutation;
- β2-microglobulin (B2M) level;
- clinical stage;
- Immunoglobulin Heavy Chain Variable Region Genes (IgHV) mutation status.

The scoring grid used to identify the risk groups is presented in Table 1-1.

- **Table -5 CLL-IPI Scoring grid**

| Variable | Adverse factor | Scoring |
|---|---|---|
| TP53 (17p) | Deleted and/or mutated | 4 |
| IgHV status | Unmutated | 2 |
| B2M, mg/L | >3.5 | 2 |
| Clinical stage | Binet B/C or Rai I-IV | 1 |
| Age | >65 | 1 |
| **Prognostic Score** | | **0-10** |

| Risk group | Prognostic Score |
|---|---|
| Low | 0-1 |
| Intermediate | 2-3 |
| High | 4-6 |
| Very high | 7-10 |

Each patient group had a significantly different OS [93%, 79%, 64% and 23% OS at 5 years for the low to very high risk group respectively, p <0.001; C-statistic c = 0.72 (95% CI, 0.69-0.76)].

Treatment recommendations based on CLL-IPI combining the most important genetic risk factors (*IgHV*, del(17p)/*TP53* mutation) with clinical stage, age and B2M levels suggest treating patients with High and Very High risk subgroups, hereafter referred to as High risk group.

Approximately 30% of patients are in the high risk group: 78 patients (33%) in the ofatumumab arm and 64 patients (26%) in the observation arm, respectively.

- **Table -6 Subgroups in the PROLONG study based on CLL-IPI**

| Risk subgroup | Ofatumumab N=240 | Observation N=240 | Total N=480 |
|---|---|---|---|
| Low | 63 (26) | 80 (33) | 143 (30) |
| Medium | 99 (41) | 96 (40) | 195 (41) |
| High | 72 (30) | 61 (25) | 133 (28) |
| Very high | 6 (3) | 3 (1) | 9 (2) |

***Subject disposition, median exposure, baseline characteristics***

***Subject Disposition and exposure***

The disposition of subjects in the High risk group is similar to that in the overall population (Table 1-3). The median treatment duration for High risk group subjects in the ofatumumab maintenance arm was 318.5 days (1 day to 815 days); 28% received at least 10 cycles of treatment.

- **Table 1-7 Treatment disposition and exposure to treatment**

| Phase/Status | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | OFA N=78 | Obs N=64 | OFA N=240 | Obs N=240 |
| **Treatment/Observation Phase Status, n (%)** | | | | |
| Ongoing | 10 (13) | 5 (8) | 31 (13) | 36 (15) |
| Completed [a] | 55 (71) | 56 (88) | 166 (69) | 187 (78) |
| Discontinued Treatment/Observation [b] | 13 (17) | 3 (5) | 43 (18) | 17 (7) |
| AE as primary reason for discontinuation | 9 (12) | 1 (2) | 26 (11) | 2 (<1) |
| **Exposure to ofatumumab** | **n=78** | | **n=239** | |
| Median duration (range) - days | 318.5 (1, 815) | NA | 486.0 (1, 867) | NA |

| Phase/Status | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | OFA N=78 | Obs N=64 | OFA N=240 | Obs N=240 |
| Total no. of infusions - % ≥ 10 cycles | 28% | NA | 46% | NA |

a. Subjects who completed treatment and entered follow-up phase, or subjects with PD/death
b. Subjects who withdrew from study drugs with reasons other than PD, death or consent withdrawal.

***Baseline characteristics***

The subjects in this group are representative of a high risk population; most baseline characteristics are balanced between arms (Table 1-5) with the exception of minimal residual disease (MRD) positivity and IgHV unmutated status, which both favour the observation arm. The patients in the High risk group are older patients (median age 71 year old; approximately 75% >65 years), with a majority in advanced Binet and Rai stages; in both arms, 78% of patients had B2M levels >3500 µg/L. MRD status showed positive MRD for 82% vs. 59% of patients in the ofatumumab and observation arms, respectively; unmutated IgHV status was present in for 90% vs. 83% of patients in the ofatumumab and observation arms, respectively.

Furthermore, analysis of duration of response to the first induction therapy (Table 1-4) shows that 68% of subjects in the high risk group have a short remission or an early relapse (<24 months), similar to the overall population (62%).

- **Table -8 Duration of response to first induction therapy**

| | High Risk Group | | | Overall population | | |
|---|---|---|---|---|---|---|
| | Ofa N=78 | Obs N=64 | Total N=142 | Ofa N=240 | Obs N=240 | Total N=480 |
| Long Remission (Duration ≥ 24 months) | 20 (26) | 24 (38) | 44 (31) | 87 (36) | 90 (38) | 177 (37) |
| Short Remission (Duration <24 months) | 57 (73) | 40 (62) | 97 (68) | 150 (63) | 149 (62) | 299 (62) |
| Missing Duration | 1 (<1) | 0 | 1 (<1) | 3 (1) | 1 (<1) | 4 (<1) |
| Total | 78 (100) | 64 (100) | 142 (100) | 240 (100) | 240 (100) | 480 (100) |

- **Table -9 Baseline Characteristics**

| | High/Very High Risk | | | Overall population | | |
|---|---|---|---|---|---|---|
| | Ofa N=78 | Obs N=64 | Total N=142 | Ofa N=240 | Obs N=240 | Total N=480 |
| Age | | | | | | |
| Median | 71.0 | 71.0 | 71.0 | 64.0 | 64.5 | 64.0 |
| Range | 39 - 86 | 39 - 87 | 39 - 87 | 33 - 86 | 39 - 87 | 33 - 87 |
| ≤ 65 | 21 (27) | 15 (23) | 36 (25) | 133 (55) | 134 (56) | 267 (56) |
| >65 | 57 (73) | 49 (77) | 106 (75) | 107 (45) | 106 (44) | 213 (44) |
| <70 | 36 (46) | 28 (44) | 64 (45) | 167 (70) | 166 (69) | 333 (69) |
| ≥ 70 | 42 (54) | 36 (56) | 78 (55) | 73 (30) | 74 (31) | 147 (31) |
| Gender | | | | | | |
| Male | 53 (68) | 40 (63) | 93 (65) | 161 (67) | 160 (67) | 321 (67) |
| Female | 25 (32) | 24 (38) | 49 (35) | 79 (33) | 80 (33) | 159 (33) |
| Rai Staging | | | | | | |
| Rai Stage 0 | 8 (10) | 9 (14) | 17 (12) | 69 (29) | 86 (36) | 155 (32) |
| Rai Stage I, II | 36 (46) | 24 (38) | 60 (42) | 81 (34) | 71 (30) | 152 (32) |
| Rai Stage III, IV | 19 (24) | 20 (31) | 39 (27) | 36 (15) | 38 (16) | 74 (15) |

| | High/Very High Risk | | | Overall population | | |
|---|---|---|---|---|---|---|
| | Ofa N=78 | Obs N=64 | Total N=142 | Ofa N=240 | Obs N=240 | Total N=480 |
| Binet Staging | | | | | | |
| Binet Stage A | 31 (40) | 22 (34) | 53 (37) | 124 (52) | 135 (56) | 259 (54) |
| Binet Stage B | 20 (26) | 15 (23) | 35 (25) | 55 (23) | 38 (16) | 93 (19) |
| Binet Stage C | 20 (26) | 22 (32) | 42 (30) | 33 (14) | 44 (18) | 77 (16) |
| Response to last CLL treatment | | | | | | |
| CR | 5 (6) | 7 (11) | 12 (8) | 46 (19) | 47 (20) | 93(19) |
| PR | 73 (94) | 57 (89) | 130 (92) | 194 (81) | 192 (80) | 386 (80) |
| MRD status | | | | | | |
| Negative | 3 (4) | 12 (19) | 15 (11) | 31 (13) | 42 (18) | 73 (15) |
| Positive | 64 (82) | 38 (59) | 102 (72) | 139 (58) | 108 (45) | 247 (51) |
| No. prior treatments | | | | | | |
| 2 | 51 (65) | 44 (69) | 95 (67) | 169 (70) | 168 (70) | 337 (70) |
| 3 | 26 (33) | 17 (27) | 43 (30) | 67 (28) | 63 (26) | 130 (27) |
| Other | 1 (1) | 3 (5) | 4 (3) | 4 (2) | 9 (4) | 13 (3) |
| Type of prior treatment | | | | | | |
| Chemoimmunotherapy | 62 (79) | 49 (77) | 111 (78) | 193 (80) | 193 (80) | 386 (80) |
| Only alkylating monotherapy | 6 (8) | 2 (3) | 8 (6) | 14 (6) | 9 (4) | 23 (5) |
| Other prior therapies | 10 (13) | 13 (20) | 23 (16) | 33 (14) | 38 (16) | 71 (15) |
| Baseline cytogenetics | | | | | | |
| 17p deletion | 7 (9) | 4 (6) | 11 (8) | 7 (3) | 4 (2) | 11 (2) |
| B2 microglobulin group | | | | | | |
| ≤ 3500 µg/L | 16 (21) | 14 (22) | 30 (21) | 157 (65) | 169 (70) | 326 (68) |
| >3500 µg/L | 61 (78) | 50 (78) | 111 (78) | 80 (33) | 68 (28) | 148 (31) |
| IgHV mutation status | | | | | | |
| Mutated | 6 (8) | 5 (8) | 11 (8) | 54 (23) | 74 (31) | 128 (27) |
| Unmutated | 70 (90) | 53 (83) | 123 (87) | 139 (58) | 116 (48) | 255 (53) |

***Clinical relevance of observed effects***

***Primary endpoint: PFS***

The median PFS in the ofatumumab arm was 23.23 months compared with 5.5 months in the observation arm and demonstrates that the patients in the High risk group derive more prolonged benefit from maintenance treatment with ofatumumab compared with observation (Figure 1-1). The HR was 0.47 (0.31, 0.71) with a statistically significant p-value of <0.0001.

- **Table -10 Kaplan-Meier estimates of PFS according to Investigator**

| | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | Ofatumumab N=78 | Observation N=64 | Ofatumumab N=240 | Observation N=240 |
| Number of Subjects Endpoint (event) | 42 (54) | 51 (80) | 87 (36) | 137 (57) |
| Median PFS in months (95% CI) | 23.23 (10.91, 30.95) | 5.55 (4.01, 9.59) | 32.85 (28.58, 38.08) | 16.76 (13.01, 22.28) |
| Adjusted Hazard Ratio (95% CI) | 0.47 (0.31, 0.71) | | 0.49 (0.37, 0.63) | |
| Stratified Log-Rank p-value | <0.0001 | | <0.0001 | |

- **Figure 1-1 Kaplan-Meier of PFS according to Investigator in High risk group**

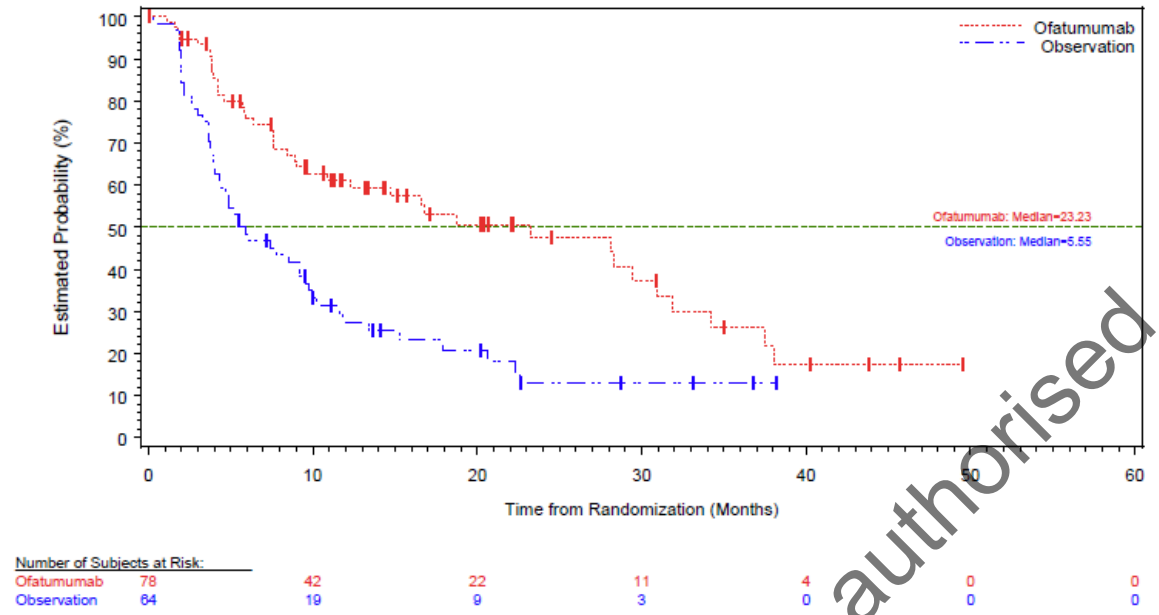
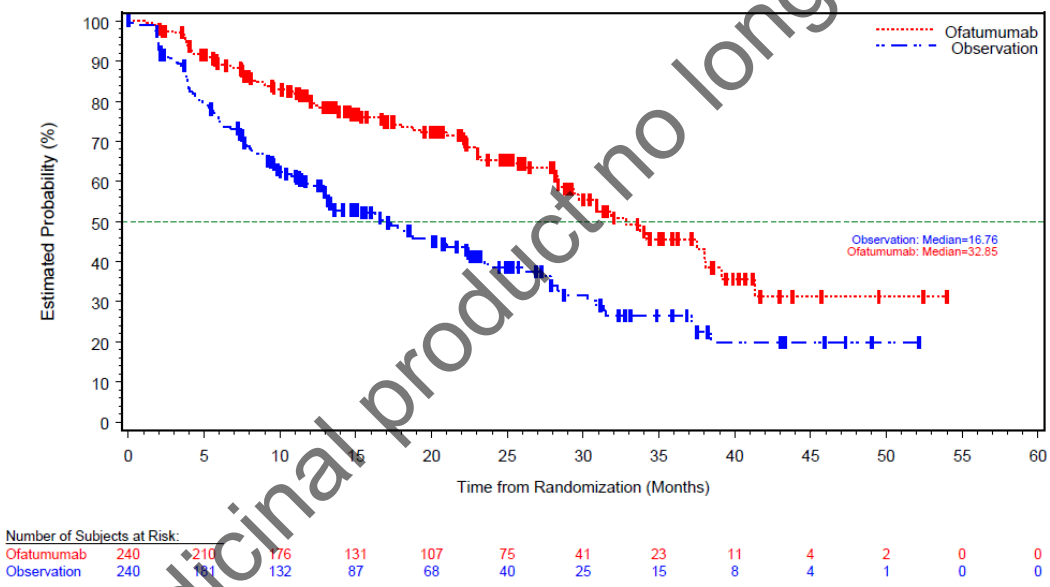



**Figure -2 Kaplan-Meier of PFS according to Investigator in Overall population**






***Robustness of PFS sensitivity analyses***

Three sensitivity analyses of the primary PFS endpoint for the High risk group were conducted: per Independent Review Committee (IRC) assessment, per Investigator assessment where CT scans were considered, and per IRC assessment where CT scans were considered (Table 1-7). The PFS by IRC is supportive of the primary endpoint with a median PFS of 23.23 months compared with 7.39 months in the observation arm. The HR was 0.55 (95% CI: 0.35, 0.85).

A shorter median PFS was observed when CT scans are considered, based on both investigator-assessed and IRC-assessed PFS. However, the PFS benefit still favours the ofatumumab arm with robustness demonstrated in HRs ranging from 0.55 to 0.67, similar to the PFS benefit observed in the overall population.

- **Table -11 PFS Sensitivity Analyses: CT scans and IRC assessment**

| | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=240** | **Observation N=240** |
| **PFS per Investigator where CT scans considered** | | | | |
| Median PFS in months (95% CI) | 12.29 (9.66,24.54) | 5.50 (4.01,9.23) | 28.09 (23.06, 29.70) | 13.17 (11.79, 17.35) |
| Adjusted Hazard Ratio (95% CI) | 0.56 (0.37,0.83) | | 0.58 (0.46, 0.74) | |
| Stratified Log-Rank p-value | 0.0010 | | <0.0001 | |
| **PFS per IRC** | | | | |
| Median PFS in months (95% CI) | 23.23 (9.23,35.58) | 7.39 (3.68,9.72) | 35.58 (29.70, NE) | 18.69 (13.01, 24.02) |
| Adjusted Hazard Ratio (95% CI) | 0.55 (0.35,0.85) | | 0.55 (0.42, 0.72) | |
| Stratified Log-Rank p-value | 0.0028 | | <0.0001 | |
| **PFS per IRC where CT scans considered** | | | | |
| Median PFS in months (95% CI) | 13.86 (11.27, 22.97) | 9.72 (6.54,13.44) | 28.91 (23.69, NE) | 19.81 (13.40, 23.26) |
| Adjusted HR (95% CI) | 0.67 (0.42, 1.06) | | 0.63 (0.48, 0.83) | |
| Stratified Log-Rank p-value | 0.0572 | | 0.0005 | |

***Secondary efficacy endpoint: overall survival***

As discussed previously, OS is difficult to demonstrate in patients with CLL with expected long survival post progression and with many next line therapies taken upon progression to confound the result. In addition, in this high risk group as in the general population of PROLONG, imbalance in several baseline prognostic factors put ofatumumab at a disadvantage, specifically, MRD status showed positive MRD for 82% vs. 59% of patients in the ofatumumab and observation arms, respectively; unmutated IgHV status was present in for 90% vs. 83% of patients in the ofatumumab and observation arms, respectively.

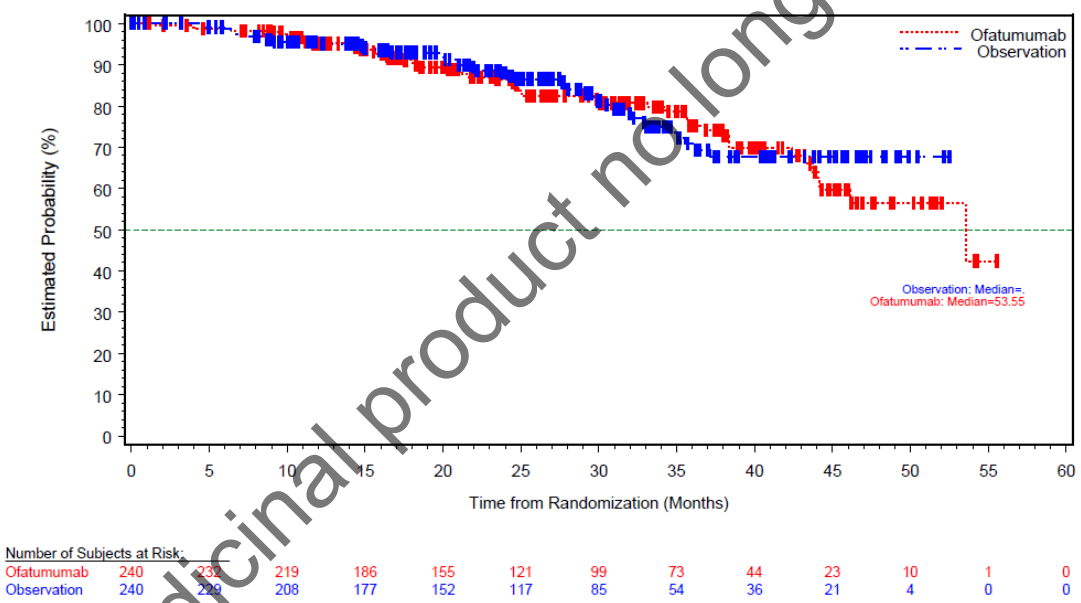
The OS analysis between the two randomised arms for the High risk group (Figure 1-3) showed that approximately 40% of the High risk patients had an event; the HR is 0.86 with 95% CI (0.51, 1.48).

- **Table -12 Kaplan-Meier estimates of OS**

| | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=240** | **Observation N=240** |
| Number of Subjects Endpoint (event) | 30 (38) | 25 (39) | 51 (21) | 42 (18) |
| Median OS in months (95% CI) | 43.76 (24.80, NE) | 34.66 (28.02, NE) | 53.55 (44.16, NE) | NR |
| Adjusted Hazard Ratio (95% CI) | 0.86 (0.51,1.48) | | 1.08 (0.72, 1.62) | |
| Stratified Log-Rank p-value | 0.5639 | | 0.7205 | |

- **Figure -3 Kaplan-Meier of Overall survival in High risk group**


- **Figure -4 Kaplan-Meier of Overall survival in Overall population**



***Secondary endpoint: Time to Next Therapy or Death***

The median time to next therapy or death favours ofatumumab with a prolongation of approximately 7 months. The Physician's decision to start next therapy likely considered all sources of evidence for progression, including CT scans. This may explain why the median Time to Next Therapy or Death (TTNToD) is shorter than the observed median PFS. However, the PFS sensitivity analysis taking into account CT scans shows concordant results between PFS and TTNToD.

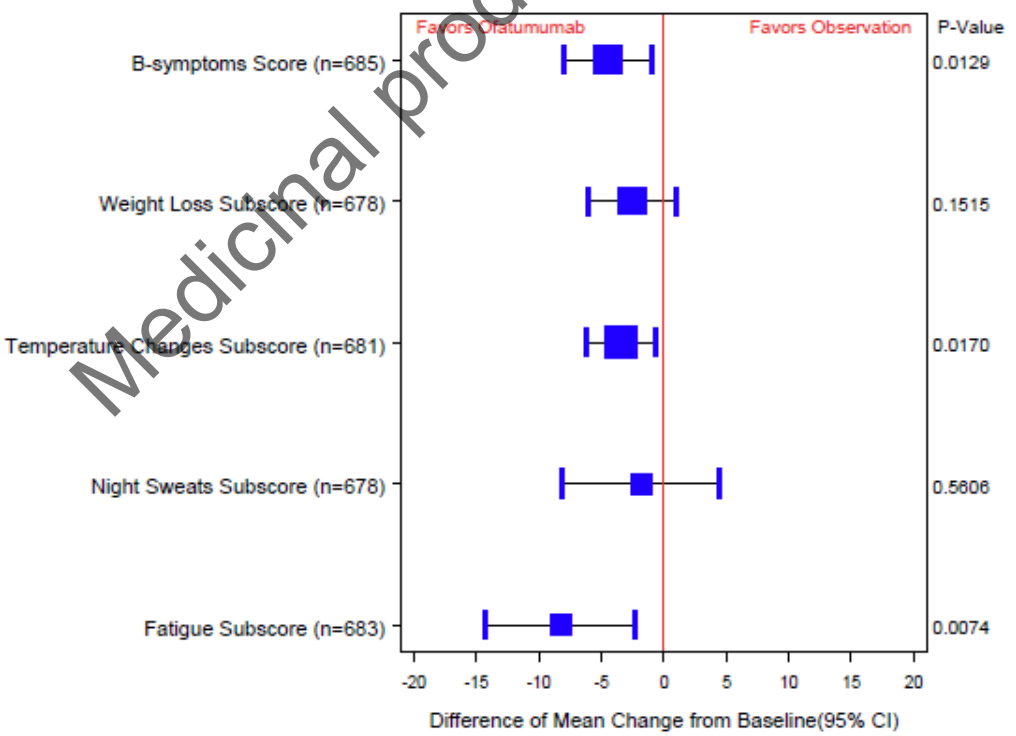
- **Table -13 Time to Next Therapy or Death**

| | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=240** | **Observation N=240** |
| Number of Subjects | | | | |
| Endpoint (event) | 45 (58) | 47 (73) | 101 (42) | 117 (49) |
| Censored, Last contact date | 33 (42) | 17 (27) | 139 (58) | 123 (51) |
| Event Summary | | | | |
| Anticancer therapy | 36 (46) | 43 (67) | 86 (36) | 107 (45) |
| Death | 9 (12) | 4 (6) | 15 (6) | 10 (4) |
| Median TTNToD in months (95% CI) | 18.83 (15.74, 29.67) | 11.50 (8.28, 13.86) | 36.07 (28.06, 41.40) | 26.25 (20.99, 31.57) |
| Adjusted HR (95% CI) | 0.54 (0.36, 0.83) | | 0.72 (0.55, 0.94) | |
| Stratified Log-Rank p-value | 0.0014 | | 0.0146 | |

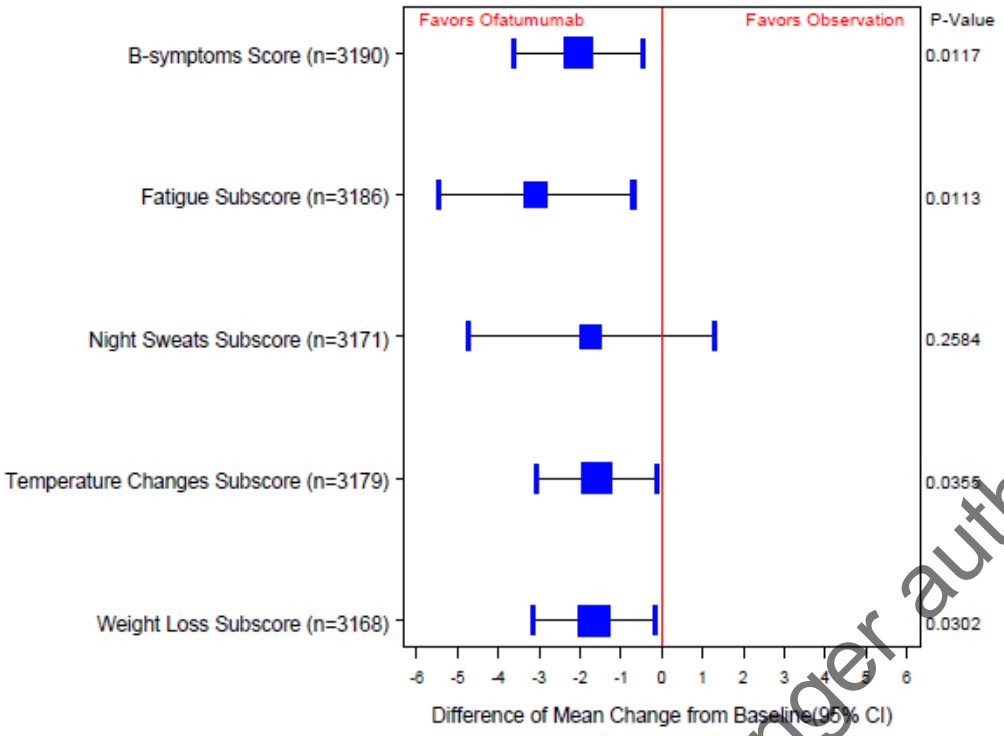
***Secondary endpoint: quality-of-life and patient-reported outcome data-Constitutional symptoms***

As for the overall population in Figure 1-6, constitutional symptoms in the High risk group (Figure 1-5) were maintained with ofatumumab therapy, including a clinically significant improvement for fatigue.

- **Figure -5 Constitutional symptoms in High risk group**



- **Figure -6 Constitutional symptoms in Overall population**




Even though the CLL-IPI guideline recommends treatment for the High risk group only in the presence of symptoms, we need to keep in mind that the recommendation is for treatment-naïve patients, and the recommended treatment is induction therapy. For patients receiving maintenance treatment in the PROLONG study, it is conceivable that all would have presented with an indication for treatment according to the IWCLL guidelines prior to their previous re-induction treatment. Subsequently, all subjects entered the trial in remission, therefore it was not expected that they would present with symptoms at baseline. As seen in Table 1-3, these subjects do not have a deep remission (>90% PR response to last treatment), the majority does not have MRD negative status (>70% positive), and has poor prognostic factors (78% with B2M >3500 µg/L, 87% with IgHV unmutated).

As expected in this patient population, there were not many subjects with B-symptoms at baseline in the High risk group (6% in both arms) or in the overall population. However, a trend of B-symptoms control favouring the ofatumumab arm is apparent (Table 1-10). This is evident for subjects who did not have B-symptoms at baseline and then became symptomatic during the treatment/observation period, in 10% of ofatumumab subjects and in 27% of observation subjects. Therefore, the benefit of receiving ofatumumab maintenance regarding B-symptoms control was clearly evident in the High risk group.



- **Table -14 Summary of shift from baseline in B-symptoms**

| Period | Baseline | Post-baseline | High Risk Group | | Overall population | |
|---|---|---|---|---|---|---|
| | | | Ofatumumab N=78 | Observation N=64 | Ofatumumab N=240 | Observation N=240 |
| Throughout Study | Present | Present | 4 (5) | 2 (3) | 11 (5) | 11 (5) |
| | | Absent | 1 (1) | 2 (3) | 4 (2) | 3 (1) |
| | | Not available | 0 | 0 | 0 | 1 (<1) |
| | Absent | Present | 14 (18) | 21 (33) | 45 (19) | 65 (27) |
| | | Absent | 59 (76) | 39 (61) | 179 (75) | 158 (66) |
| | | Not available | 0 | 0 | 1 (<1) | 2 (<1) |

| Period | Baseline | Post-baseline | High Risk Group | | Overall population | |
|---|---|---|---|---|---|---|
| | | | Ofatumumab N=78 | Observation N=64 | Ofatumumab N=240 | Observation N=240 |
| Throughout treatment period | Present | Present | 4 (5) | 2 (3) | 11 (5) | 11 (5) |
| | | Absent | 1 (1) | 2 (3) | 4 (2) | 3 (1) |
| | | Not available | 0 | 0 | 0 | 1 (<1) |
| | Absent | Present | 8 (10) | 17 (27) | 31 (13) | 53 (22) |
| | | Absent | 64 (82) | 43 (67) | 191 (80) | 169 (70) |
| | | Not available | 1 (1) | 0 | 3 (1) | 3 (1) |

***Secondary endpoint: PFS2 and ORR after next line therapy***

Approximately 40% of patients in the high risk group had an event. PFS2 analysis shows KM medians of 43.76 and 33.18 months, and an HR of 0.79 (95% CI: 0.47, 1.33) but not statistically significant.

The Overall Response Rate in the two arms in the high risk group is presented in table 16.

- **Table -15 PFS after next line of therapy**

| | High/Very High Risk | | Efficacy update | |
|---|---|---|---|---|
| | Ofatumumab N=78 | Observation N=64 | Ofatumumab N=240 | Observation N=240 |
| Number of Subjects | | | | |
| Endpoint (event) | 31 (40) | 28 (44) | 58 (24) | 52 (22) |
| Censored, Last contact date | 47 (60) | 36 (56) | 182 (76) | 188 (78) |
| Event Summary | | | | |
| Death | 28 (36) | 16 (25) | 42 (18) | 31 (13) |
| Progression | 3 (4) | 12 (19) | 16 (7) | 21 (9) |
| Median PFS in months (95% CI) | 43.76 (24.44, NR) | 33.18 (27.93, NR) | 53.55 (43.76, NE) | NE |
| Adjusted Hazard Ratio (95% CI) | 0.79 (0.47, 1.33) | | 0.98 (0.68, 1.43) | |
| Stratified Log-Rank p-value | 0.3577 | | 0.9261 | |

- **Table -16 Best Response of first next line of therapy**

| | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | Ofatumumab N=36 | Observation N=43 | Ofatumumab N=85 | Observation N=108 |
| Best response | | | | |
| CR/CRi/CR unconfirmed | 5 (14) | 3 (7) | 11 (13) | 11 (10) |
| PR | 10 (28) | 14 (33) | 26 (31) | 33 (31) |
| Stable Disease | 4 (11) | 11 (26) | 8 (9) | 14 (13) |
| Progression of Disease | 2 (6) | 4 (9) | 9 (11) | 10 (9) |
| Response rate | 15 (42) | 17 (40) | 37 (44) | 44 (41) |
| 95% CI | (26%, 59%) | (25%, 56%) | (33%, 55%) | (31%, 51%) |

***Summary of main study***

**Table 28: Summary of Efficacy for trial OMB112517 (PROLONG)**

| | | | |
|---|---|---|---|
| **Title:** Phase III trial in relapsed CLL of a monoclonal antibody ofatumumab maintenance therapy to delay progression vs. observation | | | |
| Study identifier | OMB112517, 2009-012518-39, NCT01039376, UTN U1111-1148-0253 | | |
| Design | A phase III, open label, randomized, 2-arm, multicenter study | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 2 years treatment phase followed by 5 year follow-up phase<br>NA<br>NA |
| Hypothesis | Superiority | | |
| Treatments groups | Ofatumumab maintenance | | Treatment: Ofatumumab N=238 |
| | Observation only | | Treatment: Observation N=236 |
| Endpoints and definitions | Primary endpoint | Progression-Free Survival (PFS) | Time from the date of randomization to the date of death or PD, whichever occurred first |
| | Secondary endpoint | Improvement in response | Percentage of subjects who changed from PR at baseline to CR during the study |
| | Secondary endpoint | Overall survival (OS) | The interval (in months) between the randomization date and date of death due to any cause |
| | Secondary endpoint | Time to next therapy for CLL | Time (in months) from randomization until next-line treatment |
| Database lock | 19 June 2014 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | ITT population | | |
| Descriptive statistics and estimate variability | Treatment group | Ofatumumab | Observation |
| | Number of subjects | 238 | 236 |
| | PFS (months) Median | 29.44 | 15.24 |
| | 95% CI | 26.18, 34.17 | 11.79, 18.76 |
| | Treatment group | Ofatumumab | Observation |
| | Number of subjects | 193 | 189 |
| | Improvement in Response from baseline N (%) | 11 (6) | 2 (1) |
| | Treatment group | Ofatumumab | Observation |
| | Number of subjects | 238 | 236 |
| | OS (months) Median | Not reached yet | Not reached yet |
| | Treatment group | Ofatumumab | Observation |
| | Number of subjects | 238 | 236 |
| | Time to Next Therapy (months) Median | 37.98 | 31.11 |

| | | | |
|---|---|---|---|
| | 95% CI | 28.29, NE | 21.62, NE |
| Effect estimate per comparison | Primary Endpoint: PFS | Comparison groups | Ofatumumab vs observation |
| | | Hazard Ratio | 0.50 |
| | | (95% CI) | 0.38, 0.66 |
| | | P-value (Stratified log-rank test) | <0.0001 |
| Effect estimate per comparison | Secondary Endpoint Improvement in Response from baseline | Comparison groups | Ofatumumab vs observation |
| | | Hazard Ratio | |
| | | (95% CI) | |
| | | P-value (Stratified log-rank test) | |
| | Secondary Endpoint OS | Comparison groups | Ofatumumab vs observation |
| | | Hazard Ratio | 0.85 |
| | | 95% CI | 0.52, 1,37 |
| | | P-value (Stratified log-rank test) | 0.4877 |
| | Secondary Endpoint Time to Next Therapy | Comparison groups | Ofatumumab vs observation |
| | | Hazard Ratio | 0.66 |
| | | (95% CI) | 0.47, 0.92 |
| | | P-value (Log-rank test) | 0.0108 |
| Notes | Stratification factors: CR or PR at study entry ; Number of previous induction treatments; Type of prior treatment: chemo immunotherapy, only alkylating monotherapy, or other treatment | | |

## 2.5.3. Discussion on clinical efficacy

**Design and conduct of clinical studies**

To support the request, the applicant submitted efficacy data from an interim analysis of one single clinical trial, OMB112517 (PROLONG). The OMB112517 trial was a Phase III, open-label, randomised, multi-centre trial of ofatumumab (OFA) maintenance treatment versus no further treatment in subjects with relapsed CLL who have responded to induction therapy (n=474). Of note, patients that were resistant to fludarabine were excluded from the trial.

The choice of "no treatment" as comparator was accepted by the SAWP (2009). In fact, even in the current, expanding treatment landscape (with the introduction of protein kinase inhibitors), "no-treatment" might still be the most relevant option for patients in the intervals between relapses and induction therapies. In this particular disease, where initiation of treatment upon relapse is rather individual and to a large extent dependent on symptoms, the patient might experience "loss of chance" by being treated with the maintenance agent when a symptomatic relapse arise at a later stage.

To avoid bias introduced by the open-label design of the study, an independent review committee (IRC) and an independent data monitoring committee (IDMC) was used. Still, the investigators' judgement might have been influenced and biased by knowing the patients maintenance treatment/no-maintenance treatment status.

The primary endpoint is PFS as assessed by the investigator. The choice of primary endpoint was thoroughly discussed by the SAWP in an advice given in 2009. According to guidelines, PFS is an acceptable primary endpoint, as long as OS is reported as a secondary endpoint in situations where there is a long expected survival after progression and/or further lines of treatment with effect on OS may hamper the detection of a relevant treatment effect on OS. However, in the setting of maintenance treatment this might be different. Relapse on treatment with ofatumumab signifies resistance to the experimental agent and is likely to be predictive of reduced activity of rituximab. It may be predictive of reduced activity also of pharmacologically non-related medicinal products. Events on therapy in the experimental arm are thus likely to have a different meaning to those in the control arm.

PFS was accepted as primary endpoint by the SAWP, but it should be supported by OS and other endpoints, in particular "time to need for next line therapy or death" and PFS2. In the present trial, to achieve interpretable survival data according to the SAWP advice, the sample size is not considered sufficient to provide robust interpretable OS data. Altogether 666 evaluable patients would have been needed to reach a power of 80% with a study duration of more than 7 years at an event rate of 382. The SAWP advised against performing a second IA, but if to be performed, not until 2/3 events had occurred. The company chose a follow-up period of 5 yrs. Yet, the study was prematurely terminated based on the results from the 2nd pre-planned IA, based on PFS. In addition, enrolment was stopped (Amendment 5 of the study protocol) and fewer (474 instead of 532) patients than planned were included in the study. Consequently, the assessment of OS will be nearly un-informative due to an unacceptably low power to detect a meaningful survival difference. The study protocol included no stopping rule for efficacy; therefore at the time point of the 2nd IA the IDMC reported a significant difference for PFS and advised to continue the study as planned under the assumption that this would not result in stopping of enrolment. The protocol amendment which resulted in the cessation of enrolment (Amendment 5) was not in place before two months after these results were reported to the company but before the database lock. This gives raise to uncertainties related to the statistical robustness of the trial.

However, recruitment was slower than expected, events accumulated faster than expected, the number for the pre-specified IA was reached before full enrolment, the IA showed a greater than assumed treatment effect, and thus the MAH considered that it would be unethical to enrol further subjects.

The Applicant following the SAG recommendation (see section below), provided data from a subgroup of patients defined as high risk and very high risk patients according to the international Prognostic Index for patients with CLL (CLL-IPI) as proposed by Kutsch, et al (2015). The CLL-IPI system is based on a comprehensive meta-analysis of 26 prognostic factors to develop an internationally applicable prognostic index for CLL patients. Data were collected from treatment–naive patients and by methods of multivariable statistics, five independent predictors for OS were identified; age, del(17p) and/or TP53 mutation, β2-microglobulin (B2M) level, clinical stage and IgHV mutation status. The model was externally validated in a third dataset comprised of 845 newly diagnosed CLL patients from the Mayo Clinic. Based on an algorithm, patients were grouped into low, intermediate, high and very high risk, and recommendations for initiating induction therapy was made. The CLL-IPI system is new and it remains to be seen to what degree it will be taken into clinical use and further validated. However, this definition of a higher risk group seems relevant with the present knowledge of prognostic factors in CLL.

**Efficacy data and additional analyses**

A statistically significant improvement in the investigator-assessed PFS was observed for the ofatumumab maintenance arm compared with the Obs arm, HR 0.50, $p<0.0001$; with a median PFS of 29.44 months in the ofatumumab maintenance arm compared with 15.24 months in the Obs arm. However, the efficacy data supporting the present application are based on the pre-defined interim analysis of efficacy and safety performed by the IDMC. Updated PFS analysis continues to support the primary findings.

The median OS has not been reached in any arm. Due to the nature of the disease and the short median follow-up time of only 19.1 month, this is not unexpected. Since enrolment has stopped, up-dated survival data will be based on the same number of patients as this 2nd IA.

OS data remain immature even with the 8 months update, with only 19.4% of patient deaths reported across the two arms. Of the 480 patients constituting the Safety Population, 51 patients (21.3%) and 42 patients (17.4%) from the ofatumumab and observation groups, respectively, died. The OS data may have been confounded by some imbalances favouring the observation group,

Another key secondary endpoint is time to start of next treatment. The difference in median PFS (ofatumumab 29.44 mo, Obs 15.24 mo, gain 14.2 mo) was not translated into a subsequently longer median "time to next anti-cancer therapy" (TTNT) (ofatumumab 37.98 mo, Obs 31.11 mo, gain 6.9 mo). The MAH was asked discuss whether these findings can be explained by bias caused by the open-label design of the study or whether maintenance treatment with ofatumumab might have led to more aggressive tumors. The MAH has provided an analysis showing that TTNT was confounded by several factors: 1) in the PFS analysis death is considered an event, while in the TTNT analysis death is censored, 2) a sensitivity analysis incorporating death as an event in TTNT analysis showed that TTNT was postponed by 10.5 months in favour of the OFA arm (35.4 months ofatumumab vs. 24.9 months Observation), 3) TTNT seems to also be influenced by clinical practice. Some investigators gave next treatment without any evidence of progression of disease. This occurred much more often in the ofatumumab arm than in the Obs arm. Sensitivity analyses in the overall population show that TTNT is delayed by more than 10 months in favour of the ofatumumab arm, therefore part of the discrepancy in the gains of the variables PFS and TTNT can be explained by differences in statistical handling. However, the estimates appear to be influenced by differences in clinical practice (and could at least partly be in violation of the study protocol) and the question of investigator bias in this open label trial cannot be completely ruled out.

Data from other secondary endpoints as PFS2 and B-cell monitoring are too immature at present to add any support to the PFS result. Data on changes in MRD status are also based on few patients and results should be interpreted with caution.

No detrimental effect was shown by the PRO data, nor could the opposite be concluded due to the open-label design of the study.

Applying the CLL-IPI scoring algorithm to the PROLONG study showed that approximately 30% of patients were in the high or very high risk group (hereafter defined as a "high risk" group); 78 patients (33%) in the ofatumumab arm and 64 patients (26%) in the observation arm, respectively. The vast majority of the patients included in this "high risk" group were in the high risk category, and only 2 % in the very high risk. The Applicant also looked into duration of response to the first induction therapy, which did not differ to a large extent from the overall population, as 68% of patients in the "high risk" group had a short remission or an early relapse (<24 months) versus 62% in the overall population.

Since, this newly identified "high risk" group constitutes a post-hoc defined subgroup, imbalances between arms are to be expected. This increases the chance that any uncertainties related to the statistical analysis in the overall population, will be further accentuated in this subgroup.

In the new subgroup defined as "high risk", the median PFS in the ofatumumab arm was 23.2 months compared with 5.5 months in the observation arm (HR 0.47 [0.31, 0.71], p-value <0.0001). The sensitivity analyses of PFS by IRC is supportive of the primary endpoint (median 23.2 months OFA vs. 7.4 months Obs, HR 0.55 [95% CI: 0.35, 0.85]). A significantly shorter median PFS was observed when CT scans were considered, based on both investigator-assessed and IRC-assessed PFS, but with HRs ranging from 0.55 to 0.67. In the OS analysis approximately 40% of the patients in the subgroup had an event,

but also in this subgroup, no differences in OS can be seen (HR 0.86 [0.51, 1.48]). The OS data are still regarded as immature.

The median TTNToD showed a prolongation of approximately 7 months with ofatumumab treatment (median months OFA 18.8 vs. 11.5 Obs, HR 0.54 [0.36, 0.83]). The PFS2 was analysed as suggested by the CHMP, taking all progressions and all deaths into consideration, ignoring censoring rules due to large gap between observed event and last adequate tumour assessment. With approximately 40% events, mainly deaths, the numbers are still immature, KM medians are 43.8 and 33.2 months (HR 0.79 [95% CI: 0.47, 1.33]).

The ORR after next line therapy is comparable between arms, but also here data are still immature and no firm conclusions can be drawn.

In the "high risk" group, 6% in both arms had B-symptoms at baseline. The number of patients who did not have B-symptoms at baseline and then became symptomatic during the treatment/observation period was 10% in OFA arm and 27% in the obs arm.



**Additional expert consultation**

The SAG-Oncology was consulted in April 2016 on the following questions:

- Please discuss the rationale and potential added value of a maintenance treatment regimen like the currently proposed regimen with ofatumumab compared to "watchful waiting" in patients with CLL in the present treatment landscape.

The SAG considered unanimously that there are major concerns about the rationale and potential added value of the proposed extra line of ("maintenance") treatment regimen for ofatumumab.

Theoretically, a rationale for maintenance therapy with the aim of shifting MRD-positive responses to MRD-negative responses and delaying progression instead of watchful waiting might be justifiable in patients at high risk of symptomatic progression or death or for a treatment with a very good safety profile. However, the population in the PROLONG trial appeared to include primarily good prognosis patients as shown in the long duration of survival in both treatment groups. In a good prognosis population without symptomatic disease, the toxicity profile of ofatumumab, in particular grade 3 or 4 neutropenia and infections, is of concern. Whether a subgroup of patients at high risk of symptomatic progression or death exists for whom maintenance treatment with ofatumumab might be a useful option has not been established.

Concerning the added value of maintenance treatment, only an effect on PFS has been observed. However, the clinical relevance of this effect is doubtful because progression is often asymptomatic and can be managed with acceptable (including recently approved) treatment options that are fairly well tolerated. Thus, treatment-free periods associated with watchful waiting and avoiding severe and life-threatening toxicity are considered more clinically important rather than delaying progression. In the absence of an effect on OS or HRQoL, the maintenance regimen proposed cannot be considered to be clinically justified. This is in line with EMA scientific advice that had recommended OS as the primary endpoint for the study.

Given the heterogeneity of CLL, it may be of interest to characterise the prognosis of the studied population, including molecular characterisation at study entry, response to previous therapy and response duration and explore the effect of ofatumumab in higher risk patients.

- Does the improvement in PFS of approximately 16 months in CLL maintenance setting indicate clinical benefit, when seen in light of the results of the analyses of OS and HRQoL?

The difference in PFS is highly statistically significant but its clinical significance is questionable (see answer to question no. 1). The available analyses do not allow establishing a group of patients for whom delaying progression with maintenance treatment with ofatumumab is a clinical benefit compared to watchful waiting. There was no effect on OS and the differences observed in terms of HRQoL cannot be considered clinically significant.

- Is the safety profile of the proposed maintenance treatment regimen acceptable for the intended patient population, also taking into account that not all patients will benefit from this regimen?

The toxicity profile of ofatumumab, in particular grade 3 or 4 neutropenia and infections, is of concern in this maintenance setting (asymptomatic disease) in which watchful waiting is the standard of care. Given the long duration of survival for some patients, long-term toxicity would also need to be assessed. In the absence of a clear effect in terms of OS or quality of life, the balance of benefits and harms is negative.

- Please discuss the clinical value of PFS2 and time-to-next-therapy (TTNT) in the maintenance setting for the intended patient population and the need for further data on these endpoints.

In theory, PFS2 has some interest particularly in situations where data on OS are impractical to collect. Concerning the PFS2 analyses presented, depending on the different censuring rules, the effect on PFS2 varied widely (HR from 0.7 to 1). However, PFS2 in this setting is difficult to measure and interpret considering the heterogeneity of treatments used and the lack of information on prior therapies and the quality and duration of response to prior therapies as these have a significant influence on PFS2. An effect on PFS2 has not been shown conclusively.

Concerning TTNT, this cannot be considered of clinical importance in view of the toxicity profile and the availability of subsequent treatments. In addition, the potential bias in determining start of next-line therapy in the observation group is difficult to assess (many patients in the observation arm started therapy before evidence of disease progression).

Following advice from the SAG-O a high –risk for relapse patient population was identified as per the Prognostic factors of age; del(17p); Tp53 mutation; beta2-microglobulin level; clinical stage (Binet or Rai); IgVH mutation status in accordance with the CLL-IPI prognostic index (The International CLL-IPI working group, Lancet 2016). In this subgroup PFS was 23.2 with ofatumumab vs 5.6 months with observation (HR=0.47, p<0.0001) and the OS was 43.8 vs 34.7 months (HR=0.86, p=0.5639).

Following assessment of responses and definition of a population at high risk of relapse, the SAG-O was asked for a follow up consultation:

1. Is the improvement in PFS by 17.6 months (23.2 vs. 5.6) of clinical relevance in patients with CLL at high-risk of relapse based on genetic, biological and clinical criteria (CLL-IPI prognostic index). Please discuss this question in relation of:
a) the overall population taking into account the same HRs, but shorter period of time of progression in the high risk control group (5.6 months):

In terms of magnitude, the improvement in PFS for this high-risk (HR) without 17p deletion, is substantial (about 1.5 years difference in medians).

However, the relevance of PFS as a clinically relevant endpoint is questioned. This is due to the indolent nature of the disease and the availability of acceptable further treatments. Thus, progression (as defined) is not expected to result in significant deterioration or symptoms or quality of life so that the clinical relevance of this endpoint is questioned.

Indeed, if CT scans are considered in the definition of progression, the magnitude of improvement is much smaller (about 4 months difference in medians). Thus, the activity of ofatumumab seems to affect predominantly circulating leukaemia cells rather than lymph nodes.

Lastly, there are no data in cytogenetic high-risk patients ( e.g p53, del 17p which respond worse to treatment).

b) the clinical benefit in terms of improvement in time to next therapy (TNT) or death and PFS2:

It is possible that TNT reflects symptomatic progression and in fact agrees with the PFS taking into account CTScans. Again, although TNT favors the ofatumumab group, the magnitude of improvement is much smaller compared to PFS as defined in the protocol. In addition, the interpretation of this endpoint is difficult since TNT may reflect different practices, may be less objective than PFS, and may be influenced by availability of subsequent treatments. Thus, the results in terms of TNT are not sufficient to establish a clinically relevant benefit for ofatumumab.

Similarly, although there are no specific concerns about the PFS2 results in terms of a possible detrimental effect of ofatumumab treatment on subsequent treatments, the PFS2 results are not sufficient to establish a clinically relevant benefit in terms of post-progression survival.

c) the results of the analysis of OS in the high-risk subgroup (data not mature yet).

There is no clear effect on OS and the survival. It is unlikely that longer follow-up will reveal small differences in view of subsequent treatments that can affect overall survival. Also, a theoretical risk that ofatumumab maintenance could delay subsequent effective treatments cannot be ruled out (although a dramatic effect seems unlikely based on the current data).

d) the analysis of HRQoL:

The differences observed in terms of HRQoL are of small magnitude and below the conventional thresholds for clinical significance. Indeed many patients that entered into the study were asymptomatic, except for the presence of B symptoms in a relatively high proportion of patients. However, B symptoms are expected to quickly disappear in patients with PR or VGPR.

e) the observed difference with regard to serious and fatal infection events.

In principle, the observed difference with regard to serious and fatal infection events would be acceptable if a clearly relevant clinical benefit could be established in terms of OS. However, this is not the case and therefore the observed toxicity cannot be considered acceptable.

In addition, there is a signal of delayed fatal infections (after the treatment phase) that should be considered, possibly due to prolonged immunosuppression, depletion of CD20 B cells and increased risk of fatal infections in patients receiving subsequent therapies.

2. Is the safety profile of the proposed maintenance treatment regimen acceptable for the identified population at high-risk of relapse?

In principle, the observed safety profile is considered acceptable if a clearly relevant clinical benefit could be established in terms of OS. However, this is not the case and therefore the observed toxicity cannot be considered acceptable.

Conclusion

"Consolidation/maintenance" is a field of active research (many trials are underway) although combination treatments may be more relevant to address patients at very high-risk of progression.

The SAG considers that there is insufficient evidence of a clinically relevant benefit for ofatumumab maintenance treatment in the proposed HR population.

The CLL-IPI scoring system was devised for treatment naïve patients and their value on previously treated patients already in PR or CR is not well established. The impact of this IPI system was on OS but not on PFS. Furthermore, the current recommendations for patients of high risk is to treat if only are symptomatic. Lastly, the number of patients included in patients with TP53 deletion or mutation, which are considered at high-risk and respond poorly to conventional treatments, is very small.

In conclusion, the concerns as already expressed in the previous SAG conclusions still apply to the HR subgroup.

### 2.5.4. Conclusions on the clinical efficacy

A statistically significant improvement in the primary endpoint, investigator-assessed PFS, was observed for the ofatumumab maintenance arm compared with Obs arm. However, in the setting of maintenance treatment in CLL, PFS has weaknesses as a primary endpoint and needs support from secondary endpoints. The latter could not be robustly shown in the present data.

At present, no mature OS data are available, thus a clinically relevant benefit cannot be concluded.

## *2.6. Clinical safety*

**Introduction**

The safety profile of ofatumumab has been defined based on 2603 oncology patients including 1555 patients with CLL receiving OFA in clinical trials (through December 2014).

The evaluation of clinical safety in this application is based on data from the PROLONG study (study OMB112517), a Phase III, open-label, randomized, multicentre trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed CLL who were in complete or partial response after induction therapy. Observation is the current standard of care to manage subjects with relapsed CLL who respond to induction treatment. A total of 237 subjects were exposed to OFA treatment in this pivotal study.

Data were collected from 06 May 2010 (first subject enrolled) through the data cut-off date of 19 June 2014. A safety update was submitted by the MAH, with a data cut-off on 28 September 2015.

**Patient exposure**

Study OMB112517 enrolled a total of 474 subjects with relapsed CLL who were in complete or partial response after induction therapy (complete response [CR] or partial response [PR] within 3 months after last dose).

The safety population in study OMB112517 included all randomized subjects based on the actual treatment received (n=237 in both arms). One subject (Subject 828) was randomized to the ofatumumab maintenance arm but did not receive any study treatment; therefore, this subject was included in the Obs

arm for all safety analyses.

The ITT population included all subjects who were randomized in the study according to randomized treatment group. The ITT population was used in all summaries of subject demographics and baseline characteristics.

**Table 33: Study OMB112517 - Analysis Populations**

| | Number of Subjects | | |
|---|---|---|---|
| | OFA | Obs | Total |
| Safety population[a] | 237 | 237 | 474 |
| Intent-to-treat population[b] | 238 | 236 | 474 |

[Data Source: m5.3.5.1 OMB112517 CSR Table 1.0010]

a. Includes all randomized subjects but subjects were grouped based on the actual treatment received.
b. Includes all randomized subjects by randomized treatment group.

Subjects assigned to the ofatumumab maintenance arm received an initial infusion of 300 mg on Day 1, followed by an infusion of 1000 mg on Day 8. Following the first 1000 mg dose, subjects in the ofatumumab maintenance arm received infusions of 1000 mg every 8 weeks for up to 2 years. Subjects assigned to the Obs arm had observation and assessments according to the same schedule as subjects in the OFA maintenance arm, but received no protocol-required treatments.

At the time of the data cut-off (19 June 2014), the median treatment duration for subjects in the OFA maintenance arm was 382 days (range: 1 day to 834 days). Almost half (49%) of the subjects received at least 8 cycles of treatment, and 25% of the subjects received all 14 infusions (Cycle 13).

The median cumulative dose of ofatumumab received by subjects in the OFA maintenance arm was 7300 mg (range: 300 mg to 13,300 mg), with the median duration of OFA infusion of 4.25 hours (range: 0.8 hours to 8.6 hours).

**Adverse events**

The majority of subjects in both arms had 1 or more AEs during the Treatment/Obs Phase (ofatumumab maintenance: 87%, Obs: 75%) A higher proportion of subjects in the ofatumumab maintenance arm had AEs that were Grade ≥3. In the ofatumumab maintenance arm, 62% of AEs were considered treatment-related and 8% of the subjects discontinued study treatment due to an AE.

**Table 34: Overview of AEs (Safety population)**

| | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any AE, n (%)** | **206 (87)** | **177 (75)** |
| AE treatment-related | 147 (62) | NA |
| AE leading to permanent discontinuation of study treatment | 20 (8) | 1 (<1) |
| AE leading to death | 8 (3) | 19 (8) |
| AE leading to infusion interruption/delay | 95 (40) | NA |
| AE ≥Grade 3 | 120 (51) | 85 (36) |
| **Any SAE, n (%)** | **78 (33)** | **70 (30)** |
| SAE treatment-related | 33 (14) | NA |
| Fatal SAE | 8 (3)[a] | 19 (8) |
| Fatal SAE treatment-related | 0 | NA |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0100]
Abbreviations: AE=adverse event; NA=not applicable; SAE=serious adverse event.
a. One subject died after the data cut-off date and was not included in the count of fatal SAEs (Subject 184: cause of death T cell lymphoma and liver failure).



**Common Adverse Events**

**Table 35: Frequent AEs occurring in 5% or more of subjects (Safety population)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any Event, n (%)** | **206 (87)** | **177 (75)** |
| Neutropenia | 58 (24) | 24 (10) |
| Cough | 50 (21) | 22 (9) |
| Upper respiratory tract infection | 45 (19) | 23 (10) |
| Infusion-related reaction[a] | 39 (16) | NA |
| Pyrexia | 38 (16) | 25 (11) |
| Diarrhea | 33 (14) | 9 (4) |
| Fatigue | 27 (11) | 16 (7) |
| Pneumonia | 26 (11) | 18 (8) |
| Rash | 23 (10) | 10 (4) |
| Headache | 22 (9) | 5 (2) |
| Bronchitis | 21 (9) | 16 (7) |
| Pruritus | 21 (9) | 7 (3) |
| Nasopharyngitis | 19 (8) | 15 (6) |
| Sinusitis | 19 (8) | 11 (5) |
| Arthralgia | 17 (7) | 12 (5) |
| Influenza | 17 (7) | 8 (3) |
| Thrombocytopenia | 13 (5) | 14 (6) |
| Herpes zoster | 13 (5) | 8 (3) |
| Insomnia | 13 (5) | 5 (2) |
| Respiratory tract infection | 12 (5) | 15 (6) |
| Back pain | 12 (5) | 8 (3) |
| Rhinitis | 12 (5) | 3 (1) |
| Nausea | 11 (5) | 6 (3) |
| Febrile neutropenia | 11 (5) | 4 (2) |
| Hypogammaglobulinemia | 11 (5) | 2 (<1) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0141]
Note: 'Frequent adverse event' is defined as an incidence of ≥5% in any treatment group. 'Any Event' reflects the number of subjects with a 'frequent event.'
a. Infusion-related reaction was reported as the verbatim term with or without associated symptoms.

**Adverse Events by Causality**

**Table 36: Drug-related AEs occurring in 2% or more of subjects (Safety population)**

| Preferred Term | OFA (N=237) |
|---|---|
| Any Event, n (%) | 147 (62) |
| Neutropenia | 44 (19) |
| Infusion-related reaction[a] | 39 (16) |
| Upper respiratory tract infection | 13 (5) |
| Pyrexia | 10 (4) |
| Respiratory tract infection | 9 (4) |
| Fatigue | 8 (3) |
| Pneumonia | 7 (3) |
| Cough | 6 (3) |
| Diarrhea | 6 (3) |
| Headache | 6 (3) |
| Herpes zoster | 6 (3) |
| Rash | 6 (3) |
| ALT increased | 5 (2) |
| Bronchitis | 5 (2) |
| Febrile neutropenia | 5 (2) |
| Nausea | 5 (2) |
| Pruritus | 5 (2) |
| Thrombocytopenia | 5 (2) |
| Hypersensitivity | 4 (2) |
| Sinusitis | 4 (2) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0300]
Abbreviation: ALT=alanine aminotransferase.
a. Infusion-related reaction was reported as the verbatim term with or without associated symptoms.

**Adverse Events by Severity**

**Table 37: AEs with maximum severity of grade 3 or higher (Safety population)**

| AEs, Any Event | OFA (N=237) | | | Obs (N=237) | | |
|---|---|---|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 5 | Grade 3 | Grade 4 | Grade 5 |
| AEs, n (%) | 71 (30) | 40 (17) | 9 (4)[a] | 53 (22) | 13 (5) | 19 (8) |
| Treatment-related AEs, n (%) | 41 (17) | 25 (11) | 0[b] | NA | NA | NA |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0180 and Table 3.0181]
Abbreviations: AE=adverse event; NA=not applicable.
a. Subject 134 died after the CSR data cut-off date but was included in the count for Grade 5 events.
b. Although there were no subjects with fatal treatment-related SAEs reported on the AE eCRF, the cause of death for 1 subject in the OFA maintenance arm (Subject 27) was reported as "SAE possibly related to study medication". Subject 27 had a fatal SAE of pulmonary sepsis (pneumococcal).

More subjects in the ofatumumab arm (51%) compared with the Obs arm (36%) had Grade ≥3 AEs, with 28% considered related to treatment in the ofatumumab arm. The most common (≥2%) Grade ≥3 AEs were cytopenias. Neutropenia was more common in the ofatumumab arm (22%) compared to the Obs arm (9).

**Adverse Events of Particular Concern**

***Neoplasms***

**Table 38: AEs for neoplasms occurring in 2 or more subjects (Safetypopulation)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any Event[a], n (%)** | **29 (12)** | **17 (7)** |
| Basal cell carcinoma | 4 (2) | 2 (<1) |
| Squamous cell carcinoma of skin | 4 (2) | 1 (<1) |
| Squamous cell carcinoma[a] | 3 (1) | 4 (2) |
| Acute myeloid leukaemia | 2 (<1) | 0 |
| Myelodysplastic syndrome | 2 (<1) | 1 (<1) |
| Seborrhoeic keratosis | 2 (<1) | 0 |
| Skin papilloma | 2 (<1) | 1 (<1) |
| T-cell lymphoma | 2 (<1) | 0 |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0924]
Note: Event terms occurring in just 1 subject are not presented in this table.
a. AE terms are MedDRA Preferred Terms based on verbatim text from the AE eCRF

*Liver Events*

Per protocol, liver stopping criteria were defined in study OMB112517 for subjects in either arm as meeting 1 or more of the following conditions while on treatment:

- ALT >3 times upper limit of normal (ULN), and bilirubin ≥2 times ULN (>35% direct bilirubin; bilirubin fractionation required)
- ALT >8 times ULN
- ALT ≥5 times ULN for more than 2 weeks.

Two subjects in the ofatumumab maintenance arm had liver chemistry elevations meeting the stopping criteria. One subject had lab elevation of ALT>8 times ULN and the other subject had lab elevations of ALT >3 times ULN and bilirubin ≥2 times ULN (Hy's Law).

- Subject 1391 (Hy's Law): 67 years, 64 days after last dose, unrelated. The subject had elevated liver enzymes of ALT=849 U/L, AST=742 U/L and bilirubin=64 µmol/L. Work-up revealed gallstones and the subject subsequently underwent a cholecystectomy. The events were noted as ongoing at the time of the data cut-off.
- Subject 158 (ALT >8 times ULN): 77 years, approximately 1.5 years after initiating treatment and approximately 50 days after the last dose, possibly related. The subject had elevated liver enzymes of ALT=605 U/L (reported as SAE), AST=264 U/L, and bilirubin=20 µmol/L. The elevated enzymes were in the setting of HBV reactivation, which was treated with lamivudine. Diagnostic imaging tests of the liver or hepatobiliary system were not performed. There were no liver biopsies performed. Ofatumumab was discontinued. At the time of data cut-off, the event remained ongoing (approximately 4-months duration).

**Adverse Events of Special Interest**

Specific adverse events were expected in the patients with CLL due to the disease and CLL treatments, including anti-CD20 monoclonal antibodies such as OFA, and were therefore considered AEs of special interest. The AEs of special interest were cytopenias including autoimmune hematologic complications, infusion reactions, infections, mucocutaneous reactions, tumour lysis syndrome, cardiovascular events, and small bowel/intestinal obstruction. Progressive multifocal leukoencephalopathy (PML) and HBV infection and reactivation are included as events of clinical significance.

***Cytopenias***

*Adverse Events Associated with Decreased Neutrophil Count*

No unexpected signals regarding AEs associated with decreased neutrophil counts were detected given that this phenomenon is well described for anti-CD20 monoclonal antibodies. The proportion of subjects that had AEs associated with decreased neutrophil counts was higher in the ofatumumab maintenance arm (28%) than in the Obs arm (12%). The proportion of subjects that had SAEs associated with decreased neutrophil counts was similar in both arms (ofatumumab maintenance: 5%, Obs: 3%).

Overall, a higher proportion of subjects in the ofatumumab maintenance arm had neutropenia based on laboratory values (worst-case post-baseline) compared with the Obs arm. Median neutrophil counts increased after baseline in subjects in the ofatumumab maintenance arm, but to a lesser degree than values observed in subjects in the Obs arm.

**Table 39: AEs associated with decreased neutrophil count (Safety population)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **All AEs Associated with Decreased Neutrophil Count[a], n (%)** | **67 (28)** | **29 (12)** |
| Febrile neutropenia | 11 (5) | 4 (2) |
| Neutropenia | 58 (24) | 24 (10) |
| Neutropenic sepsis | 0 | 1 (<1) |
| Neutrophil count decreased | 7 (3) | 3 (1) |
| Drug-related AEs Associated with Decreased Neutrophil Count | 46 (19) | NA |
| **SAEs Associated with Decreased Neutrophil Count, n (%)** | **12 (5)** | **6 (3)** |
| Febrile neutropenia | 10 (4) | 3 (1) |
| Neutropenia | 4 (2) | 3 (1) |
| Neutropenic sepsis | 0 | 1 (<1) |
| Neutrophil count decreased | 0 | 0 |
| Drug-related SAEs Associated with Decreased Neutrophil Count | 7 (3) | NA |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0760]

Abbreviations: AE=adverse event; NA=not applicable; SAE=serious adverse event

a. Number of subjects may not equal total as subjects may have had multiple AEs.

The proportion of subjects that had Grade 3 and Grade 4 neutropenia was higher in the OFA maintenance arm (24%) than in the Obs arm (11%) [Data Source: m5.3.5.1 OMB112517 CSR Table 3.0770]. The increased incidence of ≥Grade 3 neutropenia did not result in an increase in ≥Grade 3 or higher infections [Data Source: m5.3.5.1 OMB112517 CSR Table 3.1381]. None of the AEs associated with decreased neutrophil counts resulted in a fatal outcome (Table 20). Treatment with granulocyte-colony stimulating factor (G-CSF) or G-CSF-related products (e.g., filgrastim) was administered to a higher proportion of subjects in the OFA maintenance arm compared with the Obs arm [Data Source: m5.3.5.1 OMB112517 CSR Table 3.1280].

**Table 40: AEs associated with decreased neutrophil count by maximum toxicity grade and by preferred term (Safety population)**

| Preferred Term, n (%) | n | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|---|
| **OFA (N=237)** | | | | | | |
| Neutropenia | 58 | 3 (1) | 4 (2) | 29 (12) | 22 (9) | 0 |
| Febrile neutropenia | 11[a] | 1 (<1) | 1 (<1) | 5 (2) | 3 (1) | 0 |
| Neutrophil count decreased | 7 | 1 (<1) | 2 (<1) | 3 (1) | 1 (<1) | 0 |
| **Obs (N=237)** | | | | | | |
| Neutropenia | 24 | 1 (<1) | 2 (<1) | 11 (5) | 10 (4) | 0 |
| Febrile neutropenia | 4 | 0 | 0 | 3 (1) | 1 (<1) | 0 |
| Neutropenic sepsis | 1 | 0 | 0 | 0 | 1 (<1) | 0 |
| Neutrophil count decreased | 3 | 1 (<1) | 0 | 2 (<1) | 0 | 0 |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0780]

a. One subject was missing data for the toxicity grade

*Adverse Events Associated with Decreased Haemoglobin Count*

The proportion of subjects experiencing AEs or SAEs associated with decreased haemoglobin count was similar in both arms. None of these AEs were considered to be treatment-related and none resulted in a fatal outcome. Furthermore, there were no significant differences between arms with respect to autoimmune hematologic complications. **Table 41: AEs associated with decreased haemoglobin (Safety population)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **All AEs Associated with Decreased Hemoglobin, n (%)[a]** | **9 (4)** | **12 (5)** |
| Anemia | 7 (3) | 9 (4) |
| Hemoglobin decreased | 1 (<1) | 2 (<1) |
| Hemolytic anemia | 1 (<1) | 1 (<1) |
| Iron deficiency anemia | 0 | 1 (<1) |
| Drug-related AEs Associated with Decreased Hemoglobin | 0 | NA |
| **Any AEs Grade ≥3, n (%)[a]** | **4 (2)** | **5 (2)** |
| Anemia | 3 (1) | 4 (2) |
| Hemolytic anemia | 1 (<1) | 1 (<1) |
| **SAEs Associated with Decreased Hemoglobin, n (%)[a]** | **2 (<1)** | **4 (2)** |
| Anemia | 1 (<1) | 4 (2) |
| Hemoglobin decreased | 0 | 0 |
| Hemolytic anemia | 1 (<1) | 0 |
| Iron deficiency anemia | 0 | 0 |
| Drug-related SAEs Associated with Decreased Hemoglobin | 0 | NA |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0790 and Table 3.0800]
Abbreviations: AE=adverse event; NA=not applicable; SAE=serious adverse event
a. Number of subjects may not equal total as subjects may have had multiple AEs.

*Autoimmune Hematologic Complications*

Overall, there were 5 subjects who had autoimmune hematologic complications in this study. Of these, 1 subject in the ofatumumab maintenance arm had a Grade 3 AE of haemolytic anaemia 214 days after the last dose of ofatumumab that the investigator considered to be not treatment-related and resolved after 13 days.

**Table 42: Autoimmune haematologic complication AEs (Safety population)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any AE event, n (%)** | **1 (<1)** | **4 (2)** |
| Hemolytic anemia | 1 (<1) | 1 (<1) |
| AIHA | 0 | 4 (2) |
| **Any SAE event post-treatment up to 60 days after last dose, n (%)** | **0** | **2 (<1)** |
| AIHA | 0 | 2 (<1) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0900 and Table 3.0920]
Abbreviations: AE=adverse event; AIHA= Autoimmune hemolytic anemia; SAE=serious adverse event.

No subjects in the ofatumumab maintenance arm had SAEs of AIHA and 2 subjects in the Obs arm had non-fatal SAEs of AIHA:

- Subject 1974: 65 years, Grade 3 AIHA 149 days after the first visit; recovered after 75 days. The subject had received 3 previous induction treatments including chlorambucil, rituximab, cyclophosphamide, and vincristine.

- Subject 1484: 58 years, Grade 3 AIHA 528 days after the first visit; recovered after 6 days. The subject had received 3 previous induction treatments including chlorambucil, rituximab, cyclophosphamide, and fludarabine.

One subject in the Obs arm withdrew from the study (discontinued treatment) due to non-serious AIHA (Subject 637).

*Adverse Events Associated with Decreased Platelet Count*

**Table 43: AEs associated with decreased platelet counts (Safety population)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **All AEs Associated with Decreased Platelet Count, n (%)[a]** | **19 (8)** | **18 (8)** |
| Immune thrombocytopenic purpura | 1 (<1) | 2 (<1) |
| Platelet count decreased | 6 (3) | 3 (1) |
| Thrombocytopenia | 13 (5) | 14 (6) |
| Drug-related AEs Associated with Decreased Platelet Count | 7 (3) | NA |
| **Any AEs Grade ≥3, n (%)[a]** | **4 (2)** | **10 (4)** |
| Immune thrombocytopenic purpura | 1 (<1) | 0 |
| Platelet count decreased | 1 (<1) | 3 (1) |
| Thrombocytopenia | 3 (1) | 7 (3) |
| **Serious AEs Associated with Decreased Platelet Count, n (%)[a]** | **1 (<1)** | **3 (1)** |
| Immune thrombocytopenic purpura | 1 (<1) | 0 |
| Platelet count decreased | 0 | 1 (<1) |
| Thrombocytopenia | 0 | 2 (<1) |
| Drug-related SAEs Associated with Decreased Platelet Count | 1 (<1) | NA |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0820 and Table 3.0830]
Abbreviations: AE=adverse event; NA=not applicable; SAE=serious adverse event
a. Number of subjects may not equal total as subjects may have had multiple AEs.

*Other Cytopenias*

**Table 44: Overview of AEs associated with other cytopenias (Safety population)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **All AEs Associated with Other Cytopenias, n (%)** | **9 (4)** | **10 (4)** |
| Leukopenia | 2 (<1) | 5 (2) |
| Lymphocyte count decreased | 3 (1) | 1 (<1) |
| Lymphopenia | 0 | 1 (<1) |
| Myelodysplastic syndrome | 2 (<1) | 1 (<1) |
| White blood cell count decreased | 4 (2) | 3 (1) |
| Drug-related AEs Associated with Other Cytopenias | 5 (2) | NA |
| **Any AEs Grade ≥3 Associated with Other Cytopenias, n (%)** | **3 (1)** | **6 (3)** |
| Leukopenia | 0 | 3 (1) |
| Lymphocyte count decreased | 1 (<1) | 0 |
| Myelodysplastic syndrome | 1 (<1) | 1 (<1) |
| White blood cell count decreased | 2 (<1) | 3 (1) |
| **SAEs Associated with Other Cytopenias, n (%)** | **2 (<1)** | **1 (<1)** |
| Leukopenia | 1 (<1) | 0 |
| Myelodysplastic syndrome | 1 (<1) | 1 (<1) |
| Drug-related SAEs associated with Other Cytopenias | 0 | NA |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0850 and Table 3.0860]
Abbreviations: AE=adverse event; NA=not applicable; SAE=serious adverse event.

***Infusion Reactions***

**Table 45: Infusion-related adverse events for the ofatumumab arm (Safety population)**

| | OFA (N=237) |
|---|---|
| **Any Infusion-related AE, n (%)** | **109 (46)** |
| Infusion-related AE treatment-related[a] | 67 (28) |
| Infusion-related AE leading to permanent discontinuation of study treatment | 2 (<1) |
| Infusion-related AE leading to death | 0 |
| Infusion-related AE leading to infusion interruption/delay | 42 (18) |
| Infusion-related AE ≥Grade 3 | 9 (4) |
| **Any Infusion-related SAE, n (%)** | **1 (<1)** |
| Infusion-related SAE treatment-related | 0 |
| Fatal Infusion-related SAE | 0 |
| Fatal Infusion-related SAE treatment-related | 0 |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0640]

Abbreviations: AE=adverse event; SAE=serious adverse event.

a. Infusion reactions included pre-defined events relating to an infusion which started after the beginning of the infusion and within 24 hours following the end of an infusion

Infusion-related reaction, fatigue, and headache were the most common infusion AEs at Cycle 1 Day 1. Infusion-related reaction and cough were the most common infusion AEs occurring at any cycle.

**Table 46: Infusion-related AEs reported in 2% or more subjects in the ofatumumab arm (Safety population)**

| Preferred Term | OFA (N=237) | |
|---|---|---|
| | 1st Infusion (Cycle 1 Day 1) | Any Infusion |
| **Any Event, n (%)** | **59 (25)** | **109 (46)** |
| Infusion-related reaction[a] | 33 (14) | 39 (16) |
| Cough | 1 (<1) | 11 (5) |
| Fatigue | 4 (2) | 8 (3) |
| Diarrhea | 3 (1) | 8 (3) |
| Pain | 3 (1) | 8 (3) |
| Headache | 4 (2) | 7 (3) |
| Hypertension | 3 (1) | 6 (3) |
| Pruritus | 0 | 5 (2) |
| Cardiac Events | 1 (<1) | 5 (2) |
| Rash | 2 (<1) | 4 (2) |
| Sinusitis | 0 | 4 (2) |
| Arthralgia | 1 (<1) | 4 (2) |
| Nausea | 3 (1) | 4 (2) |
| Anaphylactoid Events | 2 (<1) | 4 (2) |
| Fever/Pyrexia | 1 (<1) | 4 (2) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0650]

a. Infusion-related reaction was reported as the verbatim term with or without associated symptoms



One subject had a non-fatal, unrelated SAE of fever/pyrexia:

- Subject 134: 56 years, Grade 3 pyrexia (unrelated) the day after the first OFA infusion; resolved.

***Infections***

More subjects in the ofatumumab arm had infectious AEs (65%) compared to the Obs arm (51%). Overall, 22% of subjects in the ofatumumab arm had infectious AEs considered to be treatment-related

and 3% led to permanent discontinuation of treatment. The proportion of subjects with SAEs related to infection was similar between arms (ofatumumab: 20%, Obs: 18%). In total, 12 subjects (3%) had fatal infections (ofatumumab: 2%, Obs: 3%) but none were considered treatment-related.

The most common infectious AEs were upper respiratory tract infections and other infections. The most common infectious SAEs were lower respiratory tract infections. In the ofatumumab arm, 8 subjects had opportunistic infections while this was found in 7 subjects in the Obs arm.

**Table 47: Overview of Infections Reported as AEs (Safety Population)**

| | Original submission | | Safety update | |
|---|---|---|---|---|
| **Preferred Term** | **OFA (N=237)** | **Obs (N=237)** | **OFA (N=239)** | **Obs (N=241)** |
| **Any Infection AE, n (%)** | **154 (65)** | **120 (51)** | **174 (73)** | **136 (56)** |
| Infection AE treatment-related | 52 (22) | NA | 61 (26) | NA |
| Infection AE leading to discontinuation | 7 (3) | 0 | 7 (3) | 0 |
| Infection AE leading to death | 5 (2) | 7 (3) | 10 (4) | 7 (3) |
| Infection AE leading to infusion interruption/delay | 34 (14) | NA | 39 (16) | NA |
| Infection AE ≥Grade 3 | 47 (20) | 39 (16) | 54 (23) | 44 (18) |
| **Any Infection SAE, n (%)** | **47 (20)** | **42 (18)** | **55 (23)** | **49 (20)** |
| Infection SAE treatment-related | 21 (9) | NA | 22 (9) | NA |
| Fatal Infection SAE | 5 (2) | 7 (3) | 10 (4) | 7 (3) |
| Fatal Infection SAE treatment-related | 0 | NA | 0 | NA |

Data Source: [Appendix to EMA Response-Table 3.0460]
Abbreviations: NA=Not applicable

**Table 48: Infections Reported as AEs (Safety Population)**

| | Original submission | | Safety update | |
|---|---|---|---|---|
| **Preferred Term** | **OFA (N=237)** | **Obs (N=237)** | **OFA (N=239)** | **Obs (N=241)** |
| **Any Infection [a] AE, n (%)** | **154 (65)** | **120 (51)** | **174 (73)** | **136 (56)** |
| Lower Respiratory Tract Infections | 62 (26) | 50 (21) | 73 (31) | 55 (23) |
| Bronchitis | 23 (10) | 18 (8) | 23 (10) | 18 (7) |
| Lung Infection | 13 (5) | 20 (8) | 18 (8) | 23 (10) |
| Pneumonia | 31 (13) | 22 (9) | 39 (16) | 25 (10) |
| Upper Respiratory Tract Infections | 89 (38) | 58 (24) | 99 (41) | 68 (28) |
| Sepsis | 5 (2) | 11 (5) | 10 (4) | 11 (5) |
| Opportunistic Infections | 23 (10) | 17 (7) | 27 (11) | 24 (10) |
| Other Infections [b] | 92 (39) | 60 (25) | 107 (45) | 69 (29) |

Data Source: [Appendix to EMA Response-Table 3.0470]

a. Modified Preferred Terms are presented in this table (i.e., multiple terms comprise the term "upper respiratory tract infection" including, but not limited to, laryngitis, pharyngitis, rhinopharyngitis, sinusitis, tracheitis, common cold, cough/sore throat, ear, nose and throat infection, and head cold).

b. "Other infections" was comprised of a variety of infections including, but not limited to, influenza, cellulitis, herpes zoster, herpes simplex, and urinary tract infections.

**Table 49: Infections Reported as SAEs (Safety Population)**

| | Original submission | | Safety update | |
|---|---|---|---|---|
| Preferred Term | OFA (N=237) | Obs (N=237) | OFA (N=239) | Obs (N=241) |
| **Any Infection SAE, n (%)** | **47 (20)** | **42 (18)** | **55 (23)** | **49 (20)** |
| Lower Respiratory Tract Infections | 24 (10) | 21 (9) | 29 (12) | 27 (11) |
| Bronchitis | 2 (<1) | 0 | 2 (<1) | 0 |
| Lung Infection | 1 (<1) | 6 (3) | 1 (<1) | 7 (3) |
| Pneumonia | 21 (9) | 17 (7) | 26 (11) | 21 (9) |
| Upper Respiratory Tract Infections | 7 (3) | 5 (2) | 8 (3) | 6 (2) |
| Sepsis | 5 (2) | 9 (4) | 10 (4) | 9 (4) |
| Opportunistic Infections | 8 (3) | 7 (3) | 8 (3) | 11 (5) |
| Other Infections | 18 (8) | 17 (7) | 22 (9) | 21 (9) |
| Data Source: [Appendix to EMA Response-Table 3.0550] | | | | |

***Progressive Multifocal Leukoencephalopathy***

There were no cases of PML reported in this study.

***Hepatitis B Infection and Reactivation***

There was 1 case of HBV reactivation reported in this study for 1 Subject (Subject 158) in the OFA maintenance arm. Reactivation of HBV is a known AE of ofatumumab treatment.

***Mucocutaneous Reactions***

In the ofatumumab maintenance arm, treatment-related mucocutaneous reactions were reported in 8% of subjects.

No cases of toxic epidermal necrolysis or Stevens-Johnson syndrome (SJS) were reported in this study.

**Table 50: Mucocutaneous reactions reported as AEs (safety population)**

| | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any Mucocutaneous Reaction, n (%)** | **68 (29)** | **36 (15)** |
| Reaction treatment-related | 18 (8) | NA |
| Reaction leading to permanent discontinuation of study treatment | 1 (<1) | NA |
| Reaction leading to death | 0 | 0 |
| Reaction leading to infusion interruption/delay | 7 (3) | NA |
| Reaction ≥Grade 3 | 7 (3) | 3 (1) |
| **Any Serious Mucocutaneous Reaction, n (%)** | **2 (<1)** | **3 (1)** |
| Serious reaction treatment-related | 0 | NA |
| Fatal serious reaction | 0 | 0 |
| Fatal serious reaction treatment-related | 0 | NA |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0710]
Abbreviations: NA=not applicable

One subject in the ofatumumab maintenance arm had a treatment-related mucocutaneous reaction that led to treatment discontinuation:

Subject 176: 59 years, Grade 2 dermatitis allergic (non-serious), 56 days after the last dose; related

Five subjects had mucocutaneous reaction SAEs (ofatumumab maintenance: 2 subjects; Obs: 3 subjects. None of these events were fatal or were considered to be treatment-related.

**Table 51: Serious mucocutaneous reactions (safety population)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Serious Mucocutaneous Reactions, n (%)** | **2 (<1)** | **3 (1)** |
| Cellulitis | 1 (<1) | 1 (<1) |
| Blister | 0 | 1 (<1) |
| Erythema multiforme | 0 | 1 (<1) |
| Stomatitis | 1 (<1) | 0 |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0740]

***Tumor Lysis Syndrome***

There were no cases of tumour lysis syndrome reported in this study.

***Cardiovascular Events***

**Table 52: Cardiovascular AEs (safety population)**

| | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any Cardiac AE, n (%)** | **14 (6)** | **14 (6)** |
| Cardiac AE within 60 Days of Last Treatment | 13 (5) | 10 (4) |
| **Any Cardiac SAE, n (%)** | **6 (3)** | **6 (3)** |
| Cardiac SAE within 60 Days of Last Treatment | 5 (2) | 3 (1) |
| Fatal Cardiac SAEs, n (%) | 1 (<1) | 3 (1) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0924, Table 3.0925, Table 3.0926, Table 3.0927 and Table 3.0420]
Abbreviations: AE=adverse event; SAE=serious adverse event.

The fatal cardiac SAE in the ofatumumab maintenance arm was considered not treatment-related:

Subject 180: 79 years, Grade 5 heart failure, 317 days after last dose, not related. The subject's medical history included diabetes mellitus, cerebrovascular accident, pulmonary hypertension, atrial septal defect, left atrial dilatation, hypertension, venous thrombosis, and venous insufficiency. The cause of death was noted as heart failure.

Three subjects in the Obs arm had fatal cardiac SAEs:

Subject 307: 67 years, Grade 5 cardiac arrest, 883 days after first visit, medical history included hypertension. The subject developed Grade 4 pneumonia, was hospitalized, and then died of cardiac arrest the following day.

Subject 268: 67 years, Grade 5 cardiac arrest, 206 days after first visit.

Subject 250: 64 years, Grade 5 cerebrovascular accident 89 days after first visit.

***Small Bowel Obstruction***

One subject in the ofatumumab maintenance arm had a fatal SAE and 2 subjects in the Obs arm had AEs of small bowel obstruction during the study.

Subject 58: 76 years; Grade 5 small bowel obstruction 54 days after last dose; not related.

**Analysis of Adverse Events by Organ System or Syndrome**

A higher proportion of subjects in the ofatumumab maintenance arm had AEs in the majority of System Organ Class (SOC)s compared with the Obs arm.

**Table 53: Summary of adverse events in study OMB112517 by SOC**

| System organ class | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any event** | **206 (87)** | **177 (75)** |
| Infections and infestations | 154 (65) | 120 (51) |
| General disorders and administration site conditions | 77 (32) | 59 (25) |
| Blood and lymphatic system disorders | 76 (32) | 46 (19) |
| Respiratory, thoracic and mediastinal disorders | 75 (32) | 52 (22) |
| Gastrointestinal disorders | 72 (30) | 40 (17) |
| Skin and subcutaneous tissue disorders | 67 (28) | 38 (16) |
| Injury, poisoning and procedural complications | 58 (24) | 22 (9) |
| Musculoskeletal and connective tissue disorders | 57 (24) | 45 (19) |
| Investigations | 51 (22) | 29 (12) |
| Nervous system disorders | 47 (20) | 24 (10) |
| Vascular disorders | 31 (13) | 13 (5) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 29 (12) | 17 (7) |
| Metabolism and nutrition disorders | 27 (11) | 20 (8) |
| Psychiatric disorders | 24 (10) | 15 (6) |
| Immune system disorders | 20 (8) | 6 (3) |
| Cardiac disorders | 14 (6) | 14 (6) |
| Ear and labyrinth disorders | 13 (5) | 2 (<1) |
| Renal and urinary disorders | 12 (5) | 12 (5) |
| Reproductive system and breast disorders | 12 (5) | 6 (3) |
| Eye disorders | 10 (4) | 11 (5) |
| Hepatobiliary disorders | 8 (3) | 5 (2) |
| Surgical and medical procedures | 3 (1) | 6 (3) |
| Endocrine disorders | 2 (<1) | 0 |
| Congenital, familial and genetic disorders | 1 (<1) | 1 (<1) |
| Social circumstances | 0 | 1 (<1) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.0130]



**Serious adverse event/deaths/other significant events**

*Serious adverse event*

Approximately one-third of subjects had SAEs (OFA: 33%, Obs: 30%) during the study, with similar proportions of subjects in both arms. Of these, 22% occurred within 60 days after last dose/last Treatment/Obs Phase visit (OFA: 24%, Obs: 20%).

**Table 29. Serious Adverse Events Occurring in ≥1% of Subjects (Safety Population- Study OMB112517)**

| Preferred Term | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Any Serious Event, n (%)** | **78 (33)** | **70 (30)** |
| Pneumonia | 18 (8) | 14 (6) |
| Pyrexia | 12 (5) | 6 (3) |
| Febrile neutropenia | 10 (4) | 3 (1) |
| Neutropenia | 4 (2) | 3 (1) |
| Upper respiratory tract infection | 3 (1) | 2 (<1) |
| Herpes zoster | 3 (1) | 1 (<1) |
| Sepsis | 2 (<1) | 3 (1) |
| Anemia | 1 (<1) | 4 (2) |
| **Any Treatment-related Serious Event, n (%)** | **33 (14)** | NA |
| Pneumonia | 7 (3) | NA |
| Febrile neutropenia | 5 (2) | NA |
| Neutropenia | 4 (2) | NA |
| Pyrexia | 3 (1) | NA |

*Deaths*

The proportion of subjects that died during the study was similar in both arms (i.e. 14% in each arm) (Table 26). No subject in the OFA arm died while in the Treatment/Obs Phase compared with 3 subjects in the Obs arm. Causes of death in the Obs arm were cardiac arrest (1 subject), disease under study (1 subject), and subdural hematoma in the setting of supratherapeutic international normalized ratio (INR) and sepsis (1 subject).

**Table 1. Deaths (Safety Population- Study OMB112517)**

| | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **All Deaths, n (%)** | 32 (14) | 34 (14) |
| **Primary Cause of Death** | | |
| Disease Under Study, n (%) | 19 (8) | 12 (5) |
| Other[a], n | 13 | 22 |
| **Time to Death Group, n (%)** | | |
| On Treatment[b] | 0 | 3 (1) |
| ≤60 Days After Last Treatment/Visit[c] | 2 (<1) | 2 (<1) |
| >60 Days After Last Treatment/Visit | 30 (13) | 29 (12) |
| **Fatal SAEs, n(%)** | | |
| All Fatal SAEs | 8 (3%)[e] | 19 (8%) |
| Fatal SAEs up to 60 days After Last Treatment/Visit[d] | 3 (1%) | 6 (3%) |

Note: 'Alive at last contact' is based on data at end of study.

a. Other primary causes of death were: general deterioration, heart failure, multiorgan failure, pneumatitis, pneumonia/flu, respiratory insufficiency with pneumonia, right leg soft tissue infection, SAE possibly related to study medication (AE eCRF for Subject 27 noted "SAE possibly related to study medication" however, per the SAE Report the subject had a fatal SAE of pulmonary sepsis which was considered not related [280 days after last dose]. This discrepancy was noted at the time of this interim analysis and is being further investigated), septic shock, septicemia, small bowel obstruction, unrecovering condition following allogeneic transplantation, bilateral pneumonia, cardiac arrest, cardiac arrest due to pneumonia, complications from a fall and myelodysplastic syndrome/acute myeloid leukemia, disease under study and pulmonary infection, diffuse large B-cell lymphoma, dyspnea and hypoxia, fever and gastric pain, heart failure due to heart muscle hypertrophy, immunosuppression and respiratory infection which caused ARDS, prostate cancer, Pseudomonas aeruginosa pneumonia, unspecified SAE not related to study medication, cerebrovascular accident and ventricular fibrillation, skin melanoma, small cell lung carcinoma, subdural hematoma in setting of supratherapeutic INR and sepsis, transformed disease: plasmablastic lymphoma, urothelial cell cancer of urinary bladder, worsening of general conditions and unknown cause. .

b. On treatment for OFA was defined as the time from treatment initiation until the date of last dose +30 days. On treatment for Obs was defined as the time from randomisation until the date of entry into the follow-up period +30 days.

c. Time to death for <60 days after last treatment is based on date of death.

d. Data for 'Fatal SAEs up to 60 days after last treatment/visit' is based on the SAE start date, not the date of death.

e. One subject died after the CSR cut-off date and is not included in the count of fatal SAEs (Subject 134: cause of death was T-cell lymphoma and liver failure). The fatal event was counted in the total "Grade 5" event count in Table 11.

**Table 30. Fatal SAEs by System Organ Class (Safety Population- Study OMB112517)**

| System Organ Class | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **All Fatal SAEs, n (%)** | **8 (3)[a]** | **19 (8)** |
| Infections and infestations | 5 (2) | 7 (3) |
| Cardiac disorders | 1 (<1) | 3 (1) |
| General disorders and administration site conditions | 1 (<1) | 2 (<1) |
| Gastrointestinal disorders | 1 (<1) | 1 (<1) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 0 | 5 (2)[b] |
| Injury, poisoning and procedural complications | 0 | 2 (<1) |
| Nervous system disorders | 0 | 2 (<1) |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 (<1) |

a. Subject 134 died of liver failure and T-cell lymphoma after CSR data cut-off date. These events are not included in this table. The fatal event was counted in the total "Grade 5" event count in Table 11.
b. Fatal SAEs in the neoplasms system organ classification included bladder cancer, diffuse large B-cell lymphoma, malignant melanoma, prostate cancer, and small cell lung cancer.



**Laboratory findings**

***Hematologic assessment***

Median neutrophil counts at baseline were similar between the arms. After study entry, neutrophil counts increased but remained closer to the baseline values for subjects in the OFA arm. In comparison, neutrophil counts increased above baseline values to higher values within the normal range for subjects in the Obs arm.

Median haemoglobin counts were similar between the arms at baseline and over the duration of study. Median values were within normal limits.

Median platelet counts were similar between the arms at baseline and during the duration of the study. There were no noted differences in platelet counts over time between the 2 arms.

***Biochemistry assessments***

Liver function tests were assessed at baseline, over the course of therapy and in follow-up phase. The majority of subjects in both arms had similar grades of liver function tests at baseline as well as worst grades on study. Two subjects (<1%) in the OFA arm had a Grade 3 for liver parameters. One subject

had an SAE of HBV re-activation and 1 subject had gallstones.

Subjects in both arms had similar baseline serum creatinine levels. There was no difference in worst grade creatinine during the study, and none of the subjects had a worst grade of Grade 3 or 4 for renal toxicity parameters.

Subjects in both arms had similar grades of electrolytes at baseline as well as worst grades on study. Subjects in both arms had similar worst grade serum glucose while glucocorticoids were administered as a premedication to only the OFA arm, steroids for various indications were reported as concomitant medications for subjects in both arms.

***Immunoglobulins***

The Ig levels for both arms were similar at baseline, which were slightly decreased but still were within the normal levels. Over the course of the study, the Ig levels increased in the Obs arm while no increase was observed in subjects in the OFA arm.

Median baseline levels were below the reference range for IgM in both arms, and for IgA in the OFA arm. Median serum levels of IgA remained below the reference range for the OFA arm.

***Immunogenicity***

At baseline (Cycle 1 Week 1), 225 of 228 subjects were negative for HAHA. Overall, 221 subjects could be confirmed HAHA negative at baseline based on available OFA concentration results at data cut-off. One subject was confirmed positive at baseline (titer=32) while samples at other time points were negative

At data cut-off, post-OFA HAHA data were available for 205 of 237 subjects (86%). Of these 205 subjects, 185 (90%) had all negative HAHA results with at least 1 OFA plasma concentration low enough (<200 µg/mL) for the negative HAHA results to be considered conclusive, and one subject who had received prior OFA treatment was HAHA-positive at the 6-month FU visit (titer=16) while all other samples were negative.

Formation of anti-OFA antibodies was reported in <1% of subjects with CLL after treatment with OFA in more than 550 subjects tested across the CLL program (treatment periods ranging from 8 weeks to 2 years).

**Vital signs**

Vital signs parameters (systolic and diastolic blood pressure, pulse, temperature) varied for subjects within and between the OFA and Obs arms throughout the study, but showed no apparent trends or patterns in changes from baseline. Most subjects had unchanged post-baseline vital signs at the majority of assessments. Adverse events of hypertension or hypotension were reported infrequently during the study, and the incidence of each AE was similar between arms.

Most subjects had an ECOG performance status of 0 at baseline and baseline ECOG scores were balanced between the arms. The majority of subjects had an ECOG status of 0 or 1 during the study and did not show a shift during the study.

Nearly all subjects had ECG results at screening that were read as normal or abnormal/not clinically significant. Six subjects in the Obs arm (3%) had abnormal/clinically significant ECG results at screening.

Most subjects had normal liver and spleen assessments at screening and throughout the study. The low proportion of subjects who had an enlarged liver or spleen at screening declined in both arms starting

with Cycle 2 and for the remainder of the study, including follow-up.

AEs by age

The incidence of AEs in younger (<65 years) and older (≥65 years) subjects in the OFA arm in Study OMB112517 is presented in.

**Table 2.** AEs Reported in at Least 10% of Subjects by Age Subgroups-Study OMB112517

| Preferred term | OFA (N=237) | | Obs (N=237) | |
|---|---|---|---|---|
| | <65 years | ≥65 years | <65 years | ≥65 years |
| n | 120 | 117 | 117 | 120 |
| **Any event** | **106 (88)** | **100 (85)** | **80 (68)** | **97 (81)** |
| Upper respiratory tract infection | 30 (25) | 15 (13) | 10 (9) | 13 (11) |
| Neutropenia | 28 (23) | 30 (26) | 12 (10) | 12 (10) |
| Pyrexia | 26 (22) | 12 (10) | 10 (9) | 15 (13) |
| Cough | 25 (21) | 25 (21) | 8 (7) | 14 (12) |
| Infusion related reaction[a] | 17 (14) | 22 (19) | NA | NA |
| Fatigue | 16 (13) | 11 (9) | 6 (5) | 10 (8) |
| Diarrhoea | 15 (13) | 18 (15) | 2 (2) | 7 (6) |
| Headache | 15 (13) | 7 (6) | 2 (2) | 3 (3) |
| Rash | 13 (11) | 10 (9) | 6 (5) | 4 (3) |
| Sinusitis | 13 (11) | 6 (5) | 6 (5) | 5 (4) |
| Pneumonia | 12 (10) | 14 (12) | 5 (4) | 13 (11) |
| Bronchitis | 11 (9) | 10 (9) | 4 (3) | 12 (10) |

a. Infusion-related reaction was reported as the verbatim term with or without associated symptoms

Common AEs of upper RTI, pyrexia, and fatigue were reported more frequently in younger subjects than the older ones in the OFA arm or either age groups in the Obs arm. Neutropenia, cough, and diarrhea were reported more frequently in the OFA arm regardless of age compared with the Obs arm. In the OFA maintenance arm, the only common AE reported at a higher incidence (>5% difference) in older subjects compared with younger ones was infusion-related. AEs reported more frequently in younger subjects compared with older subjects were upper RTI, pyrexia, headache, and sinusitis.

AEs by gender

Overall, the proportion of subjects with any AE and the types of AEs reported were similar in both men and women who were treated with ofatumumab, with the exception of AEs of neutropenia. Neutropenia AEs were reported more frequently in women (31%) than men (21%) in the OFA arm, and the incidence of neutropenia AEs in women treated with ofatumumab (31%) was approximately 5-times higher than in women in the Obs arm (6%). The incidence of neutropenia in men in the OFA arm (21%) was also higher than men in the Obs arm (12%), consistent with the overall safety population.

In the OFA arm, the female subset reported a greater incidence (>5% difference) of neutropenia, bronchitis, arthralgia, and sinusitis compared with males. Conversely, a higher proportion of males in the OFA arm reported pruritus compared with females.

AEs by race

Subjects enrolled in Study OMB112517 were predominantly White (96%), which is consistent with the typical epidemiology of subjects with relapsed CLL. Consequently, analysis of the safety profile of ofatumumab by race subgroups was limited. No new safety issues were identified in non-White population enrolled in the study.

AEs by body weight

Adverse events in the OFA arm were similar between subgroups of subjects based on median BW at screening (80 kg; range: 42 to 196 kg). In the OFA arm, the incidences of any AE or SAE observed in subjects with BW <80 kg were 87% and 37%, respectively. These incidences were similar to those observed in subjects with BW ≥ 80 kg (86% and 31%, respectively). Safety results for subjects in the Obs arm with BW <80 kg (any AE 78%; any SAE 37%) were also consistent with those reported in both subgroups of the OFA arm.

The proportion of subjects with any AE was slightly higher in subjects in the OFA arm with BW<25th percentile or >75th percentile, compared with OFA subjects with body weight ≥25th percentile and ≤75th percentile. A similar pattern was observed across weight subgroups in the OFA arm with regard to any SAE and AEs/SAEs leading to permanent discontinuation of study treatment.

AEs by extrinsic factors

No significant differences in prevalence of AEs were identified with regards to prior therapies or no interpretation could be made due to the limited number of subjects in some subgroups (considering chemoimmunotherapy, only alkylating monotherapy or other therapies). The safety profile of ofatumumab was similar in subgroups of subjects based on the number of prior induction therapies received. AEs in each of these subgroups were also consistent with the overall safety population.

There were no important safety signals noted for subjects enrolled in the study from different geographic regions.

**Safety Results Across Ofatumumab Monotherapy Studies in CLL**

Ofatumumab monotherapy was evaluated in 6 clinical studies with completed enrolment in subjects with relapsed or refractory CLL. A total of 614 subjects from [Study OMB112517] (n=237), [Study Hx-CD20-402] (n=33), [Study Hx-CD20- 406/OMB111773] (n=223), [Study GEN416/OMB111827] (n=29), [Study OMB114242] (n=78), and [Study OMB112855] (n=14) were included in the safety population.

Study OMB112517 investigated ofatumumab maintenance treatment in subjects with relapsed CLL who had responded to induction therapy and were in remission (i.e. CR or PR). The remaining 5 studies (Hx-CD20-402, Hx-CD20-406, GEN416, OMB114242, and OMB112855) were conducted in subjects with active CLL disease that was heavily pre-treated and refractory. These results were not integrated due to differences in the enrolment criteria, subject population, study durations, and doses of ofatumumab administered in the individual studies.

The majority of subjects had at least 1 AE during study participation regardless of ofatumumab dosing regimen. More than 50% of subjects in each study also had AEs that were Grade ≥3 in severity, with the exception of subjects in Study Hx-CD20-402.

**Table 3. Overview of Adverse Events Across Ofatumumab Monotherapy Studies in CLL (Safety Populations)**

| | Ofatumumab Monotherapy Studies in CLL, n (%) | | | | | |
|---|---|---|---|---|---|---|
| | 402 2000 mg (N=33) | 406 2000 mg (N=223) | 416 2000 mg (N=29) | 242 OFA Arm 2000 mg (N=78)[a] | 855 2000 mg (N=14) | 517 OFA Arm 1000 mg (N=237) |
| **Any event** | **27 (82)** | **213 (96)** | **27 (93)** | **71 (91)** | **14 (100)** | **206 (87)** |
| Any related event | 26 (79) | 149 (67) | 20 (69) | 49 (63) | 13 (93) | 147 (62) |
| Any event Grade ≥3 | 11 (33) | 139 (62) | 23 (79) | 50 (64) | 8 (57) | 120 (51) |
| **Adverse Events of Special Interest** | | | | | | |
| **Any infection event** | 16 (48) | 162 (73) | 23 (79) | 46 (59) | 12 (86) | 154 (65) |
| Infections Grade ≥3 | 3 (9) | 64 (29) | 15 (52) | 23 (29) | 6 (43) | 47 (20) |
| Opportunistic infection | 3 (9) | 26 (12) | 8 (28) | 7 (9) | 2 (14) | 23 (10) |
| **Any infusion-related event** | 25 (76) | 153 (69) | 21 (72) | 33 (42) | 14 (100) | 109 (46) |
| Infusion-related Grade ≥3 | 2 (6) | 14 (6) | 2 (7) | 4 (5) | 2 (14) | 9 (4) |
| **Cytopenias** | | | | | | |
| Any event associated with decreased neutrophil count | 2 (6) | 46 (21) | 5 (17) | 23 (29) | 5 (36) | 67 (28) |
| Any event associated with decreased neutrophil count Grade ≥3 | 2 (6) | 38 (17) | 5 (17) | 20 (26) | 2 (14) | 57 (24) |
| Any event associated with decreased Hb | 2 (6) | 46 (21) | 4 (14) | 9 (12) | 1 (7) | 9 (4) |
| Any event associated with decreased Hb Grade ≥3 | 1 (3) | 14 (6) | 2 (7) | 7 (9) | 0 | 4 (2) |
| Any event associated with decreased platelet count | 3 (9) | 12 (5) | 2 (7) | 10 (13) | 1 (7) | 19 (8) |
| Any event associated with decreased platelet count Grade ≥3 | 3 (9) | 9 (4) | 0 | 6 (8) | 0 | 4 (2) |

Note: Dose of ofatumumab administered in each study is provided in the table.
a. Includes only subjects with events during the first 24 weeks of treatment. Events reported during ofatumumab salvage therapy were not included.

Infection AEs were common in subjects with CLL across the ofatumumab monotherapy studies. The incidence of serious and severe infections in each study was consistent with the disease status of enrolled subjects. Permanent discontinuation of study treatment due to infection AEs was infrequent.

High proportion of subjects in each study had at least 1 infusion-related AEs, but most events were low grade in severity, few cases were serious and/or resulted in treatment discontinuation.

**Safety related to drug-drug interactions and other interactions**

*Drug Interactions*

Although limited formal drug-drug interaction data exist for ofatumumab, there are no known clinically significant interactions of ofatumumab with other medicinal products. Ofatumumab does not have a clinically relevant effect on the PK of chlorambucil or its active metabolite, phenylacetic acid mustard.

*Adverse Events by Type and Number of Prior Therapies*

There were more AEs observed in subjects that received 'only alkylating monotherapy' as the most recent prior therapy to ofatumumab, although the absolute numbers were small (ofatumumab: 14 subjects, Obs: 9 subjects). The most common AE of this population was infusion-related reactions (64%). In contrast, neutropenia was the most common AE for subjects that received chemoimmunotherapy (29%) or 'other therapy' (30%).

**Table 70: Key safety summary by type of most recent prior treatment (Safety population)**

| | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Subgroup: Type of Prior Treatment – Chemoimmunotherapy, n (%)** | | |
| n | 190 | 190 |
| Any AE | 166 (87) | 144 (76) |
| AE Grade ≥3 | 98 (52) | 70 (37) |
| Neutropenia Grade ≥3 | 47 (25) | 23 (12) |
| Infusion-related Grade ≥3 | 8 (4) | NA |
| Infections Grade ≥3 | 40 (21) | 33 (17) |
| AE leading to death | 6 (3) | 16 (8) |
| **Subgroup: Type of Prior Treatment - Only Alkylating Monotherapy, n (%)** | | |
| n | 14 | 9 |
| Any AE | 14 (100) | 6 (67) |
| AE Grade ≥3 | 9 (64) | 3 (33) |
| Neutropenia Grade ≥3 | 2 (14) | 1 (11) |
| Infusion-related Grade ≥3 | 0 | NA |
| Infections Grade ≥3 | 5 (36) | 0 |
| AE leading to death | 2 (14) | 0 |
| **Subgroup: Type of Prior Treatment - Other Prior Treatment, n (%)** | | |
| n | 33 | 38 |
| Any AE | 26 (79) | 27 (71) |
| AE Grade ≥3 | 13 (39) | 12 (32) |
| Neutropenia Grade ≥3 | 8 (24) | 1 (3) |
| Infusion-related Grade ≥3 | 1 (3) | NA |
| Infections Grade ≥3 | 2 (6) | 6 (16) |
| AE leading to death | 0 | 3 (8) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.1300]
Abbreviations: AE=adverse event; NA=not applicable.

**Table 71: Key safety summary by number of previous induction therapies (Safety population)**

| | OFA (N=237) | Obs (N=237) |
|---|---|---|
| **Subgroup: Number of Previous Induction Therapies - 2 Induction Treatments, n (%)** | | |
| n | 168 | 166 |
| Any AE | 146 (87) | 123 (74) |
| AE Grade ≥3 | 86 (51) | 58 (35) |
| Neutropenia Grade ≥3 | 42 (25) | 14 (8) |
| Infusion-related Grade ≥3 | 6 (4) | NA |
| Infections Grade ≥3 | 33 (20) | 27 (16) |
| AE leading to death | 6 (4) | 13 (8) |
| **Subgroup: Number of Previous Induction Therapies - 3 Induction Treatments, n (%)** | | |
| n | 65 | 63 |
| Any AE | 57 (88) | 48 (76) |
| AE Grade ≥3 | 33 (51) | 25 (40) |
| Neutropenia Grade ≥3 | 15 (23) | 11 (17) |
| Infusion-related Grade ≥3 | 3 (5) | NA |
| Infections Grade ≥3 | 14 (22) | 10 (16) |
| AE leading to death | 2 (3) | 5 (8) |
| **Subgroup: Number of Previous Induction Therapies - Other Induction Treatments, n (%)** | | |
| n | 4 | 8 |
| Any AE | 3 (75) | 6 (75) |
| AE Grade ≥3 | 1 (25) | 2 (25) |
| Neutropenia Grade ≥3 | 0 | 0 |
| Infusion-related Grade ≥3 | 0 | NA |
| Infections Grade ≥3 | 0 | 2 (25) |
| AE leading to death | 0 | 1 (13) |

[Data Source: m5.3.5.1 OMB112517 CSR Table 3.1320]
Abbreviations: AE=adverse event; NA=not applicable.



**Discontinuation due to adverse events**

Eight percent of subjects in the OFA maintenance arm had AEs leading to permanent treatment discontinuation. The AEs that led to discontinuation of OFA included neutropenia (3 subjects), hypersensitivity (2 subjects), and pneumonia (2 subjects); and all remaining AEs leading to discontinuation were reported for single subjects only.

**Post marketing experience**

The first marketing approval of ofatumumab was in the United States in October 2009 for treatment of CLL patients refractory to fludarabine and alemtuzumab. Per September 2014, the cumulative postmarketing exposure to ofatumumab was estimated to be approximately 7269 patients (data from IMS -Intercontinental Medical Statistics). As of December 2014, a total of 825 spontaneous and post-marketing reports from 29 countries were received by the Company. Within these reports, there were a total of 2206 AEs (serious and non-serious).

The ten most commonly reported AE's were; pyrexia (4%), infusion related reaction (3%), rash (3%), urticaria (2%), dyspnoea (2%), neutropenia (2%), chills (2%), disease progression (2%), pruritus (2%) and off-label use (3%). Seven of these AEs were descriptive of infusion reactions, a well-characterized and expected event associated with ofatumumab treatment.

Of the 825 reports from spontaneous and PMS activities in-scope for this analysis, 118 (14%) were fatal. Distribution of AEs by system organ class (SOC) for 502 reports were presented in Table below, which

included also the 118 cases with fatal outcome.

**Table 4.** Distribution of events per System Organ Class (5% cut-off)

| MedDRA Preferred Term | Adverse Events n (%) |
|---|---|
| **All Preferred Terms** | **502 (100)[a]** |
| General disorders and administration site conditions | 103 (21%) |
| Infections and infestations | 92 (18%) |
| Respiratory, thoracic and mediastinal disorders | 46 (9%) |
| Blood and lymphatic system disorders | 43 (9%) |
| Investigations | 33 (7%) |
| Gastrointestinal disorders | 27 (5%) |

a. These 502 adverse events were contained in the total 118 spontaneous and PMS reports with a fatal outcome which are in-scope for this evaluation as of the data lock point.

***Safety in the High-risk group***

Noting that in this study subjects on active treatment are compared to subjects on observation, the safety profile in this high risk group is acceptable and comparable between arms. Despite a greater incidence of overall AEs, there was a lower incidence of SAEs and a similar incidence of grade ≥ 3 AEs reported with ofatumumab.

- **Table -17 Overview of adverse events**

| | High/Very High Risk | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=239** | **Observation N=241** |
| **Adverse Events – n (%)** | **72 (92)** | **50 (78)** | **217 (91)** | **188 (78)** |
| AEs related to treatment | 49 (63) | NA | 156 (65) | NA |
| AEs leading to treatment discontinuation | 8 (10) | NA | 24 (10) | 0 |
| AEs leading infusion interrupt/delay | 36 (46) | NA | 98 (41) | NA |
| AEs grade ≥ 3 | 49 (63) | 38 (59) | 132 (55) | 96 (40) |
| **SAEs – n (%)** | **36 (46)** | **34 (53)** | **90 (38)** | **81 (34)** |
| SAE related to treatment | 8 (10) | NA | 35 (15) | NA |
| Fatal SAEs | 10 (13) | 12 (19) | 14 (6) | 21 (9) |
| Fatal SAEs related to treatment | 0 | NA | 0 | NA |

The incidence of deaths was similar between arms (Table 1-14); there was no death on treatment in the ofatumumab arm. While there were more deaths due to infections in the ofatumumab arm, these occurred well after end of treatment and are mostly confounded by post-treatment anticancer therapy.

- **Table -18 Overview of Deaths**

| | High Risk Group | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=239** | **Observation N=241** |

| | High Risk Group | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=239** | **Observation N=241** |
| **Status at end of study – n (%)** | | | | |
| Died | 30 (38) | 25 (39) | 51 (21) | 42 (17) |
| Alive, Follow-up ongoing | 41 (53) | 35 (55) | 168 (70) | 168 (70) |
| Alive, Follow-up Ended | 7 (9) | 4 (6) | 20 (8) | 31 (13) |
| **Primary cause of death – n (%)** | | | | |
| Disease Under study | 18 (23) | 13 (20) | 31 (13) | 19 (8) |
| Fatal infection SAEs | 8 (10) | 4 (6) | 10 (4) | 7 (3) |
| Other (mostly single SAEs) | 4 (5) | 8 (13) | 8 (3) | 17 (7) |
| **Time to Death – n (%)** | | | | |
| On Treatment | 0 | 1 (2) | 0 | 3 (1) |
| ≤ 60 Days after last treatment | 1 (1) | 1 (2) | 2 (<1) | 2 (<1) |
| >60 days after last treatment | 29 (37) | 23 (36) | 49 (21) | 37 (15) |

A higher incidence of overall AEs of neutropenia was observed in the ofatumumab arm, however neutropenia SAEs were lower compared to the observation arm (Table 1-15) and the grade ≥ 3 neutropenia AEs were comparable (Table 1-16). The frequencies of febrile neutropenia and neutropenic sepsis were similar between the two arms.

- **Table -19 Overview of AEs associated with decreased neutrophil count**

| | High Risk Group | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=239** | **Observation N=241** |
| **Neutropenia Adverse Events – n (%)** | **24 (31)** | **14 (22)** | **75 (31)** | **30 (12)** |
| Neutropenia | 20 (26) | 13 (20) | 64 (27) | 25 (10) |
| Febrile neutropenia | 4 (5) | 3 (5) | 14 (6) | 7 (3) |
| Neutrophil count decreased | 1 (1) | 0 | 7 (3) | 3 (1) |
| Neutropenic sepsis | 1 (1) | 1 (2) | 1 (<1) | 1 (<1) |
| Neutropenia AEs related to study treatment | 15 (19) | NA | 48 (20) | NA |
| **SAEs – n (%)** | **5 (6)** | **6 (9)** | **16 (7)** | **8 (3)** |
| Neutropenia | 1 (1) | 3 (5) | 4 (2) | 3 (1) |
| Febrile neutropenia | 4 (5) | 3 (5) | 13 (5) | 5 (2) |
| Neutropenic sepsis | 1 (1) | 1 (2) | 1 (<1) | 1 (<1) |
| Neutropenia SAEs related to treatment | 2 (3) | NA | 8 (3) | NA |

- **Table -20 Grade 3 and above AEs associated with decreased neutrophil count**

| | High Risk Group | | Overall population | |
|---|---|---|---|---|
| | **Ofatumumab N=78** | **Observation N=64** | **Ofatumumab N=239** | **Observation N=241** |
| **Grade ≥ 3 AEs associated with decreased neutrophils – n (%)** | **19 (24)** | **13 (20)** | **63 (26)** | **27 (11)** |
| Febrile neutropenia | 3 (4) | 2 (3) | 11 (5) | 6 (2) |
| Neutropenia | 17 (22) | 12 (19) | 55 (23) | 22 (9) |
| Neutropenic sepsis | 1 (1) | 1 (2) | 1 (<1) | 1 (<1) |
| Neutrophil count decreased | 0 | 0 | 4 (2) | 2 (<1) |
| **Grade ≥ 3 drug-related AEs associated** | **15 (19)** | **0** | **45 (19)** | **NA** |

| | High Risk Group | | Overall population | |
|---|---|---|---|---|
| | Ofatumumab N=78 | Observation N=64 | Ofatumumab N=239 | Observation N=241 |
| **with decreased neutrophils – n (%)** | | | | |
| **Grade ≥ 3 SAEs associated with decreased neutrophils – n (%)** | **4 (5)** | **5 (8)** | **15 (6)** | **7 (3)** |
| Febrile neutropenia | 3 (4) | 2 (3) | 11 (5) | 4 (2) |
| Neutropenia | 1 (1) | 3 (5) | 4 (2) | 3 (1) |
| Neutropenic sepsis | 1 (1) | 1 (2) | 1 (<1) | 1 (<1) |
| **Grade ≥ 3 drug-related SAEs associated with decreased neutrophils – n (%)** | **2 (3)** | **0** | **8 (3)** | **NA** |

Infection AEs in the High risk group have a similar pattern to those reported in the overall population (Table 1-17), although the incidence of deaths due to infections was slightly higher in the ofatumumab arm vs. the observation arm; however these occurred more than 30 days after the last dose of study treatment, i.e. in the post maintenance treatment survival follow-up and were mostly confounded by next therapies, as presented in RSI 2.

- **Table -21 Overview of infection events**

| | High Risk Group | | Overall population | |
|---|---|---|---|---|
| | Ofatumumab N=78 | Observation N=64 | Ofatumumab N=239 | Observation N=241 |
| **Infection Adverse Events – n (%)** | **56 (72)** | **38 (59)** | **174 (73)** | **136 (56)** |
| Infection AEs related to treatment | 20 (26) | NA | 61 (26) | NA |
| Infection AEs leading to treatment discontinuation | 1 (1) | NA | 7 (3) | NA |
| Infection AEs leading infusion interrupt/delay | 17 (22) | NA | 39 (16) | NA |
| Infection AEs ≥ Grade 3 | 21 (27) | 24 (38) | 54 (23) | 44 (18) |
| **Infection SAEs – n (%)** | **21 (27)** | **26 (41)** | **55 (23)** | **49 (20)** |
| Infection SAEs related to treatment | 5 (6) | NA | 22 (9) | NA |
| Fatal infection SAEs | 8 (10) | 4(6) | 10 (5) | 7 (3) |
| Fatal infection SAEs related to treatment | 0 | NA | 0 | NA |

## 2.6.1. Discussion on clinical safety

In this study, 237 subjects were exposed to ofatumumab and in this application the safety experience of the subjects is compared to the current safety profile of OFA which is based on 2603 oncology patients including 1555 CLL patients receiving ofatumumab in clinical trials (through December 2014). The number of patients exposed in this trial is regarded sufficient to evaluate the safety of maintenance ofatumumab in the current study.

Overall, the most common AEs observed were neutropenia, cough, upper respiratory tract infections, infusion reactions and pyrexia. This pattern of AEs is expected based on previous safety experience with ofatumumab. The common infusion reactions are sought alleviated by administration of steroids prior to ofatumumab infusion.

In case of a mild or moderate ADR, the infusion should be interrupted and restarted at half of the infusion rate at the time of interruption, when the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 ml/hour prior to interrupting due to an ADR, the infusion should be restarted at 12 ml/hour, the standard starting infusion rate. The infusion rate can continue to be increased according to standard procedures, according to physician discretion and patient tolerance (not to exceed increasing the rate every 30 minutes).

In case of a severe ADR, the infusion should be interrupted and restarted at 12 ml/hour, when the patient's condition is stable. The infusion rate can continue to be increased according to standard procedures, according to physician discretion and patient tolerance (not to exceed increasing the rate every 30 minutes).

The most frequently reported SAEs were in the Infections and Infestations SOC. No cases of PML, toxic epidermal necrolysis, Stevens-Johnson syndrome or tumour lysis syndrome were reported in this study.

With regard to special populations, no safety signals of concern were detected in relation to Age, Gender, Race or Body Weight. The safety of ofatumumab during Pregnancy and Lactation has not been established.

No known clinically significant interactions of ofatumumab have been detected. Overall, 40% of subjects experienced AEs leading to dose delays or interruptions whereas 8% of subjects permanently discontinued treatment due to AEs. This is considered acceptable.

When looking at the subgroup of patients defined as "high risk", the numbers of AEs between arms are slightly changed compared with the overall population. As in the overall group, there was a greater incidence of overall AEs in the ofatumumab arm. There was a lower incidence of SAEs and nearly a similar incidence of grade ≥ 3 AEs reported with ofatumumab. The incidence of deaths was similar between arms, and there was no death on treatment in the ofatumumab arm.

Concerning neutropenia, a higher incidence of overall AEs of neutropenia was observed in the ofatumumab arm, however neutropenia SAEs were slightly lower compared to the observation arm and the grade ≥ 3 neutropenia AEs were comparable. The frequencies of febrile neutropenia and neutropenic sepsis were similar between the two arms.

Overall, the safety profile of ofatumumab in the present study is considered in line with expectations based on previous safety experience with ofatumumab. The safety profile must be evaluated in the clinical context that maintenance therapy is currently not recommended for CLL.



### 2.6.2. Conclusions on clinical safety

The safety findings observed in the ofatumumab maintenance treatment population (n=237) in the pivotal study OMB112517 were consistent with the well-established safety profile of ofatumumab, including main safety issues such as infusion reactions, neutropenia and infections. No new or unexpected safety signals were detected in relation to the maintenance treatment, and most AEs observed in the study were in general manageable.

### 2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

## *2.7. Risk management plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 12 (dated 15 June 2015) is acceptable. In addition, several revisions were recommended to be taken into account within the next RMP update, as outlined below. The PRAC endorsed PRAC Rapporteur Updated Assessment Report is attached.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with the proposed new indication, the update of the RMP cannot be agreed at this stage. Revisions of the RMP that may be warranted due to availability of additional data are recommended to be taken into account within the next RMP update.

## *2.8. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC were proposed to be updated.

### 2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

Amendments proposed for the PL as a result of this submission are minimal and are not considered to require further consultation with target patient groups. The only change that has been made as a result of this submission is the addition of sentences specific to the maintenance indication in Section 3. How to use ARZERRA. This change would not be expected to impact readability of the PL.

There are no proposed changes to any other section of the PL.

# 3. Benefit-Risk Balance

***Benefits***

**Beneficial effects**

The primary endpoint was PFS. A PFS gain in favour of maintenance was shown with a median of 29.44 vs. 15.24 months (investigator-assessment) and 30.36 vs. 14.75 months (IRC assessment).

Of the secondary endpoints, the median OS has not been reached in any arm. The time to next therapy (as determined from the time of randomization) was improved by ofatumumab maintenance treatment as compared to no further treatment. Data on PFS2 were scarce.

Maintenance therapy with ofatumumab is associated with a prolongation in TTNT (38.0 months vs. 29.2 months) (HR 0.68; 95% CI: 0.51, 0.90; p=0.0054) but of smaller magnitude than the increase in PFS.

Most patients (94%) had no B-symptoms at baseline and this continued in both arms throughout the follow-up period, with slightly varying results at each visit. There was a trend of increased depletion in the ofatumumab arm during maintenance treatment, but numbers were scarce at the later visits.

Baseline values were similar for both arms in PRO evaluations. The completion rate was higher in the ofatumumab maintenance arm, as patients only completed questionnaires if they remained on treatment.

Health-related quality of life assessments showed no statistical difference or clinically relevant difference between the arms at any time point. The B-symptoms Index analysis, showed a statistically significant difference in favour of ofatumumab compared with no further treatment (p=0.002) but an analysis on whether the results were clinically relevant, has not been performed.

In the high- risk subgroup the median PFS in the ofatumumab arm was 23.2 months compared with 5.5 months in the observation arm (HR 0.47 [0.31, 0.71], p-value <0.0001). The sensitivity analysis of PFS by IRC is supportive of the primary endpoint (median 23.2 months OFA vs. 7.4 months no further treatment, HR 0.55 [95% CI: 0.35, 0.85]). A significantly shorter median PFS was observed when CT scans were considered, based on both investigator-assessed and IRC-assessed PFS, but with HRs ranging from 0.55 to 0.67. In the OS analysis approximately 40% of the patients in the subgroup had an event, but also in this subgroup, no differences in OS can be seen (HR 0.86 [0.51, 1.48]). The OS data are still regarded as immature.

The median TTNToD showed a prolongation of approximately 7 months with ofatumumab treatment (median months OFA 18.8 vs. 11.5 Obs, HR 0.54 [0.36, 0.83]). With approximately 40% events, mainly deaths, PFS2 numbers are still immature, KM medians are 43.8 and 33.2 months (HR 0.79 [95% CI: 0.47, 1.33]).

**Uncertainty in the knowledge about the beneficial effects**

In the CHMP scientific advice from 2009 it was clearly stated that the PFS endpoint could not stand alone in a maintenance therapy study. Currently, no clinical treatment guideline recommends maintenance for CLL. Due to a relatively short follow-up with a median of about 20 months a potential effect on OS cannot be detected. It is recognised that OS is a difficult endpoints in a disease with a relatively indolent course occurring mainly in elderly people. Moreover, the sample size calculation was based on the number of PFS events, and enrolment was prematurely stopped when the primary objective was met. Therefore, there is a risk that the submitted study is underpowered for the OS endpoint.

There are no additional data showing that the median 16.1 months gain in PFS and median 8.8 months gain in TTNT is translated into further benefits for the patients who received maintenance treatment. The latter pertains in particular to the lack of OS data. No PFS2 data are available. When given ofatumumab as maintenance treatment, this treatment might no longer be an option when a symptomatic relapse arises at a later stage. This question of a potential “loss of chance” remains unresolved due to immature data.

Since the difference in median PFS (ofatumumab 29.44 mo, Obs 15.24 mo, gain 14.2 mo) was not fully translated into a subsequently longer median “time to next anti-cancer therapy” (ofatumumab 37.98 mo, Obs 31.11 mo, gain 6.9 mo). These data seem to indicate that there is a shorter time from progression to start of next treatment in the ofatumumab arm (8.5 mo) as compared to the Obs arm (15.9 mo). This can be partly explained by different event definitions and censoring rules. The Applicant is also referring to differences in clinical practice as an important factor that explains the discrepancy in the PFS and TTNT estimates. This concerns primarily the decision on when to start next therapy. Of notice is that a large proportion of the patients (ofatumumab 45%, Obs 37%) had PD but did not start next therapy. Furthermore, a much larger proportion of the patients in the ofatumumab arm (31%) as compared to the Obs arm (5%) had no documented progression but started next therapy. The question of investigator bias in this open label trial cannot be completely ruled out.

***Risks***

**Unfavourable effects**

Clinical safety of ofatumumab maintenance treatment is primarily derived from 237 patients based on the interim analysis of the pivotal trial OMB112517. At the time of cut-off for the interim analysis 50% of the patients had received maintenance treatment for 16 months while only 25% of the subjects had received all planned cycles.

AEs occurred more frequently in the ofatumumab arm compared to the Obs arm (87% vs 75%, respectively). Most commonly reported AEs in both arms included neutropenia, cough, upper respiratory tract infection and pyrexia, except from infusion reactions which were naturally observed only in the ofatumumab arm. However, the frequencies of these AEs were in general higher in ofatumumab arm than in the Obs arm.

There was an imbalance in frequency of neutropenia observed in the ofatumumab arm (24%) compared to the Obs arm (10%) which led to a higher frequency of grade≥ 3 neutropenia (21% vs 9%, respectively). The frequency of febrile neutropenia was lower in both arms, but still slightly higher in the ofatumumab arm (5% vs 2%). This holds true also for SAEs related to febrile neutropenia (4% vs 1%, respectively).

The imbalance in frequency of neutropenia between the arms seems to be reflected in an increased frequency of infectious AEs in the ofatumumab arm (65%) compared with the obs arm (51%). The proportion of subjects with serious infectious AEs was however comparable between the arms. The most common infectious AEs were respiratory tract infections (RTIs) in the ofatumumab arm (64%) vs Obs arm (45%). This imbalance was driven by the upper RTIs in the ofatumumab arm (38%) than the Obs arm (24%). There was also an imbalance in the category of “other infections” reported (ofatumumab: 39%, Obs: 25%), which included infections like influenza, cellulitis, herpes zoster, herpes simplex, and urinary tract infections.

During the study, patients in the active arm received more blood- and blood supportive care products (mainly G-CSFs) and anti-infective medication consistent with the higher incidence of neutropenia and infection in the ofatumumab maintenance arm.

Infusion related AEs were observed with a frequency of 46% in the ofatumumab arm. Of these events, only 28% were considered treatment-related and 18% resulted in in treatment delay/interruption. Most infusion-related reactions were of mild to moderate severity and primarily occurred on the first day of Cycle 1 (25%), and then reduced to <~2-10% at other cycles

The frequency of grade ≥3 AEs was also higher in the ofatumumab arm than the Obs arm (51% vs 36%, respectively). However, the observed SAEs were comparable between the arms. Furthermore, the fatal AEs were less frequent in the OFA arm (3%) than the Obs arm (8%).

**Uncertainty in the knowledge about the unfavourable effects**

There are no important uncertainties in the knowledge about the unfavourable effects.
Since no new safety signals have been detected and the adverse event profile is well-known for ofatumumab as for other anti-CD20 antibodies, the safety of ofatumumab should be viewed in the context that patients with CLL currently do not receive maintenance therapy.

***Effects Table***

**Table 77: Effects Table for ofatumumab / maintenance CLL (data cut-off: 19 June 2014)**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| PFS | Progression-free survival | Median in months | 29.44 (26.18, 34.17) | 15.24 (11.79, 18.76) | HR = 0.5 (95%CI: 0.38, 0.66), p<0.0001 | |
| Time and response to next-line therapy | | Median in months | 37.98 (28.29, NE) | 31.11 (21.62, NE) | HR=0.66 (95%CI: 0.47, 0.92), p=0.0108<br><br>No data on OS | |
| **Unfavourable Effects** | | | | | | |
| Grade ≥ 3 AEs | | N(%) | 120 (51%) | 85 (36%) | | |
| Neutropenia | | N(%) | 58 (24%) | 24 (10%) | | |
| Any Infection | | N(%) | 154 (65%) | 120 (51%) | | |
| Treatment related infections | | N (%) | 52 (22%) | 0 | | |
| Infusion related AEs | | N(%) | 67 (28%) | 0 | | |

***Benefit-Risk Balance***

**Importance of favourable and unfavourable effects**

A PFS gain of 14-15 months could be viewed as a favourable outcome in most cancer studies, however for a new treatment concept in maintenance therapy the evidence should be compelling, meaning that PFS needs to be supported by other outcome measures for efficacy, preferably OS.

Even if the safety of ofatumumab is well-known, the risk of neutropenic complications and other known anti-CD20 effects is increased and this burden must be taken into the context of a maintenance therapy.

**Benefit-risk balance**

The improvement in the primary endpoint, investigator-assessed PFS for the ofatumumab maintenance not being supported by robust OS data cannot be considered sufficient to outweigh the risk of the additional safety burden of Arzerra in the context of the indication as maintenance treatment for adult patients with CLL at high risk of relapse who are in complete or partial response after at least two lines of induction therapy.

**Discussion on the Benefit-Risk Balance**

"Consolidation/maintenance" is a field of active research (many trials are underway) although combination treatments may be more relevant to address patients at very high-risk of progression. Concerning the added value of maintenance treatment, only an effect on PFS has been observed.

However, the clinical relevance of this effect is doubtful because progression is often asymptomatic and can be managed with acceptable (including recently approved) treatment options that are fairly well tolerated. Thus, treatment-free periods associated with watchful waiting and avoiding severe and life-threatening toxicity are considered more clinically important rather than delaying progression. In the absence of an effect on OS or HRQoL, the maintenance regimen proposed cannot be considered to be clinically justified.

In terms of magnitude, the improvement in PFS for this high-risk (HR) without 17p deletion, is substantial, however, the relevance of PFS as a clinically relevant endpoint is questioned. This is due to the indolent nature of the disease and the availability of acceptable further treatments. Thus, progression (as defined) is not expected to result in significant deterioration of symptoms or quality of life so that the clinical relevance of this endpoint is questioned. Indeed, if CT scans are considered in the definition of progression, the magnitude of improvement is much smaller (about 4 months difference in medians). Thus, the activity of ofatumumab seems to affect predominantly circulating leukaemia cells rather than lymph nodes. Lastly, there are no data in cytogenetic high-risk patients ( e.g p53, del 17p which respond worse to treatment). It is possible that TTNT reflects symptomatic progression and in fact agrees with the PFS taking into account CTScans. Therefore, the magnitude of improvement is much smaller compared to PFS as defined in the protocol. There is no clear effect on OS or time without need for therapy. It is unlikely that a longer follow-up will reveal small differences in view of subsequent treatments that can affect overall survival. Also, a theoretical risk that ofatumumab maintenance could delay subsequent effective treatments cannot be ruled out (although a dramatic effect seems unlikely based on the current data).

Furthermore, apart from a clear decrease in fatigue, the differences observed in terms of HRQoL are of small magnitude and below the conventional thresholds for clinical significance. Indeed many patients that entered into the study were asymptomatic, except for the presence of B symptoms in a relatively high proportion of patients. However, B symptoms are expected to quickly disappear in patients with PR or VGPR.

In principle, the observed safety profile would have been considered acceptable if a clearly relevant clinical benefit could have been established in terms of OS. However, this is not the case in the present assessment and therefore the observed toxicity cannot be considered acceptable.

Even if the safety of ofatumumab is well-known, the risk of neutropenic complications and other known anti-CD20 effects is increased and this burden must be taken into the context of a maintenance therapy, where the alternative would be treatment-free periods associated with watchful waiting. Without a clear clinical benefit the risks may outweigh the observed benefits since the majority of the patients receiving ofatumumab maintenance sooner or later will require new therapy.

Taken together, the benefit of the maintenance treatment is not considered to outweigh the risk.



# 4. Recommendations

**Similarity with authorised orphan medicinal products**

The CHMP by consensus is of the opinion that Arzerra is not similar to Imbruvica or Gazyvaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

***Outcome***

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and

therefore does not recommend, by a majority of 23 out of 30 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

| Variation rejected | | Type |
|---|---|---|
| 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 |

Extension of Indication to include maintenance therapy in Chronic Lymphocytic Leukaemia (CLL) based on the interim analysis of the pivotal study OMB112517 (PROLONG).

**Grounds for refusal:**

- Although an improvement in PFS was observed in the pivotal trial, there is insufficient evidence to quantify the translation of that effect to other clinical outcomes, in particular OS, also PFS2. Furthermore, the impact on clinical symptoms and quality of life remains uncertain. Therefore a clinically relevant benefit for ofatumumab maintenance treatment in the proposed population, both for the broad, initially applied indication and the subsequently applied indication in high-risk population defined by the CLL-IPI prognostic index is not considered demonstrated.

- Although no new safety signals have been detected and the adverse reaction profile is well-known - most common adverse reactions being infusion reactions, neutropenia and upper respiratory tract infections- the safety of ofatumumab is not acceptable in the context of a maintenance therapy where the alternative would be treatment-free periods associated with watchful waiting.

Therefore, the benefit- risk balance of Arzerra in the proposed indication as maintenance treatment for adult patients with CLL at high risk of relapse who are in complete or partial response after at least two lines of induction therapy; is considered negative.